www.medicinescience.org

ISSN 2147-0634

MEDICINE SCIENCE

International Medical Journal

ISSN 2147-0634

Volume 10, Number 1, March 2021, Pages 1-271

photo by Osman CELBIS

ORIGINAL RESEARCHES

CASE REPORTS

SHORT COMMUNICATIONS

REVIEW ARTICLE

Correction

Available online at www.medicinescience.org

ORIGINAL ARTICLE

Medicine Science International Medical Journal

Medicine Science 2021;10(1):1-6

CHA2DS2-VASC Score and this score components in predicting radial artery complications of among patients who underwent elective transradial coronary angiogram

Mehmet Timur Selcuk[1], Hatice Selcuk[1], Orhan Maden[1], Ozge Cakmak Karaaslan[1] Muharrem Tola[2], Habibe Kafes[1] ,Elif Hande Cetin[1], Kevser Gulcihan Balci[1], Mustafa Mucahit Balci[1]

[1]Ankara City Hospital, Department of Cardiology, Ankara, Turkey
[2]Ankara City Hospital, Department of Radiology, Ankara, Turkey

Received 29 July 2020; Accepted 09 September 2020
Available online 20.12.2020 with doi: 10.5455/medscience.2020.09.9225

Abstract

Transradial approach (TRA) has been more and more accepted for cardiovascular operations. TRA uncommonly leads to hemorrhagic and vascular complications. CHA2DS2-VASc score is utilized to estimation the risk of thrombosis in patients with atrial fibrillation. We intended to assess the relationship between the CHA2DS2-VASc score or components of this score and radial artery complications after transradial coronary angiography. A total of 412 consecutive patients who underwent a TRA were evaluated in this study. Patients were divided into two groups as total complications (n= 73) and no-complications (n= 339) groups. The CHA2DS2-VASc score was higher in patients who had total complications group yet it was not statistically significant (p=.149). Total complication group were older compared to control group (p=.017). As the radial artery diameter decreased, and sheath/radial artery diameter increased, the risk of the total complication group higher significantly (for all; p<.001). Known coronary artery disease (OR: 2.230, 95% CI: 1.007- 4.975, p= .048) was independent risk factors for predictor of radial artery thrombosis, DM was an independent predictor of radial artery pseudoaneurysm (OR: 4.746, 95% CI: 1.269- 17.747, p= .021), age was an independent predictor of radial artery hematoma (OR: 1.054, 95% CI: 1.005- 1.106, p= .029) and radial artery total complications (OR: 1.047, 95% CI: 1.005- 1.087, p= .015). The CHA2DS2-VASc score alone is not connected with the risk of radial artery complications after transradial catheterization but CHA2DS2-VASc score components may help to predict complications the risk of in radial interventions.

Keywords: CHA2DS2-VASC, radial artery complications, transradial coronary angiogram

Introduction

Transradial approach (TRA) has been more and more accepted for cardiovascular operations [1]. TRA has been exhibited that the ratio of vascular access complications is few compared with transfemoral access [2,3]. Therefore, in our cardiac catheter laboratory, TRA is utilized in over 80% of the procedures.

TRA uncommonly leads to hemorrhagic and vascular complications, including pseudoaneurysm, , perforation, access site bleeding and arteriovenous fistula [4]. Radial artery occlusion (RAO) is a well-known complication and occurs in 2% to 18% of TRA procedures [5]. Many of these complications are silent and asymptomatic.

***Coresponding Author:** Ozge Cakmak Karaaaslan, Ankara City Hospital, Department of Cardiology, Ankara, Turkey
E-mail: ozgecakmak2323@gmail.com

CHA2DS2-VASc score is utilized to estimation the risk of thrombosis in patients with atrial fibrillation and CHA2DS2-VASc score includes the parameters such as heart failure, hypertension, age, diabetes mellitus (DM), cerebrovascular event, gender, peripheral vascular disease [6, 7]. On the other hand, it has more recently been practised for different diseases. Moreover, it was shown to be a predictor of thrombosis different patient groups. For instance, it has been utilized to predict the risk of development of thrombosis and stroke in patients with chronic heart failure and assessment risk of the cerebrovascular event after bypass graft surgery who are in sinus rhythm [8-10]. The relationship between comorbid diseases and radial artery thrombosis is not clear. There is insufficient data on the effect of comorbid conditions or high risk of thrombosis on radial artery occlusion due to thrombosis after radial intervention. According to data obtained from many studies, CHA2DS2-VASC score may help in the prediction of complication risk in TRA.

We intended to assess the relationship between the CHA2DS2-VASc score or components of this score and radial artery complications after transradial coronary angiography (TRCA).

Material and Methods

This prospectively study enrolled 412 patients aged 40 to 80 years who underwent TRCA from January 2011 to January 2014. Patients who participated in the study has been examined complications such as hematoma, thrombosis and pseudoaneurysm. Patient's data was obtained from our previous study data [11]. Patients were grouped as patients with no complications and those with at least one complication, and the groups were compared with each other. In this study, an optimal radial artery pulsation was most important condition for the elective TRA; otherwise, physicians preferred with a transfemoral approach. All of the patients in the study were performed TRCA by experienced physicians.

Patients with emergent procedures, nonpalpable radial pulse, abnormal Allen test, oral anticoagulant therapy, bleeding diathesis, thrombocytopenia, coagulation disorder, severe hepatic disease, known of coronary artery by-pass graft surgery (CABG), ad hoc percutaneous coronary intervention and chronic renal disease on hemodialysis were excluded from in this study. Written informed consent was obtained from all patients who accepted to participate in the study. The local ethics committee approved the study protocol. The Allen test was applied and the existence of duple blood flow and openness of the palmar bridge was approved. Following sterilized preparing and injection of 2% lidocaine at puncturing location, a 20-gauge catheter was inserted into the radial artery from the 4 to 6 cm upper crease of the wrist, utilization Seldinger's technique. A guidewire was positioned in the centre of the catheter, and the mechanism was slowly removed. A 6F radio focus radial sheath was forwarded through the guidewire into the radial artery. A combination of 5 mg Diltiazem, 200 mcg nitroglycerin and 5000 IU unfractionated heparin was administered intraarterially. Six French diagnostic coronary artery catheters (Boston Scientific, Maple Grove, MN, USA) were used during elective TRCA. After the ending of the angiography, radial sheaths were extracted and regional pressure was put on with a bandage. The procedure duration was admitted time between the entry of the radial sheath and withdrawal of the sheath. Following 45 or 60 minutes, the tampon bandage was unloosed and maintained for three or four hours [12].

For each patient, we enrolled baseline characteristic and demographic features on sex, age, DM, hypertension, smoking, known coronary and peripheral artery diseases, unfractionated heparin dose, radial sheath external diameter/radial artery inside diameter, procedural time and all complications. DM was assigned as using of oral hypoglycemic drug or insulin or known diagnosis of DM. Hypertension was assigned as known diagnosis of hypertension or using of antihypertensive agent. The definition of heart failure is a previously known diagnosis of heart failure. Stenosis of ≥ 50% in peripheral arteries was described as peripheral arterial disease and stenosis of ≥ 50% in coronary arteries was described as coronary arterial disease. Hypercholesterolemia has depend on the existence of a total cholesterol level of ≥200 mg/dL or usage of medical therapy. Total complication group was defined as occurring radial artery thrombus, hematoma and pseudoaneurysm after TRCA. All patients receive ultrasound evaluations of the radial artery one day after the TRCA. The ultrasound dimensions were performed by an experienced physician, usage a duplex ultrasound system (Siemens Ultrasonography Systems, Tokyo, Japan) with 5 to 10 MHz. The patients had repose 15 minutes ago evaluations and after that radial artery variable was quantified at the location 2-3 cm near to the radial styloid. Additionally, the radial artery was evaluated from the radial styloid process to the brachial artery. Radial artery pseudoaneurysm, thrombus, hematoma and radial artery diameter were enrolled by ultrasound and doppler ultrasound.

Complete occlusion was defined as no flow in the radial artery. Partial occlusion was defined as a low flow velocity in the radial artery lumen that a partly obstructed in the radial artery [11]. The pseudoaneurysm was described as a pulsatile mass with existed turbulent flow aneurysmal sac at the entry location [4]. CHA2DS2-VASc score includes the parameters such as gender, age, heart failure, DM, hypertension, stroke, predicts atheroembolic events and peripheral vascular disease [6]. The CHA2DS2-VASc score was calculated according to inclusion 2 points for ≥ 75 years of age and stroke, and 1 point for other components.

Statistical Analysis

Data were analyzed with the SPSS 22.0 statistics package for Windows. All datas were presented as means ± standard deviation and percentage. Student t-test was utilized for comparison of mean values and Chi-square test for comparative of percentages. The Mann-Whitney U test was utilized to compare continuous variables that were not distributed normally. The differences between groups were statistically significant with a p value of < 0.05. To explore the association between the components of CHA2DS2-VASc score and total radial artery complications, an univariate logistic regression analysis was used and variables with P-value of less than 0.05 were utilized in the multivariate logistic regression analysis. The results of regression analysis are displayed as adjusted odds ratio and 95% confidence interval. The predictive value of the CHA2DS2-VASc score was tested using receiver operating characteristic analysis for radial artery complications. A p-value lower than 0.05 was regarded as statistically significant.

Results

Baseline clinical, demographic echocardiographic and laboratory characteristics of the study population were showed Table 1. The study population consisted of 412 patients (mean age 59.7 ± 0.4 years, 245 men [72.3%]), of whom 339 patients were in the no-complications group (control group) and 73 patients (17.7%) were in the total complication group. There were no significant difference in the incidence of hypertension, DM, dyslipidemia, known coronary and peripheral artery disease, known diagnosis of heart failure and smoking between the two groups. Compared to control group, total complication group were older (63 ± 0.04 vs 59 ± 0.4, p=.017). Median body surface area was higher in the total complication group compared to control group (p=.019). The procedure duration was significantly more in have total complication group compared to no-complication group (11.2 ± 0.3 vs 14.2 ± 1.1, p=.019). As the radial artery diameter decreased, and sheath/radial artery diameter increased, the risk of the total complication group higher significantly (for all; p<.001). The observed incidence was 17.7% (73 of 412 patients) for hemorrhagic and vascular complications. Of these 73 patients; 40 patients (54.7% of all complications, 9.7% of all patients) presented hematoma, 27 patients (36.9% of all complications, 6.5% of all patients) presented with thrombosis, and 15 patients

(20.5% of all complications, 3.6% of all patients) presented with radial artery pseudoaneurysm (Figure1). In the regression analysis were separately evaluated the possible risk factors of radial artery complications. (Table 2-3-4-5). Known coronary artery disease (OR: 2.230, 95% CI: 1.007- 4.975, p= .048) was independent risk factors for predictor of radial artery thrombosis, DM was an independent predictor of radial artery pseudoaneurysm (OR: 4.746, 95% CI: 1.269- 17.747, p= .021), age was an independent predictor of radial artery hematoma (OR: 1.054, 95% CI: 1.005- 1.106, p= .029) and radial artery total complications (OR: 1.047, 95% CI: 1.005- 1.087, p= .015).

Table 1. Baseline Characteristics of the Study Population.

	No Complication n = 339	Total Complication n = 73	p-Value
Age (year)	59.7 ± 0.4	63.04 ± 1.1	0.017
Male/Female, n (%)	245/94 (72.3%- 27.7%)	55/24 (67.1%- 32.9%)	0.459
Body surface area (m²)	28.1 ± 0.2	29.2 ± 0.5	0.019
Current Smoking	149 (85.1 %)	31 (14.9 %)	0.239
EF, %	59.6 ± 0.3	59.6 ± 0.5	0.264
Past medical history			
Diabetes mellitus, n (%)	103 (30.4 %)	29 (39.7 %)	0.158
Hypertension, n (%)	152 (44 %)	29 (39.7 %)	0.423
Dyslipidemia, n (%)	173 (51 %)	45 (61.6 %)	0.129
Known peripheral artery disease	24 (7.1 %)	3 (4.1 %)	0.503
Known coronary artery disease	133 (39.2 %)	35 (20.8 %)	0.127
Previous heart failure	15 (4.4 %)	0 (0 %)	0.137
Laboratory values			
Creatinine (mg/dl)	0.9 ± 0.01	0.9 ± 0.03	0.048
LDL (mg/dL)	121.3 ± 2.0	125.7 ± 4.2	0.323
Total cholesterol (mg/dl)	201.0 ± 2.2	202.1 ± 4.7	0.776
Wbc (x10³/uL)	7.0 ± 0.09	7.5 ± 0.2	0.045
Hemoglobin (mg/dL)	14.4 ± 0.07	13.7 ± 0.1	<0.001
Platelet (x10³/ul)	272.9 ± 4.3	282.2 ± 12.6	0.656
Fasting plasma glucose (mg/dl)	113.7 ± 1.9	110.3 ± 3.4	0.416
Procedural properties			
Peak activated clotting time (seconds)	286.9 ± 2.6	258.7 ± 7.1	0.134
Procedure duration (minutes)	11.2 ± 0.3	14.2 ± 1.1	0.019
Radial artery diameter (mm)	2.6 ± 0.01	2.4 ± 0.03	<0.001
Sheath diameter/radial artery diameter	0.75 ± 0.04	0.81 ± 0.01	<0.001
CHA2DS2-VASc score	2.1 ± 0.08		0.149

Table 2. Multivariate Predictors of Total Complications.

	Univariate		Multivariate	
	Odds Ratio (95% confidence interval)	**p-Value**	**Odds Ratio (95% confidence interval)**	**p-Value**
Age	1.040 (1.011- 1.069)	0.006	1.047 (1.005- 1.087)	0.015
Diabetes mellitus	1.510 (0.895- 2.547)	0.122		
Hypertension	0.811 (0.484- 1.358)	0.425		
Hyperlipidemia	1.542 (0.919- 2.588)	0.101		
Known coronary artery disease	1.427 (0.858- 2.372)	0.171		
Known peripheral artery disease	0.563 (0.165- 1.920)	0.358		
CHA2DS2VASC score	1.179 (1.006- 1.382)	0.042		

Table 3. Multivariate Predictors of Radial Artery Trombosis

	Univariate		Multivariate	
	Odds Ratio (95% confidence interval)	**p-Value**	**Odds Ratio (95% confidence interval)**	**p-Value**
Age	1.024 (0.981- 1.068)	0.278		
Diabetes mellitus	0.886 (0.378- 2.080)	0.781		
Hypertension	0.869 (0.393- 1.923)	0.730		
Hyperlipidemia	0.815 (0.373- 1.780)	0.608		
Known coronary artery disease	2.230 (1.007- 4.975)	0.048	2.230 (1.007- 4.975)	0.048
Known peripheral artery disease	1.880 (0.528- 6.691)	0.330		
CHA2DS2VASC score	1.043 (0.814- 1.336)	0.741		

Table 4. Multivariate Predictors of Radial Artery Pseudoanurysm

	Univariate		Multivariate	
	Odds Ratio (95% confidence interval)	**p-Value**	**Odds Ratio (95% confidence interval)**	**p-Value**
Age	1.037 (0.980- 1.098)	0.202		
Diabetes mellitus	6.273 (1.953- 20.093)	0.002	4.746 (1.269- 17.747)	0.021
Hypertension	1.480 (0.526- 4.160)	0.457		
Hyperlipidemia	2.524 (0.790- 8.061)	0.118		
Known coronary artery disease	1.693 (0.602- 4.761)	0.318		
Known peripheral artery disease	0.00 (0.00-)	0.998		
CHA2DS2VASC score	1.491 (1.095- 2.029)	0.011		

Table 5. Multivariate Predictors of Hematoma

	Univariate		Multivariate	
	Odds Ratio (95% confidence interval)	**p-Value**	**Odds Ratio (95% confidence interval)**	**p-Value**
Age	1.058 (1.019- 1.098)	0.003	1.054 (1.005- 1.106)	0.029
Diabetes mellitus	1.652 (0.850- 3.210)	0.278		
Hypertension	0.937 (0.485- 1.813)	0.848		
Hyperlipidemia	2.235 (1.103- 4.529)	0.026	2.126 (0.997- 4.531)	0.051
Known coronary artery disease	0.859 (0.438- 1.683)	0.657		
Known peripheral artery disease	0.000 (0.000-)	0.998		
CHA2DS2VASC score	1.303 (1.066- 1.592)	0.010		

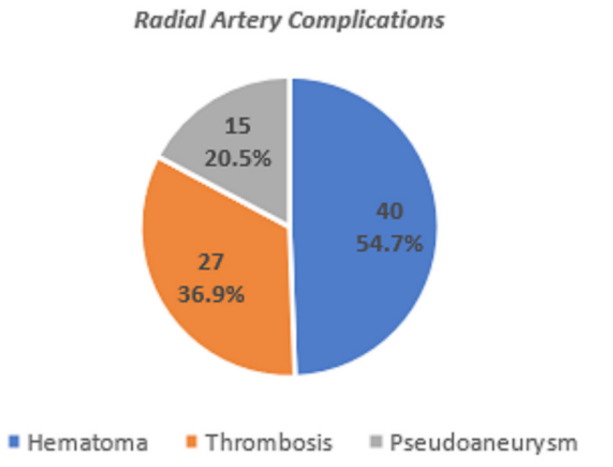


Figure 1. Vasculer and Hemorrhagic Complications

Discussion

In this study, although the CHA2DS2–VASc score was higher in the total complication group; this was not statistically significant. Nevertheless, the components of the CHA2DS2–VASc score has been related with radial artery complications. Age has been associated with radial artery hematoma and total complication. In addition, known coronary disease has been associated with hematoma; DM has been associated with pseudoaneurysm.

TRA for coronary angiography has been progressively widespread owing to its reduced ratio of major adverse complications [13, 14]. Previous studies showed the ratio of vascular complications after radial artery catheterization between 1.5% and 30.5% [15]. All patients included in our study, whether symptomatic or not, were evaluated with ultrasound proceeding of the radial artery one day after TRCA. Therefore, total complication rate was found to be 18.3% in our study.

The CHA2DS2-VASc score is a cheap, easy and generalizable risk scoring system that is based on non-laboratory parameters and can be easily applied by physicians. The CHA2DS2-VASC score was firstly formulated for cerebrovascular ischemic event risk estimation in patients with AF [7, 16]. Recent studies have demonstrated that the CHA2DS2-VASc score could forecast major adverse clinical outcomes in stable coronary artery disease, acute coronary syndrome [17-19]. Ünal et al reported the CHA2DS2-VASc score of >2 had established to be an independent predictor for stent thrombosis [20]. Ipek et al showed in the study the utility of CHA2DS2–VASc score in forecasting no-reflow phenomenon after primary percutaneous coronary intervention in an acute ST-elevation myocardial infarction patients [21]. In this study, the effectiveness of the CHA2DS2-VASc score was assessed in forecast radial artery complications among patients undergoing elective diagnostic TRCA.

The components of CHA2DS2-VASc score are widespread risk factors of microvascular dysfunction, vascular spasm, thromboembolic events and stroke.[7, 22] DM is a component of the CHA2DS2-VASc score and has risen the propensity to thrombosis and endothelial vasoconstriction [23, 24]. DM, female gender and hypertension were proved to be risk factors of microvascular disorder [25, 26]. Prior studies showed, insulin-requiring DM increases the possibility of developing pseudoaneurysm [27]. Pseudoaneurysm is an unusual complication of intervention through TRA with an incidence ranging between less than 0.1% to 0.4% [4, 28]. Our study has shown; DM an independent predictor of radial artery pseudoaneurysm.

Microvascular dysfunction, vascular spasm and thromboembolism are risk factors that increase the ratio of complications after TRCA. CHA2DS2-VASc score covered the various diseases associated with the common risk factors in radial artery complications. While singly CHA2DS2-VASc score was not associated radial artery thrombosis, presence of coronary artery disease, which is a component of the CHA2DS2-VASc score was an independent predictor of radial artery thrombosis. Process of atherosclerosis in coronary arterial disease has been connected to flow and shear stress, local wall stress following damage to the vessel wall [29, 30]. Thrombosis can be occurred by rupture or erosion of atherosclerotic plaque, and subtotal or total occlusion may be developed in the artery.

In the vascular system, age-related decline in function comprise continuous pathological remodelling with stiffening, typically related with alterations in collagen and elastin [31, 32]. Cardiovascular aging is defined by a progressive deterioration of endothelial function [33]. In this instance, when all components of CHA2DS2-VASc score were evaluated, age was an independent predictor of radial artery total complications.

Since the risk of vascular spasm, atherosclerosis and microvascular dysfunction increased at high CHA2DS2-VASc score, radial complications were expected to increase. Although high CHA2DS2-VASc score alone is not related with the risk of radial artery complications after TRCA, CHA2DS2-VASc score components may help to indicate the risk of complications in radial interventions.

Conclusion

The CHA2DS2-VASc score is an easy, cheap, generalizable risk scoring system and predictor for thromboembolic events. The components of CHA2DS2-VASc score may be used risk factors in radial artery complications after transradial catheterization. In additions, prospective more studies may be needed for the relationship between radial artery complications after TRA and the CHA2DS2-VASc score.

Limitations

Firstly, the number of patients included in the study is limited. Some complications may not be diagnosed, as the pain threshold may differ between patients. There were absent control ultrasound or Doppler ultrasound measurements in patients during the follow-up time.

Conflict of interests
The authors report no financial relationships or conflicts of interest regarding the content herein.

Financial Disclosure
All authors declare no financial support.

Ethical approval

This article was approved by the Türkiye Yüksek İhtisas Training and Research Hospital Ethics Committee on 11/20/2012 (no. 295)

References

1. Feldman DN, RV Swaminathan, LA Kaltenbach, et al. Adoption of radial access and comparison of outcomes to femoral access in percutaneous coronary intervention: an updated report from the national cardiovascular data registry (2007-2012). Circulation. 2013;127:2295-306.
2. Cooper CJ, RA El-Shiekh, DJ Cohen, et al. Effect of transradial access on quality of life and cost of cardiac catheterization: A randomized comparison. Am Heart J. 1999;138:430-6.
3. Spaulding C, T Lefevre, F Funck, et al. Left radial approach for coronary angiography: results of a prospective study. Cathet Cardiovasc Diagn.1996; 39:365-70.
4. Tatli E, A Buturak, A Cakar, et al. Unusual vascular complications associated with transradial coronary procedures among 10,324 patients: case based experience and treatment options. J Interv Cardiol. 2015;28:305-12.
5. Hirsh J, R Raschke. Heparin and low-molecular-weight heparin: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest. 2004;126:188-203.
6. Saliba W, N Gronich, O Barnett-Griness, et al. Usefulness of CHADS2 and CHA2DS2-VASc Scores in the prediction of new-onset atrial fibrillation: a population-based study. Am J Med. 2016;129:843-9.
7. Lip GYR. Nieuwlaat, R Pisters, et al. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest. 2010;137:263-72.
8. Melgaard LA, Gorst-Rasmussen. DA Lane et al. Assessment of the CHA2DS2-VASc score in predicting ischemic stroke, thromboembolism, and death in patients with heart failure with and without atrial fibrillation. Jama. 2015;314:1030-8.
9. Biancari F, MA Asim Mahar, OP Kangasniemi. CHADS2 and CHA2DS2-VASc scores for prediction of immediate and late stroke after coronary artery bypass graft surgery. J Stroke Cerebrovasc Dis. 2013;22:1304-11.
10. Mitchell LB, DA Southern, D Galbraith, et al. Prediction of stroke or TIA in patients without atrial fibrillation using CHADS2 and CHA2DS2-VASc scores. Heart. 2014;100:1524-30.
11. Balci KG, O Maden, MM Balci, et al. Relation Between TRCA complication rates and peak ACT levels stratified according to the BMI tertiles. Angiology. 2018;69:400-5.
12. Burzotta FC, Trani MA, Mazzari et al. Vascular complications and access crossover in 10,676 transradial percutaneous coronary procedures. Am Heart J. 2012;163:230-8.
13. Agostoni P, GG Biondi-Zoccai, ML de Benedictis, et al. Radial versus femoral approach for percutaneous coronary diagnostic and interventional procedures; Systematic overview and meta-analysis of randomized trials. J Am Coll Cardiol. 2004;44:349-56.
14. Louvard Y, T Lefevre, A Allain, et al. Coronary angiography through the radial or the femoral approach: The CARAFE study. Catheter Cardiovasc Interv. 2001;52:181-7.
15. Mattea V, C Salomon, N Menck, et al. Low rate of access site complications after transradial coronary catheterization: A prospective ultrasound study. Int J Cardiol Heart Vasc. 2017;14:46-52.
16. Camm AJ, GY Lip, R De Caterina, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation--developed with the special contribution of the European Heart Rhythm Association. Europace. 2012;14:1385-413.
17. Trantalis G, K Aggeli, K Toutouzas, et al. The prognostic value of CHA2DS2-VASc and GRACE risk scores in patients with ACS. Hellenic J Cardiol, 2018.
18. Mirbolouk F, M Gholipour, A Salari, et al. CHA2DS2-VASc score predict no-reflow phenomenon in primary percutaneous coronary intervention in primary percutaneous coronary intervention. J Cardiovasc Thorac Res. 2018;10:46-52.
19. Kurtul A. Usefulness of the CHA2DS2-VASc score in predicting in-stent restenosis among patients undergoing revascularization with bare-metal stents. Clin Appl Thromb Hemost. 2018;24:589-95.
20. Unal S, B Acar, C Yayla, et al. Importance and usage of the CHA2DS2-VASc score in predicting acute stent thrombosis. Coron Artery Dis. 2016; 27:478-82.
21. Ipek G, T Onuk, MB Karatas, et al. CHA2DS2-VASc score is a predictor of no-reflow in patients with st-segment elevation myocardial infarction who underwent primary percutaneous intervention. Angiology. 2016;67:840-5.
22. Chan YH, KH Yiu, KK Lau, et al. The CHADS2 and CHA2DS2-VASc scores predict adverse vascular function, ischemic stroke and cardiovascular death in high-risk patients without atrial fibrillation: role of incorporating PR prolongation. Atherosclerosis. 2014;237:504-13.
23. Iwakura K, H Ito, M Ikushima, et al. Association between hyperglycemia and the no-reflow phenomenon in patients with acute myocardial infarction. J Am Coll Cardiol. 2003;41:1-7.
24. Di Carli MF, J Janisse, G Grunberger, et al. Role of chronic hyperglycemia in the pathogenesis of coronary microvascular dysfunction in diabetes. J Am Coll Cardiol. 2003;41:1387-93.
25. Dean J, SD Cruz, PK Mehta, et al. Coronary microvascular dysfunction: sex-specific risk, diagnosis, and therapy. Nat Rev Cardiol. 2015;12:406-14.
26. Crea F, PG Camici, CN Bairey Merz. Coronary microvascular dysfunction: an update. Eur Heart J. 2014;35:1101-11.
27. Badr S, H Kitabata, R Torguson, et al. Incidence and correlates in the development of iatrogenic femoral pseudoaneurysm after percutaneous coronary interventions. J Interv Cardiol. 2014;27:212-6.
28. Sanmartin M, D Cuevas, J Goicolea, et al. Vascular complications associated with radial artery access for cardiac catheterization. Rev Esp Cardiol. 2004;57:581-4.
29. Ge J. R Erbel, HJ Rupprecht, et al. Comparison of intravascular ultrasound and angiography in the assessment of myocardial bridging. Circulation. 1994;89:1725-32.
30. Ge J, R Erbel, G Gorge, et al. High wall shear stress proximal to myocardial bridging and atherosclerosis: intracoronary ultrasound and pressure measurements. Br Heart J. 1995;73:462-5.
31. Wilk G, G Osmenda, P Matusik, et al. Endothelial function assessment in atherosclerosis: comparison of brachial artery flow-mediated vasodilation and peripheral arterial tonometry. Polish Arc Int Med. 2013;123:443-52.
32. Duca L, S Blaise, B Romier, et al. Matrix ageing and vascular impacts: focus on elastin fragmentation. Cardiovas res. 2016;110:298-308.
33. Lakatta EG. Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises: Part III: cellular and molecular clues to heart and arterial aging. Circulation. 2003;107:490-7.

Available online at www.medicinescience.org

ORIGINAL ARTICLE

Medicine Science International Medical Journal

Medicine Science 2021;10(1):7-12

Therapeutic approaches to children with enuresis: A retrospective study

Ilknur Ucuz[1], Ayla Uzun Cicek[2]

[1]*Inonu University, Faculty of Medicine, Department of Child and Adolescent Psychiatry, Malatya, Turkey*
[2]*Cumhuriyet University, Faculty of Medicine, Department of Child and Adolescent Psychiatry, Sivas, Turkey*

Received 03 November 2020; Accepted 20 November 2020
Available online 20.12.2020 with doi: 10.5455/medscience.2020.11.232

Abstract

Enuresis is a common pediatric condition and there are different treatment options. This study aimed to evaluate treatment options for enuresis in a sample of the child and adolescent psychiatry clinic. The data and treatment results of 98 patients (mean age: 10.38±2.15 years, range=6-16 years) diagnosed with enuresis between 1 May 2015 and 1 October 2020 were retrospectively reviewed. We found that 57 of the patients had previously applied to the hospital for enuresis, and 14 of them have applied to child and adolescent psychiatry, 10 of them to pediatric surgery, 20 of them to other branches of pediatrics, and 13 of them to the urology clinic. In previous hospital applications, behavioral treatment only had been applied to 40.4% of the patients, and pharmacotherapy had been applied in 59.6% of the patients. On the other hand, in the child and ado-lescent psychiatry clinic, 26.5% of the patients received behavioral treatment only, and 73.5% used drugs along with behavioral treatment, and the most frequently preferred drugs were imipramine (oftenest) and desmopressin. Also, the rates of psychiatric comorbidity in those who received medical treatment were significantly higher than those who treated behavioral treatment only. In conclusion, this study revealed that different clinical branches apply different treatment approaches to enuresis. In child and adolescent psychiatry, imipramine was the most commonly used agent in medical treatment, and this has been attributed to the high rate of psychiatric comorbidity

Keywords: Enuresis, child/adolescent, pharmacotherapy, behavioral therapy, treatment

Introduction

Enuresis refers to repeated urinary incontinence into bed or clothes (whether involuntary or intentional) that is not consistent with one's development age (5 years or more) [1]. Enuresis is classified into two groups as primary or secondary depending on the type of onset and course. If it continues since infancy without any dry period, it is called primary enuresis. When it occurs at any age after at least 6 months of toilet training and the dry period, it is defined as secondary enuresis [1, 2]. In addition, enuresis is categorized into three groups according to the time of the day when the problem is seen: nocturnal only, diurnal only, and nocturnal and diurnal [1,2]. The prevalence of enuresis is highly variable, and its overall prevalence ranged from 2.3 to 25%, however, 10-15% of enuretic children show spontaneous recovery every year [3, 4].

Although enuresis tends to improve spontaneously with age, it usually leads to psychosocial and emotional negative effects on the life of both the child and his/her family and impairs the quality of life, as well as its deep impact on a child's self-esteem [5-8].

***Coresponding Author:** Ayla Uzun Cicek, Cumhuriyet University, Faculty of Medicine, Department of Child and Adolescent Psychiatry, Sivas, Turkey
E-mail: dr.f.ayla@hotmail.com

Therefore, the aim of the treatment is to solve the enuresis problem in the early period before the child's self-esteem decreases and serious unfavorable psychosocial effects occur.

It has been stressed that if enuresis has become an important problem for the child and family and the child is older than 6 years old, it should be treated [9].

There are many different treatment options for enuresis, but the treatment modality varies according to the type, frequency, and severity of enuresis, the age and emotional state of the child, and the motivation of the child and his/her family [9]. Behavioral treatments such as behavior modification, enuresis alarm, restricting fluid intake at night and pharmacotherapy including desmopressin, anticholinergic agents, and tricyclic antidepressants constitute two groups of treatment options [9-11]. The first and most important step in the treatment of enuresis is to motivate the child to the treatment. Thus, the recommended first line treatment is psychoeducation and behavioral treatments. When behavioral approaches are inadequate or unsuccessful, pharmacological agents are added to the treatment. The most preferred treatment is the combination of conditioning therapy by alarm and receiving desmopressin, in this context. However, a clinical evaluation showing the pharmacological agents preferred in clinical practice in the treatment of enuresis in our country is limited to a few studies and studies have been conducted in different clinical

branches [11,12]. For this reason, in this study, the treatment options for children with enuresis were examined retrospectively and cross-sectionally, and it was aimed to obtain information about the treatment practices in children and adolescents treated with the diagnosis of enuresis.

Materials and Methods

Between 1 May 2015 and 1 October 2020, 146 children between the ages of 6 and 16 who were diagnosed and treated with monosymptomatic enuresis at the child and adolescent psychiatry outpatient clinic were retrospectively evaluated. Only patients who were treated under the supervision of a child and adolescent psychiatry clinic were included in the study. 48 patients with incomplete data were excluded from the study, thus, a total of 98 patients who attended regular control visits were included in the study. Data on the patients' age, gender, type of enuresis and the kind of onset, family history, previous treatments and their results, comorbidity status, the treatment model and results preferred in our clinic were obtained from hospital files and computer records. Enuresis and comorbid psychiatric disorders were diagnosed with a regular psychiatric interview in line with the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (APA 2013) criteria [1]. The evaluation was performed by a child and adolescent psychiatrist in a psychiatric interview. If children with enuresis have the direct physiological effect of a substance (e.g. a diuretic, antipsychotic, or selective serotonin reuptake inhibitor (SSRI) antidepressant) or a general medical condition (e.g. diabetes, a urological problem including urological anomalies and/or bladder instability, urinary tract infection, spina bifida or seizure disorder), intellectual disability and autism spectrum disorder were excluded from the study. The response rates of the patients were evaluated, based on the preceding. Accordingly, a 90-100% reduction in the number of wetting was considered as a complete response, a 50-90% reduction as a moderate response, and a decrease below 50% as unresponsive [11,13].The study was approved by the local Ethics Committee of the Medical Faculty of the Inonu University and performed in accordance with Good Clinical Practice procedures and the current revision of the Declaration of Helsinki (No:2020-1228).

Statistical Analysis

Statistical data were analyzed using SPSS 23.0 (IBM SPSS, Version 23.0, IBM Corporation, Armonk, NY, USA). Normality was tested using the one-sample Kolmogorov-Smirnov test. The numerical and categorical data were presented as mean ± standard deviation (SD), number (n), median (min-max), and percentage (%) whenever appropriate. During statistical analyses, statistical comparisons were performed with the chi-square test and Mann-Whitney-U-Test. The p-value of <0.05 was accepted as an indication of statistical significance.

Results

Sociodemographic and clinical characteristics of participants

Our sample consisted of 98 children and adolescents diagnosed with enuresis according to DSM-5. The mean age of the participants was 10.38 ± 2.15 years (minimum 6- maximum 16) and 61.2% (n=60) of them were male and 38.8% (n=38) were female. According to the starting type of enuresis, 63.3% (n=62) of the sample were primary and 36% (n=36) were secondary. According to the time of occurrence of enuresis, 70.4% (n=69) of the patients were enuresis nocturna (night-time, only), 7.1% (n=7) enuresis diurna (daytime, only), and 22.4% (n=22) nocturnal and diurnal enuresis. In terms of the frequency of enuresis, 42 patients (42.9%) had enuresis problems every day, 18 patients (18.4%) a few days a week, and 38 patients (38.8%) once a week or less. Regarding the recurrence during the day, 77.6% (n=76) of the patients exhibit enuresis problem once a day, and 22.4% (n=22) more than once a day. Also, 63.3% (n=62) of the patients had a positive family history of enuresis. 58.2% (n=57) of all cases had at least one comorbid psychiatric disorder. The most common accompanying comorbid disorders were attention deficit hyperactivity disorder and conduct disorders (35.7%, n=35), depressive disorder (11.2% (n=11), anxiety disorders (8.2%, n = 8), and trauma and stressor-related disorders, respectively. Descriptive statistics of the participants' clinical characteristics and demographic variables are shown in Table 1.

Features of previous seeking treatment for enuresis

It was learned that 57 of the patients (58.2%) had previously applied to the hospital for enuresis, and 14 of them (24.6%) have applied to child and adolescent psychiatry, 10 (17.5%) of them to pediatric surgery, 20 (35.1 %) of them to other branches of pediatrics, and 13 (22.8%) of them to the urology clinic. Behavioral treatment only had been applied to 40.4% (n=23) of the patients who applied for treatment, and pharmacotherapy had been applied in 59.6% (n=34) of the patients. The agents preferred in pharmacological treatment were anticholinergics (n=28), desmopressin (n=4), and imipramine (n=2), respectively. In our sample, there was no patient using an enuresis alarm. While 52.6% (n=30) of the patients who received treatment showed a partial response to the treatment, 47.4% (n=27) did not respond. Data on features of previous treatment status for enuresis are presented in Table 2.

The treatment preferences of the previously clinics applied

We found that 12 of the patients who received only behavioral treatment were treated in child and adolescent psychiatry, 2 in pediatric surgery, and 9 in other pediatrics branches. There were no patients who received only behavioral therapy in the urology clinic. Imipramine had been prescribed only in child and adolescent psychiatry, desmopressin had been prescribed in pediatric surgery and urology, and anticholinergics had been prescribed by all clinics except child and adolescent psychiatry. Table 3 shows the treatment preferences of the previously clinics applied.

Treatment options in the child and adolescent psychiatry clinic, and treatment response

It was determined that 26.5% (n=26) of the patients who applied to child and adolescent psychiatry received behavioral treatment only, and 73.5% (n=72) used drugs along with behavioral treatment, and it was observed that psychoeducation was also applied to all patients who received pharmacotherapy. The most frequently used psychotropic drug in pharmacotherapy in child and adolescent psychiatry clinic was imipramine (52%, n=51), on the other hand, desmopressin was preferred for 21 patients (21.4%). Regarding treatment response, we determined that 44.9% (n=44) of the patients showed a complete response to the treatment, 40.8% (n=40) showed a partial response to the treatment, and 14 patients (14.3%) did not respond to the treatment. Treatment options in the child and adolescent psychiatry clinic,

and treatment response are summarized in Table 4.

Clinical variables affecting drug use in the treatment of enuresis

Regarding the clinical variables predicting drug use in the treatment of enuresis, it was found that age, gender, types, frequency, and severity of enuresis and response to previous treatment did not affect the medical treatment decision, while the presence of psychiatric comorbidity and previous seeking treatment for enuresis and previous treatment modality played a significant role in the decision to initiate medication. Accordingly, we determined that the rates of psychiatric comorbidity (68.1% vs. 30.8%, respectively, p=0.001) and previous treatment admissions for enuresis (66.7% vs. 34.6%, respectively, p=0.005) in those who received medical treatment were significantly higher than those who treated behavioral treatment only. In addition, the rate of previously receiving combined treatment was significantly higher in the group receiving medical treatment than those who received behavioral treatment only (66.7% vs. 22.2%, respectively, p=0.023). Data on clinical variables affecting drug use in the treatment of enuresis are presented in Table 5.

Table 1. Sociodemographic and clinical characteristics of participants

	Number (%) or mean±SD
Age (mean-years±SD)	10.38±2.15
Gender (n,%)	
Male	60 (61.2)
Female	38 (38.8)
Starting type of the enuresis (n,%)	
Primary	62 (63.3)
Secondary	36 (36.7)
Occurrence type of the enuresis (n,%)	
Enuresis nocturna (night-time, only)	69 (70.4)
Enuresis diurna (daytime, only)	7 (7.1)
Nocturnal and diurnal	22 (22.4)
Frequency of enuresis (n,%)	
Everyday	42 (42.9)
A few days a week	18 (18.4)
Once a week or less	38 (38.8)
Recurrence during the day (n,%)	
Once a day	76 (77.6)
More than once a day	22 (22.4)
Family history of enuresis (n,%)	
Yes	57 (58.2)
No	41 (41.8)
Psychiatric comorbidity (n, %)	
Yes	57 (58.2)
No	41 (41.8)
Types of psychiatric comorbidity (n,%)	
Attention deficit hyperactivity disorder and conduct disorders	35 (35.7)
Depressive disorder	11 (11.2)
Anxiety disorders	8 (8.2)
Trauma and stressor-related disorders	3 (3.1)

Table 2. Features of previous seeking treatment for enuresis

	Number (%)
Previous seeking treatment for enuresis (n,%)	
Yes	57 (58.2)
No	41 (41.8)
Previous clinic visited for treatment (n, %)*	
Child and adolescent psychiatry	14 (24.6)
Pediatric surgery	10 (17.5)
Other branches of pediatrics	20 (35.1)
Urology	13 (22.8)
Previous enuresis treatment (n, %)**	
Behavioral therapy only	23 (40.4)
Behavioral therapy + pharmacotherapy	34 (59.6)
Previous pharmacotherapy (n, %)**	
Imipramine	2 (5.9)
Desmopressin	4 (11.8)
Anticholinergics	28 (82.4)
Response to previous treatment (n, %)*	
Partial response	30 (52.6)
No response	27 (47.4)

*After patients who do not apply for treatment were excluded.
**After patients receiving behavioral therapy only were excluded

Table 3. The treatment preferences of the previously clinics applied

	Behavioral therapy	Imipramine	Desmopressin	Anticholinergics
Child and adolescent psychiatry (n, %)	12 (85.7)	2 (14.3)	0 (0)	0 (0)
Pediatric surgery (n, %)	2 (20)	0 (0)	2 (20)	6 (60)
Other branches of pediatrics (n, %)	9 (45)	0 (0)	0 (0)	11 (55)
Urology (n, %)	0 (0)	0 (0)	2 (15.4)	11 (84.6)

Table 4. Treatment options in the child and adolescent psychiatry clinic, and treatment response

	Number (%)
Treatment options (n,%)	
Behavioral therapy only	26 (26.5)
Behavioral therapy + pharmacotherapy	72 (73.5)
Pharmacotherapeutic drug preferences (n,%)	
Imipramine	51 (52)
Desmopressin	21 (21.4)
Response to previous treatment (n,%)	
Complete response	44 (44.9)
Partial response	40 (40.8)
No response	14 (14.3)

Table 5. Clinical variables affecting drug use in the treatment of enuresis

	Pharmacotherapy		p-value*
	Yes (n=72)	No (n=26)	
Gender (n,%)			
Male	47 (65.3)	13 (50)	0.171
Female	25 (34.7)	13 (50)	
Age (mean-years±SD)	10.57±2.23	9.85±1.87	0.097
Starting type of the enuresis (n,%)			
Primary	45 (62.5)	17 (65.4)	0.794
Secondary	27 (37.5)	9 (34.6)	
Occurrence type of the enuresis (n,%)			
Enuresis nocturna (night-time, only)	52 (72.2)	17 (65.4)	0.796
Enuresis diurna (daytime, only)	5 (6.9)	2 (7.7)	
Nocturnal and diurnal	15 (20.8)	7 (26.9)	
Frequency of enuresis (n,%)			
Everyday	32 (44.4)	10 (38.5)	0.745
A few days a week	12 (16.7)	6 (23.1)	
Once a week or less	28 (38.9)	10 (38.5)	
Recurrence during the day (n,%)			
Once a day	59 (81.9)	17 (65.4)	0.083
More than once a day	13 (18.1)	9 (34.6)	
Family history of enuresis (n,%)			
Yes	25 (34.7)	11 (42.3)	0.492
No	47 (65.3)	15 (57.7)	
Psychiatric comorbidity (n, %)			0.001
Yes	49 (68.1)	8 (30.8)	
No	23 (31.9)	18 (69.2)	
Previous seeking treatment for enuresis (n,%)			
Yes	48 (66.7)	9 (34.6)	0.005
No	24 (33.3)	17 (65.4)	
Previous enuresis treatment (n,%)			
Behavioral therapy only	16 (33.3)	7 (77.8)	0.023**
Behavioral therapy + pharmacotherapy	32 (66.7)	2 (22.2)	
Response to previous treatment (n,%)			
Partial response	16 (33.3)	7 (77.8)	0.476**
No response	32 (66.7)	2 (22.2)	

*The chi-square test and Fisher's exact test (as appropriate) were used to test group differences. Bold font indicates statistical significance: p <0.05.
**After patients who do not apply for treatment were excluded.

Discussion

In this study, we specifically investigated the treatment preferences among children with enuresis in a clinical sample. Enuresis is a disorder that can pose long-term psychosocial risks and problems in the lives of children and adolescents and their families, negatively affects self-esteem, and may require treatment [5-8,14]. There are a variety of treatment alternatives for enuresis including behavioral and motivational therapy, enuretic alarm device, and pharmacotherapy. However, the consensus in the treatment of enuresis is the application of a stepwise treatment model [14,15]. Treatment should be started with psychoeducation (providing education and information to children and their families about the condition) first. Simple behavioral treatments such as fluid restriction, waking the child to urinate, daily motivation, exercises to increase bladder capacity are first-line treatment approaches [14-16]. Complex behavioral treatment methods such as enuretic alarm and dry bed training are recommended for patients over 7 years of age, but it has been reported in current studies that enuretic alarm therapy can also be applied to children aged 5 years [9-11,16]. Pharmacologic treatment is proposed when nonpharmacologic treatment interventions fail and social problems occur in the life of the child and family, and should be initiated in children seven years or above. However, the most commonly used therapeutic approach in enuresis is combined treatment strategies, and in this context, the most preferred treatment is the combination of conditioning therapy by alarm and receiving desmopressin. Treatment is accepted as successful when the patient reaches continence for 14 consecutive nights for 16 weeks. Nonresponse to treatment is described as a decrease below 50% in frequency and severity enuresis, partial response is defined as a 50-90% decrease [13].

Desmopressin, anticholinergic agents, and imipramine constitute medical treatment alternatives. However, none of these drugs are curative, and these drug options are used to temporarily reduce the frequency and severity of enuresis. It has been produced evidence of the superiority of desmopressin in previous studies [17-20]. A prior study has demonstrated that those taking desmopressin were 4.6 times more likely to stay dry for 14 consecutive nights than placebo [17]. However, it has been documented to be more effective in those with normal bladder capacity and those with nocturnal polyuria [18,19]. In addition, high recurrence rates have been reported following discontinuation of the drug [11]. Anticholinergics (e.g., oxybutynin, and hyoscyamine) reduce detrusor muscle tone and increase bladder capacity, and should be preferred only when the first-line treatment approaches (alarm or desmopressin) are unsuccessful in the treatment of enuresis [18,21,22]. A positive effect can be expected from anticholinergics in patients who do not describe lower urinary tract symptoms during the day but whose bladder capacity is restricted due to nocturnal detrusor overactivity. However, it has been emphasized that monotherapy with anticholinergics does not have a major effect on the treatment of enuresis [18]. Tricyclic antidepressants (e.g., imipramine and desipramine), another important treatment option, are thought to act by suppressing detrusor overactivity and increasing bladder capacity through their anticholinergic and myorelaxant effects. Also, it has been suggested that they suppress rapid eye movement (REM) sleep and facilitates awakening via central noradrenergic stimulation. Another possible mechanism of action is that they decrease nocturnal urine production by increasing vasopressin release [23,24]. In general, it has been shown to provide a positive effect in 50% of the patients, but it is common for symptoms to recur after the treatment is discontinued. Studies have revealed their efficacy, especially in

cases when standard treatment approaches (alarm, desmopressin, anticholinergics) have failed. However, due to their negative side effect profile and concerns about potential toxicity, TCAs are currently recommended to be used only in tertiary treatment and reference centers [9,14,23,24].

The present study revealed that more than half of the patients applied to a number of clinics including child and adolescent psychiatry for enuresis treatment before applying to our clinic. Urology, pediatric surgery, child and adolescent psychiatry, and other branches of pediatrics were the most frequently applied clinics, and behavioral therapy had been applied to 40% of the patients, and pharmacotherapy had been applied to 60%. There was no patient using an alarm. The reason why pharmacological treatment is preferred rather than behavioral treatment may be the desire of both physicians and family to respond to the treatment as soon as possible. Before applying to our clinic, the agents preferred in pharmacological treatment were anticholinergics, desmopressin, and imipramine, respectively. The most preferred drug group was anticholinergics. These results differ from those recommended in treatment guidelines. Because enuresis alarms and desmopressin are emphasized in the initial active therapies in the treatment guidelines [14]. Our conflicting results may have resulted from patients' admission to different clinics and different treatment modalities at each clinic. For example, while behavioral therapy and imipramin were not used in the urology clinic, the most used methods in the child psychiatry clinic were behavioral therapy and imipramin. Again, desmopressin was preferred only by pediatric surgery and urology. Also, we detected that almost half of the patients did not respond to the treatment, and the remaining half showed a partial response, before applying to our clinic. This result may be due to the less preference of behavioral and motivational therapy. Because although behavioral and motivational therapy requires longer treatment than pharmacological treatment, it is known that relapse rates are lower and more successful [11].

Regarding the treatment options in our clinic, it was found that 26.5% of the patients received behavioral therapy only, and 73.5% of the patients received combined therapy. The most preferred agent in pharmacotherapy was imipramine, and it has been prescribed for more than half of the patients. The other preferred pharmacological agent was desmopressin and was prescribed for one-fifth of patients, but anticholinergics were not prescribed for any patients. The pharmacotherapy profiles of children with enuresis in our study contradict the data reported in the literature. Although there are various treatment alternatives in the treatment of enuresis, it is reported that desmopressin treatment is the most preferred treatment method in daily practice [11,14]. The reason why imipramine is preferred over desmopressin in our clinic may be the high rate of psychiatric comorbidity in patients, with a frequency of 58%. In our population, the most common comorbid psychiatric disorders were attention deficit hyperactivity disorder and conduct disorders, and depressive disorder. On the other hand, imipramine is not only a treatment option for enuresis, but also for treatment-resistant enuresis in children with ADHD [25,26]. Our results suggest that the presence and type of comorbid psychiatric comorbidity play an effective role in the treatment of choice for enuresis.

Several limitations of the present study should be addressed. These were that our sample size was relatively small, the sample lacked a control group, and the study was in retrospective design, which prevents us from generalizing our results. Therefore, future prospectively planned multicenter studies with larger samples to evaluate treatment options in enuresis will be substantially valuable. Despite its limitations, our study presents considerable important data on child and adolescent psychiatry practices in the treatment of enuresis in our country. As a result, this study extends the outcomes of the previous studies in children with enuresis.

Conclusion

In conclusion, this study revealed that different clinical branches apply different treatment approaches to enuresis. In child and adolescent psychiatry, behavioral therapy only was performed on a quarter of the patients, and behavioral therapy and pharmacotherapy were applied together to the rest of the patients. Imipramine was the most commonly used agent in medical treatment, and this was attributed to the high rate of psychiatric comorbidity.

Conflict of interests

The authors declare that they have no competing interests.

Financial Disclosure

All authors declare no financial support.

Ethical approval

Local Ethics Committee of Inonu University approved the study (protocol no: 2020-1228)

Data Accessibility: *The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.*

References

1. American, Psychiatric, Association. Diagnostic and statistical manual of mental disorders. DSM-5, American Psychiatric Association Publishing, 5th edition, 2013.
2. Austin PF, Bauer SB, Bower W, et al. The standardization of terminology of lower urinary tract function in children and adolescents: Update report from the standardization committee of the International Children's Continence Society. Neu Uro. 2016;35:471-81.
3. Bayne AP, Skoog SJ. Nocturnal enuresis: an approach to assessment and treatment. Pediatr Rev. 2014;35:327-35.
4. Arda E, Cakiroglu B, Thomas DT. Primary Nocturnal Enuresis: A Review. Nephrourol Mon. 2016;8:e35809.
5. Ring JI, Neveus T, Markstrom A, et al. Nocturnal enuresis impaired children's quality of life and friendships. Acta Paediatr. 2017;106:806-11.
6. Sarici H, Telli O, Ozgur BC, et al. Prevalence of nocturnal enuresis and its influence on quality of life in school-aged children. J Pediatr Urol. 2016;12:159.1–6.
7. Van Herzeele C, De Bruyne P, De Bruyne E, et al. Challenging factors for enuresis treatment: psychological problems and non-adherence. J Pediatr Urol. 2015;11:308-13.
8. Uzun Çiçek A, Bora A, Altuntaş E. Adenoid hypertrophy and nocturnal enuresis are associated with sleep disturbances. ENT Updates. 2020;10:311-20.
9. Caldwell PHY, Deshpande AV, Gontard AV. Management of nocturnal enuresis. BMJ. 2013;347:6259.
10. Neveus T, Eggert P, Evans J, et al. Evaluation of and treatment for monosymptomatic enuresis: a standardization document from the International Children's Continence Society. J Urol. 2010;183:441-47.

11. Oğraş MS, Ağlamiş E, Yücel MÖ, et al. Treatment and follow up results of patients with monosymptomatic enuresis nocturna. Dicle Med J. 2013;40:410-13.

12. Korgalı E. Enuresis Nocturna: Diagnosis and Evaluation. Turk Urol Sem. 2011;2:41-4.

13. Nevéus T, von Gontard A, Hoebeke P, et al. The standardization of terminology of lower urinary tract function in children and adolescents: report from the Standardisation Committee of the International Children's Continence Society. J Urol. 2006;176:314-24.

14. Nevéus T, Fonseca E, Franco I, et al. Management and treatment of nocturnal enuresis an updated standardization document from the International Children's Continence Society. J Pediatr Urol. 2020;16:10-9.

15. Caldwell PH, Nankivell G, Sureshkumar P. Simple behavioural interventions for nocturnal enuresis in children. Cochrane Database Syst Rev. 2013;7:CD003637.

16. Vande Walle J, Rittig S, Bauer S, et al. Practical consensus guidelines for the management of enuresis [published correction appears in Eur J Pediatr. 2012 Jun;171(6):1005] [published correction appears in Eur J Pediatr. 2013 Feb;172:285]. Eur J Pediatr. 2012;171:971-83.

17. Robson WLM, Leung AK. Urotherapy recommendations for betwetting. J Nati Med Assoc. 2002;94:577-80.

18. Hjalmas K, Arnold T, Bower W, et al. Nocturnal enuresis: an international evidence based management strategy. J Urol. 2004;171:2545–61.

19. Ramakrishnan K. Evaluation and treatment of enuresis. Am Fam Physician. 2008;78:489-96.

20. Glazener CM, Evans JH. Desmopressin for nocturnal enuresis in children. Cochrane Database Syst Rev. 2002;CD002112.

21. Ghasemi K, Esteghamati M, Mohammadzadeh M, et al. Desmopressin versus Oxybutynin for Nocturnal Enuresis in Children in Bandar Abbas: A Randomized Clinical Trial. Electron Phy. 2016;8:2187-93.

22. Radvanska E, Kovács L, Rittig S. The role of bladder capacity in antidiuretic and anticholinergic treatment for nocturnal enuresis. J Urol. 2006;176:764-9.

23. Cendron M. Primary nocturnal enuresis: current concepts. Am Fam Phy.1999;59:1205–14,1219–20.

24. Glazener CM, Evans JH, Peto RE. Tricyclic and related drugs for nocturnal enuresis inchildren. Cochrane Database Syst Rev. 2003:CD002117.

25. Von Gontard A, Equit M. Comorbidity of ADHD and incontinence in children. Eur Child Adolesc Psychiatry. 2015;24:127–40.

26. Fritz G, Rockney R. Practice parameter for the assessment and treatment of children andadolescents with enuresis. J Am Acad Child Adolesc Psychiatry. 2004;43:1540-50.

Available online at www.medicinescience.org

ORIGINAL ARTICLE

Medicine Science International Medical Journal

Medicine Science 2021;10(1):7-12

Therapeutic approaches to children with enuresis: A retrospective study

Ilknur Ucuz[1], Ayla Uzun Cicek[2]

[1]Inonu University, Faculty of Medicine, Department of Child and Adolescent Psychiatry, Malatya, Turkey
[2]Cumhuriyet University, Faculty of Medicine, Department of Child and Adolescent Psychiatry, Sivas, Turkey

Received 03 November 2020; Accepted 20 November 2020
Available online 20.12.2020 with doi: 10.5455/medscience.2020.11.232

Abstract

Enuresis is a common pediatric condition and there are different treatment options. This study aimed to evaluate treatment options for enuresis in a sample of the child and adolescent psychiatry clinic. The data and treatment results of 98 patients (mean age: 10.38±2.15 years, range=6-16 years) diagnosed with enuresis between 1 May 2015 and 1 October 2020 were retrospectively reviewed. We found that 57 of the patients had previously applied to the hospital for enuresis, and 14 of them have applied to child and adolescent psychiatry, 10 of them to pediatric surgery, 20 of them to other branches of pediatrics, and 13 of them to the urology clinic. In previous hospital applications, behavioral treatment only had been applied to 40.4% of the patients, and pharmacotherapy had been applied in 59.6% of the patients. On the other hand, in the child and ado-lescent psychiatry clinic, 26.5% of the patients received behavioral treatment only, and 73.5% used drugs along with behavioral treatment, and the most frequently preferred drugs were imipramine (oftenest) and desmopressin. Also, the rates of psychiatric comorbidity in those who received medical treatment were significantly higher than those who treated behavioral treatment only. In conclusion, this study revealed that different clinical branches apply different treatment approaches to enuresis. In child and adolescent psychiatry, imipramine was the most commonly used agent in medical treatment, and this has been attributed to the high rate of psychiatric comorbidity

Keywords: Enuresis, child/adolescent, pharmacotherapy, behavioral therapy, treatment

Introduction

Enuresis refers to repeated urinary incontinence into bed or clothes (whether involuntary or intentional) that is not consistent with one's development age (5 years or more) [1]. Enuresis is classified into two groups as primary or secondary depending on the type of onset and course. If it continues since infancy without any dry period, it is called primary enuresis. When it occurs at any age after at least 6 months of toilet training and the dry period, it is defined as secondary enuresis [1, 2]. In addition, enuresis is categorized into three groups according to the time of the day when the problem is seen: nocturnal only, diurnal only, and nocturnal and diurnal [1,2]. The prevalence of enuresis is highly variable, and its overall prevalence ranged from 2.3 to 25%, however, 10-15% of enuretic children show spontaneous recovery every year [3, 4].

Although enuresis tends to improve spontaneously with age, it usually leads to psychosocial and emotional negative effects on the life of both the child and his/her family and impairs the quality of life, as well as its deep impact on a child's self-esteem [5-8].

***Coresponding Author:** Ayla Uzun Cicek, Cumhuriyet University, Faculty of Medicine, Department of Child and Adolescent Psychiatry, Sivas, Turkey
E-mail: dr.f.ayla@hotmail.com

Therefore, the aim of the treatment is to solve the enuresis problem in the early period before the child's self-esteem decreases and serious unfavorable psychosocial effects occur.

It has been stressed that if enuresis has become an important problem for the child and family and the child is older than 6 years old, it should be treated [9].

There are many different treatment options for enuresis, but the treatment modality varies according to the type, frequency, and severity of enuresis, the age and emotional state of the child, and the motivation of the child and his/her family [9]. Behavioral treatments such as behavior modification, enuresis alarm, restricting fluid intake at night and pharmacotherapy including desmopressin, anticholinergic agents, and tricyclic antidepressants constitute two groups of treatment options [9-11]. The first and most important step in the treatment of enuresis is to motivate the child to the treatment. Thus, the recommended first line treatment is psychoeducation and behavioral treatments. When behavioral approaches are inadequate or unsuccessful, pharmacological agents are added to the treatment. The most preferred treatment is the combination of conditioning therapy by alarm and receiving desmopressin, in this context. However, a clinical evaluation showing the pharmacological agents preferred in clinical practice in the treatment of enuresis in our country is limited to a few studies and studies have been conducted in different clinical

branches [11,12]. For this reason, in this study, the treatment options for children with enuresis were examined retrospectively and cross-sectionally, and it was aimed to obtain information about the treatment practices in children and adolescents treated with the diagnosis of enuresis.

Materials and Methods

Between 1 May 2015 and 1 October 2020, 146 children between the ages of 6 and 16 who were diagnosed and treated with monosymptomatic enuresis at the child and adolescent psychiatry outpatient clinic were retrospectively evaluated. Only patients who were treated under the supervision of a child and adolescent psychiatry clinic were included in the study. 48 patients with incomplete data were excluded from the study, thus, a total of 98 patients who attended regular control visits were included in the study. Data on the patients' age, gender, type of enuresis and the kind of onset, family history, previous treatments and their results, comorbidity status, the treatment model and results preferred in our clinic were obtained from hospital files and computer records. Enuresis and comorbid psychiatric disorders were diagnosed with a regular psychiatric interview in line with the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (APA 2013) criteria [1]. The evaluation was performed by a child and adolescent psychiatrist in a psychiatric interview. If children with enuresis have the direct physiological effect of a substance (e.g. a diuretic, antipsychotic, or selective serotonin reuptake inhibitor (SSRI) antidepressant) or a general medical condition (e.g. diabetes, a urological problem including urological anomalies and/or bladder instability, urinary tract infection, spina bifida or seizure disorder), intellectual disability and autism spectrum disorder were excluded from the study. The response rates of the patients were evaluated, based on the preceding. Accordingly, a 90-100% reduction in the number of wetting was considered as a complete response, a 50-90% reduction as a moderate response, and a decrease below 50% as unresponsive [11,13].The study was approved by the local Ethics Committee of the Medical Faculty of the Inonu University and performed in accordance with Good Clinical Practice procedures and the current revision of the Declaration of Helsinki (No:2020-1228).

Statistical Analysis

Statistical data were analyzed using SPSS 23.0 (IBM SPSS, Version 23.0, IBM Corporation, Armonk, NY, USA). Normality was tested using the one-sample Kolmogorov-Smirnov test. The numerical and categorical data were presented as mean ± standard deviation (SD), number (n), median (min-max), and percentage (%) whenever appropriate. During statistical analyses, statistical comparisons were performed with the chi-square test and Mann-Whitney-U-Test. The p-value of <0.05 was accepted as an indication of statistical significance.

Results

Sociodemographic and clinical characteristics of participants

Our sample consisted of 98 children and adolescents diagnosed with enuresis according to DSM-5. The mean age of the participants was 10.38 ± 2.15 years (minimum 6- maximum 16) and 61.2% (n=60) of them were male and 38.8% (n=38) were female. According to the starting type of enuresis, 63.3% (n=62) of the sample were primary and 36% (n=36) were secondary. According to the time of occurrence of enuresis, 70.4% (n=69) of the patients were enuresis nocturna (night-time, only), 7.1% (n=7) enuresis diurna (daytime, only), and 22.4% (n=22) nocturnal and diurnal enuresis. In terms of the frequency of enuresis, 42 patients (42.9%) had enuresis problems every day, 18 patients (18.4%) a few days a week, and 38 patients (38.8%) once a week or less. Regarding the recurrence during the day, 77.6% (n=76) of the patients exhibit enuresis problem once a day, and 22.4% (n=22) more than once a day. Also, 63.3% (n=62) of the patients had a positive family history of enuresis. 58.2% (n=57) of all cases had at least one comorbid psychiatric disorder. The most common accompanying comorbid disorders were attention deficit hyperactivity disorder and conduct disorders (35.7%, n=35), depressive disorder (11.2% (n=11), anxiety disorders (8.2%, n = 8), and trauma and stressor-related disorders, respectively. Descriptive statistics of the participants' clinical characteristics and demographic variables are shown in Table 1.

Features of previous seeking treatment for enuresis

It was learned that 57 of the patients (58.2%) had previously applied to the hospital for enuresis, and 14 of them (24.6%) have applied to child and adolescent psychiatry, 10 (17.5%) of them to pediatric surgery, 20 (35.1 %) of them to other branches of pediatrics, and 13 (22.8%) of them to the urology clinic. Behavioral treatment only had been applied to 40.4% (n=23) of the patients who applied for treatment, and pharmacotherapy had been applied in 59.6% (n=34) of the patients. The agents preferred in pharmacological treatment were anticholinergics (n=28), desmopressin (n=4), and imipramine (n=2), respectively. In our sample, there was no patient using an enuresis alarm. While 52.6% (n=30) of the patients who received treatment showed a partial response to the treatment, 47.4% (n=27) did not respond. Data on features of previous treatment status for enuresis are presented in Table 2.

The treatment preferences of the previously clinics applied

We found that 12 of the patients who received only behavioral treatment were treated in child and adolescent psychiatry, 2 in pediatric surgery, and 9 in other pediatrics branches. There were no patients who received only behavioral therapy in the urology clinic. Imipramine had been prescribed only in child and adolescent psychiatry, desmopressin had been prescribed in pediatric surgery and urology, and anticholinergics had been prescribed by all clinics except child and adolescent psychiatry. Table 3 shows the treatment preferences of the previously clinics applied.

Treatment options in the child and adolescent psychiatry clinic, and treatment response

It was determined that 26.5% (n=26) of the patients who applied to child and adolescent psychiatry received behavioral treatment only, and 73.5% (n=72) used drugs along with behavioral treatment, and it was observed that psychoeducation was also applied to all patients who received pharmacotherapy. The most frequently used psychotropic drug in pharmacotherapy in child and adolescent psychiatry clinic was imipramine (52%, n=51), on the other hand, desmopressin was preferred for 21 patients (21.4%). Regarding treatment response, we determined that 44.9% (n=44) of the patients showed a complete response to the treatment, 40.8% (n=40) showed a partial response to the treatment, and 14 patients (14.3%) did not respond to the treatment. Treatment options in the child and adolescent psychiatry clinic,

and treatment response are summarized in Table 4.

Clinical variables affecting drug use in the treatment of enuresis

Regarding the clinical variables predicting drug use in the treatment of enuresis, it was found that age, gender, types, frequency, and severity of enuresis and response to previous treatment did not affect the medical treatment decision, while the presence of psychiatric comorbidity and previous seeking treatment for enuresis and previous treatment modality played a significant role in the decision to initiate medication. Accordingly, we determined that the rates of psychiatric comorbidity (68.1% vs. 30.8%, respectively, p=0.001) and previous treatment admissions for enuresis (66.7% vs. 34.6%, respectively, p=0.005) in those who received medical treatment were significantly higher than those who treated behavioral treatment only. In addition, the rate of previously receiving combined treatment was significantly higher in the group receiving medical treatment than those who received behavioral treatment only (66.7% vs. 22.2%, respectively, p=0.023). Data on clinical variables affecting drug use in the treatment of enuresis are presented in Table 5.

Table 1. Sociodemographic and clinical characteristics of participants

	Number (%) or mean±SD
Age (mean-years±SD)	10.38±2.15
Gender (n,%)	
Male	60 (61.2)
Female	38 (38.8)
Starting type of the enuresis (n,%)	
Primary	62 (63.3)
Secondary	36 (36.7)
Occurrence type of the enuresis (n,%)	
Enuresis nocturna (night-time, only)	69 (70.4)
Enuresis diurna (daytime, only)	7 (7.1)
Nocturnal and diurnal	22 (22.4)
Frequency of enuresis (n,%)	
Everyday	42 (42.9)
A few days a week	18 (18.4)
Once a week or less	38 (38.8)
Recurrence during the day (n,%)	
Once a day	76 (77.6)
More than once a day	22 (22.4)
Family history of enuresis (n,%)	
Yes	57 (58.2)
No	41 (41.8)
Psychiatric comorbidity (n, %)	
Yes	57 (58.2)
No	41 (41.8)
Types of psychiatric comorbidity (n,%)	
Attention deficit hyperactivity disorder and conduct disorders	35 (35.7)
Depressive disorder	11 (11.2)
Anxiety disorders	8 (8.2)
Trauma and stressor-related disorders	3 (3.1)

Table 2. Features of previous seeking treatment for enuresis

	Number (%)
Previous seeking treatment for enuresis (n,%)	
Yes	57 (58.2)
No	41 (41.8)
Previous clinic visited for treatment (n, %)*	
Child and adolescent psychiatry	14 (24.6)
Pediatric surgery	10 (17.5)
Other branches of pediatrics	20 (35.1)
Urology	13 (22.8)
Previous enuresis treatment (n, %)**	
Behavioral therapy only	23 (40.4)
Behavioral therapy + pharmacotherapy	34 (59.6)
Previous pharmacotherapy (n, %)**	
Imipramine	2 (5.9)
Desmopressin	4 (11.8)
Anticholinergics	28 (82.4)
Response to previous treatment (n, %)*	
Partial response	30 (52.6)
No response	27 (47.4)

*After patients who do not apply for treatment were excluded.
**After patients receiving behavioral therapy only were excluded

Table 3. The treatment preferences of the previously clinics applied

	Behavioral therapy	Imipramine	Desmopressin	Anticholinergics
Child and adolescent psychiatry (n, %)	12 (85.7)	2 (14.3)	0 (0)	0 (0)
Pediatric surgery (n, %)	2 (20)	0 (0)	2 (20)	6 (60)
Other branches of pediatrics (n, %)	9 (45)	0 (0)	0 (0)	11 (55)
Urology (n, %)	0 (0)	0 (0)	2 (15.4)	11 (84.6)

Table 4. Treatment options in the child and adolescent psychiatry clinic, and treatment response

	Number (%)
Treatment options (n,%)	
Behavioral therapy only	26 (26.5)
Behavioral therapy + pharmacotherapy	72 (73.5)
Pharmacotherapeutic drug preferences (n,%)	
Imipramine	51 (52)
Desmopressin	21 (21.4)
Response to previous treatment (n,%)	
Complete response	44 (44.9)
Partial response	40 (40.8)
No response	14 (14.3)

Table 5. Clinical variables affecting drug use in the treatment of enuresis

	Pharmacotherapy		p-value*
	Yes (n=72)	No (n=26)	
Gender (n,%)			
Male	47 (65.3)	13 (50)	0.171
Female	25 (34.7)	13 (50)	
Age (mean-years±SD)	10.57±2.23	9.85±1.87	0.097
Starting type of the enuresis (n,%)			
Primary	45 (62.5)	17 (65.4)	0.794
Secondary	27 (37.5)	9 (34.6)	
Occurrence type of the enuresis (n,%)			
Enuresis nocturna (night-time, only)	52 (72.2)	17 (65.4)	0.796
Enuresis diurna (daytime, only)	5 (6.9)	2 (7.7)	
Nocturnal and diurnal	15 (20.8)	7 (26.9)	
Frequency of enuresis (n,%)			
Everyday	32 (44.4)	10 (38.5)	0.745
A few days a week	12 (16.7)	6 (23.1)	
Once a week or less	28 (38.9)	10 (38.5)	
Recurrence during the day (n,%)			
Once a day	59 (81.9)	17 (65.4)	0.083
More than once a day	13 (18.1)	9 (34.6)	
Family history of enuresis (n,%)			
Yes	25 (34.7)	11 (42.3)	0.492
No	47 (65.3)	15 (57.7)	
Psychiatric comorbidity (n, %)			0.001
Yes	49 (68.1)	8 (30.8)	
No	23 (31.9)	18 (69.2)	
Previous seeking treatment for enuresis (n,%)			
Yes	48 (66.7)	9 (34.6)	0.005
No	24 (33.3)	17 (65.4)	
Previous enuresis treatment (n,%)			
Behavioral therapy only	16 (33.3)	7 (77.8)	0.023**
Behavioral therapy + pharmacotherapy	32 (66.7)	2 (22.2)	
Response to previous treatment (n,%)			
Partial response	16 (33.3)	7 (77.8)	0.476**
No response	32 (66.7)	2 (22.2)	

*The chi-square test and Fisher's exact test (as appropriate) were used to test group differences. Bold font indicates statistical significance: p <0.05.
**After patients who do not apply for treatment were excluded.

Discussion

In this study, we specifically investigated the treatment preferences among children with enuresis in a clinical sample. Enuresis is a disorder that can pose long-term psychosocial risks and problems in the lives of children and adolescents and their families, negatively affects self-esteem, and may require treatment [5-8,14]. There are a variety of treatment alternatives for enuresis including behavioral and motivational therapy, enuretic alarm device, and pharmacotherapy. However, the consensus in the treatment of enuresis is the application of a stepwise treatment model [14,15]. Treatment should be started with psychoeducation (providing education and information to children and their families about the condition) first. Simple behavioral treatments such as fluid restriction, waking the child to urinate, daily motivation, exercises to increase bladder capacity are first-line treatment approaches [14-16]. Complex behavioral treatment methods such as enuretic alarm and dry bed training are recommended for patients over 7 years of age, but it has been reported in current studies that enuretic alarm therapy can also be applied to children aged 5 years [9-11,16]. Pharmacologic treatment is proposed when nonpharmacologic treatment interventions fail and social problems occur in the life of the child and family, and should be initiated in children seven years or above. However, the most commonly used therapeutic approach in enuresis is combined treatment strategies, and in this context, the most preferred treatment is the combination of conditioning therapy by alarm and receiving desmopressin. Treatment is accepted as successful when the patient reaches continence for 14 consecutive nights for 16 weeks. Nonresponse to treatment is described as a decrease below 50% in frequency and severity enuresis, partial response is defined as a 50-90% decrease [13].

Desmopressin, anticholinergic agents, and imipramine constitute medical treatment alternatives. However, none of these drugs are curative, and these drug options are used to temporarily reduce the frequency and severity of enuresis. It has been produced evidence of the superiority of desmopressin in previous studies [17-20]. A prior study has demonstrated that those taking desmopressin were 4.6 times more likely to stay dry for 14 consecutive nights than placebo [17]. However, it has been documented to be more effective in those with normal bladder capacity and those with nocturnal polyuria [18,19]. In addition, high recurrence rates have been reported following discontinuation of the drug [11]. Anticholinergics (e.g., oxybutynin, and hyoscyamine) reduce detrusor muscle tone and increase bladder capacity, and should be preferred only when the first-line treatment approaches (alarm or desmopressin) are unsuccessful in the treatment of enuresis [18,21,22]. A positive effect can be expected from anticholinergics in patients who do not describe lower urinary tract symptoms during the day but whose bladder capacity is restricted due to nocturnal detrusor overactivity. However, it has been emphasized that monotherapy with anticholinergics does not have a major effect on the treatment of enuresis [18]. Tricyclic antidepressants (e.g., imipramine and desipramine), another important treatment option, are thought to act by suppressing detrusor overactivity and increasing bladder capacity through their anticholinergic and myorelaxant effects. Also, it has been suggested that they suppress rapid eye movement (REM) sleep and facilitates awakening via central noradrenergic stimulation. Another possible mechanism of action is that they decrease nocturnal urine production by increasing vasopressin release [23,24]. In general, it has been shown to provide a positive effect in 50% of the patients, but it is common for symptoms to recur after the treatment is discontinued. Studies have revealed their efficacy, especially in

cases when standard treatment approaches (alarm, desmopressin, anticholinergics) have failed. However, due to their negative side effect profile and concerns about potential toxicity, TCAs are currently recommended to be used only in tertiary treatment and reference centers [9,14,23,24].

The present study revealed that more than half of the patients applied to a number of clinics including child and adolescent psychiatry for enuresis treatment before applying to our clinic. Urology, pediatric surgery, child and adolescent psychiatry, and other branches of pediatrics were the most frequently applied clinics, and behavioral therapy had been applied to 40% of the patients, and pharmacotherapy had been applied to 60%. There was no patient using an alarm. The reason why pharmacological treatment is preferred rather than behavioral treatment may be the desire of both physicians and family to respond to the treatment as soon as possible. Before applying to our clinic, the agents preferred in pharmacological treatment were anticholinergics, desmopressin, and imipramine, respectively. The most preferred drug group was anticholinergics. These results differ from those recommended in treatment guidelines. Because enuresis alarms and desmopressin are emphasized in the initial active therapies in the treatment guidelines [14]. Our conflicting results may have resulted from patients' admission to different clinics and different treatment modalities at each clinic. For example, while behavioral therapy and imipramin were not used in the urology clinic, the most used methods in the child psychiatry clinic were behavioral therapy and imipramin. Again, desmopressin was preferred only by pediatric surgery and urology. Also, we detected that almost half of the patients did not respond to the treatment, and the remaining half showed a partial response, before applying to our clinic. This result may be due to the less preference of behavioral and motivational therapy. Because although behavioral and motivational therapy requires longer treatment than pharmacological treatment, it is known that relapse rates are lower and more successful [11].

Regarding the treatment options in our clinic, it was found that 26.5% of the patients received behavioral therapy only, and 73.5% of the patients received combined therapy. The most preferred agent in pharmacotherapy was imipramine, and it has been prescribed for more than half of the patients. The other preferred pharmacological agent was desmopressin and was prescribed for one-fifth of patients, but anticholinergics were not prescribed for any patients. The pharmacotherapy profiles of children with enuresis in our study contradict the data reported in the literature. Although there are various treatment alternatives in the treatment of enuresis, it is reported that desmopressin treatment is the most preferred treatment method in daily practice [11,14]. The reason why imipramine is preferred over desmopressin in our clinic may be the high rate of psychiatric comorbidity in patients, with a frequency of 58%. In our population, the most common comorbid psychiatric disorders were attention deficit hyperactivity disorder and conduct disorders, and depressive disorder. On the other hand, imipramine is not only a treatment option for enuresis, but also for treatment-resistant enuresis in children with ADHD [25,26]. Our results suggest that the presence and type of comorbid psychiatric comorbidity play an effective role in the treatment of choice for enuresis.

Several limitations of the present study should be addressed. These were that our sample size was relatively small, the sample lacked a control group, and the study was in retrospective design, which prevents us from generalizing our results. Therefore, future prospectively planned multicenter studies with larger samples to evaluate treatment options in enuresis will be substantially valuable. Despite its limitations, our study presents considerable important data on child and adolescent psychiatry practices in the treatment of enuresis in our country. As a result, this study extends the outcomes of the previous studies in children with enuresis.

Conclusion

In conclusion, this study revealed that different clinical branches apply different treatment approaches to enuresis. In child and adolescent psychiatry, behavioral therapy only was performed on a quarter of the patients, and behavioral therapy and pharmacotherapy were applied together to the rest of the patients. Imipramine was the most commonly used agent in medical treatment, and this was attributed to the high rate of psychiatric comorbidity.

Conflict of interests

The authors declare that they have no competing interests.

Financial Disclosure

All authors declare no financial support.

Ethical approval

Local Ethics Committee of Inonu University approved the study (protocol no: 2020-1228)

Data Accessibility: *The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.*

References

1. American, Psychiatric, Association. Diagnostic and statistical manual of mental disorders. DSM-5, American Psychiatric Association Publishing, 5th edition, 2013.
2. Austin PF, Bauer SB, Bower W, et al. The standardization of terminology of lower urinary tract function in children and adolescents: Update report from the standardization committee of the International Children's Continence Society. Neu Uro. 2016;35:471-81.
3. Bayne AP, Skoog SJ. Nocturnal enuresis: an approach to assessment and treatment. Pediatr Rev. 2014;35:327-35.
4. Arda E, Cakiroglu B, Thomas DT. Primary Nocturnal Enuresis: A Review. Nephrourol Mon. 2016;8:e35809.
5. Ring JI, Neveus T, Markstrom A, et al. Nocturnal enuresis impaired children's quality of life and friendships. Acta Paediatr. 2017;106:806-11.
6. Sarici H, Telli O, Ozgur BC, et al. Prevalence of nocturnal enuresis and its influence on quality of life in school-aged children. J Pediatr Urol. 2016;12:159.1–6.
7. Van Herzeele C, De Bruyne P, De Bruyne E, et al. Challenging factors for enuresis treatment: psychological problems and non-adherence. J Pediatr Urol. 2015;11:308-13.
8. Uzun Çiçek A, Bora A, Altuntaş E. Adenoid hypertrophy and nocturnal enuresis are associated with sleep disturbances. ENT Updates. 2020;10:311-20.
9. Caldwell PHY, Deshpande AV, Gontard AV. Management of nocturnal enuresis. BMJ. 2013;347:6259.
10. Neveus T, Eggert P, Evans J, et al. Evaluation of and treatment for monosymptomatic enuresis: a standardization document from the International Children's Continence Society. J Urol. 2010;183:441-47.

11. Oğraş MS, Ağlamiş E, Yücel MÖ, et al. Treatment and follow up results of patients with monosymptomatic enuresis nocturna. Dicle Med J. 2013;40:410-13.

12. Korgalı E. Enuresis Nocturna: Diagnosis and Evaluation. Turk Urol Sem. 2011;2:41-4.

13. Nevéus T, von Gontard A, Hoebeke P, et al. The standardization of terminology of lower urinary tract function in children and adolescents: report from the Standardisation Committee of the International Children's Continence Society. J Urol. 2006;176:314-24.

14. Nevéus T, Fonseca E, Franco I, et al. Management and treatment of nocturnal enuresis an updated standardization document from the International Children's Continence Society. J Pediatr Urol. 2020;16:10-9.

15. Caldwell PH, Nankivell G, Sureshkumar P. Simple behavioural interventions for nocturnal enuresis in children. Cochrane Database Syst Rev. 2013;7:CD003637.

16. Vande Walle J, Rittig S, Bauer S, et al. Practical consensus guidelines for the management of enuresis [published correction appears in Eur J Pediatr. 2012 Jun;171(6):1005] [published correction appears in Eur J Pediatr. 2013 Feb;172:285]. Eur J Pediatr. 2012;171:971-83.

17. Robson WLM, Leung AK. Urotherapy recommendations for betwetting. J Nati Med Assoc. 2002;94:577-80.

18. Hjalmas K, Arnold T, Bower W, et al. Nocturnal enuresis: an international evidence based management strategy. J Urol. 2004;171:2545–61.

19. Ramakrishnan K. Evaluation and treatment of enuresis. Am Fam Physician. 2008;78:489-96.

20. Glazener CM, Evans JH. Desmopressin for nocturnal enuresis in children. Cochrane Database Syst Rev. 2002;CD002112.

21. Ghasemi K, Esteghamati M, Mohammadzadeh M, et al. Desmopressin versus Oxybutynin for Nocturnal Enuresis in Children in Bandar Abbas: A Randomized Clinical Trial. Electron Phy. 2016;8:2187-93.

22. Radvanska E, Kovács L, Rittig S. The role of bladder capacity in antidiuretic and anticholinergic treatment for nocturnal enuresis. J Urol. 2006;176:764-9.

23. Cendron M. Primary nocturnal enuresis: current concepts. Am Fam Phy.1999;59:1205–14,1219–20.

24. Glazener CM, Evans JH, Peto RE. Tricyclic and related drugs for nocturnal enuresis inchildren. Cochrane Database Syst Rev. 2003:CD002117.

25. Von Gontard A, Equit M. Comorbidity of ADHD and incontinence in children. Eur Child Adolesc Psychiatry. 2015;24:127–40.

26. Fritz G, Rockney R. Practice parameter for the assessment and treatment of children andadolescents with enuresis. J Am Acad Child Adolesc Psychiatry. 2004;43:1540-50.

Available online at www.medicinescience.org

ORIGINAL ARTICLE

Medicine Science International Medical Journal

Medicine Science 2021;10(1):13-7

Assessment of tongue depressor-related tongue swelling in pediatric patients with ultrasonography: A prospective, case-controlled observational study

Merih Onal

Selcuk University, Faculty of Medicine, Department of Otorhinolaryngology, Konya, Turkey

Received 07 September 2020; Accepted 29 September 2020
Available online 20.12.2020 with doi: 10.5455/medscience.2020.09.180

Abstract

Adenoidectomy is one of the most common surgeries performed in children. The tongue depressor is being routinely used during adenoidectomy exerts high mechanical pressure on the tongue. We aimed to discover tongue swelling created by the compression of tongue depressor by using ultrasonography (USG) in pediatric patients who were undertaken adenoidectomy. Thirty-four patients who were undertaken adenoidectomy were involved in the study group. In the control group, 33 patients who were undertaken pediatric surgery were involved. The tongue surface area (TSA) measurement was achieved for two times. In the study group, TSA^1 was performed immediately following intubation, prior to the installment of the tongue depressor, TSA^2 was performed following the removal of the tongue depressor however prior to extubation. In the control group, TSA^1 was performed immediately following intubation, TSA^2 was performed prior to extubation. An important correlation was noticed among the severity of tongue swelling (defined as TSA^2 - TSA^1) ($P = 0.000$) and tongue depressor. Tongue depressor may provoke tongue swelling in adenoidectomy procedures that can be shown with USG. This tongue swelling seems to be a result of the pressure applied by the tongue depressor. Tongue depressor related tongue swelling may cause respiratory complications in patients with already restricted airway passage even if the patients are fully awake. The tongue swelling in pediatric patients under adenoidectomy surgeries was demonstrated for the first time in the literature by USG.

Keywords: Adenoidectomy, children, complications, tongue disease, ultrasonography

Introduction

Adenoidectomy surgery, which is one of the most common ear, nose and throat procedures all over the world [1], is indispensable for children with obstructive symptoms such as nasal obstruction, sleep-disordered breathing, chronic otitis media, chronic sinusitis, as well as craniofacial changes [2]. Although the most important complication of adenoidectomy is bleeding with an incidence rate of 0.5% – 8%, postoperative respiratory complications can also be seen [3].

Although postoperative respiratory complications occur more in some risky patients, upper airway complications may also occur in healthy children with no risk factors [4]. In particular, massive swelling in the tongue and uvula can cause fatal outcomes by leading to upper airway obstruction even in healthy children [5,6].

Numerous cases of massive tongue swelling have been reported, and this life-threatening complication has been believed to be occurred due to the compression of tongue depressors, transesophageal probes, endotracheal tubes which exert direct pressure on the tongue [5].

Studies have shown that the tongue is an ideal and unique organ for ultrasonography (USG) evaluation due to its multiple muscle structure. The tongue surface area (TSA) can be easily measured when a USG probe is placed submental [7,8].

No studies have been conducted on the development and diagnosis of tongue swelling related to tongue depressor which can be a potential reason for postoperative respiratory complications in pediatric patients.

Thus, this study aimed to investigate the physiological effects of tongue depressor on the tongue and to determine through USG examination whether tongue swelling occurred in surgeries, such as adenoidectomy, which involves the short-term use of a tongue depressor.

***Corresponding Author:** Merih Onal, Selcuk University, Faculty of Medicine, Department of Otorhinolaryngology, Konya, Turkey
E-mail: drmerihonal@gmail.com

Material and Methods

Study design

We prospectively performed submental USG analysis of the tongue in pediatric patients who underwent adenoidectomy surgery at a university hospital. This research was approved by the Selçuk University Medical Faculty Research Ethics Board (No. 2018/331), with ClinicalTrials.gov Identifier: NCT NCT04256590 and it was conducted in accordance with the ethical principles laid down in the Declaration of Helsinki. Informed written consent was obtained from the parents of all the patients.

Participants

This study involved two groups of participants. The patients aged between 2 and 6 years were included for both groups. For both groups, the patients with a history of syndromic cranio facial abnormalities (e.g., Down syndrome, craniofacial trauma) and systemic disorders were excluded from this study.

The study group (n = 34) consisted of patients diagnosed with symptomatic adenoid hypertrophy and underwent adenoidectomy surgery. The second group (n = 33) consisted of the control group who underwent inguinal hernia and circumcision operation with endotracheal intubation under general anesthesia in pediatric surgery.

Measurements

For both groups, TSA values were measured twice per patient by submental USG by an experienced anesthesiologist who was trained by a staff pediatric radiologist regarding tongue assessment. Three measurements were taken, and an average of the two closest readings was used in the analysis for each measurement (Figure 1).

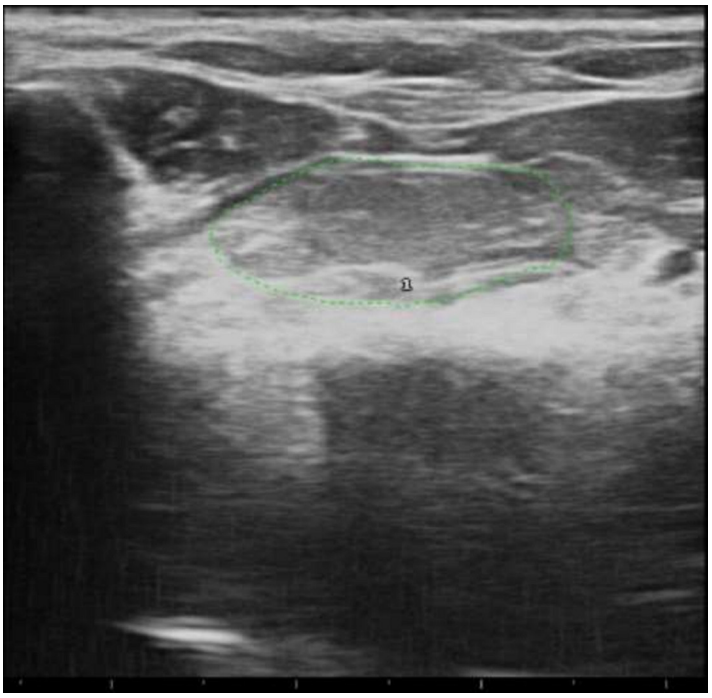


Figure 1. Tongue surface area image.

Primary outcome: The primary outcome was, the change in TSA depending on the use of tongue depressor. Our hypothesis was, depending on the use of the tongue depressor there would be an increase in TSA values measured by USG. In the study group, the first measurement (TSA^1) was performed quickly after endotracheal intubation but prior to the settlement of the tongue depressor. The second measurement (TSA^2) was performed following the completion of the adenoidectomy procedure and after the removal of the tongue depressor but just before extubation. In the control group, the first measurement (TSA^1) was performed quickly after endotracheal intubation but prior tothe surgery, whereas the second measurement (TSA^2) was obtained at the end of the surgical procedure but just before extubation (Figure 2).

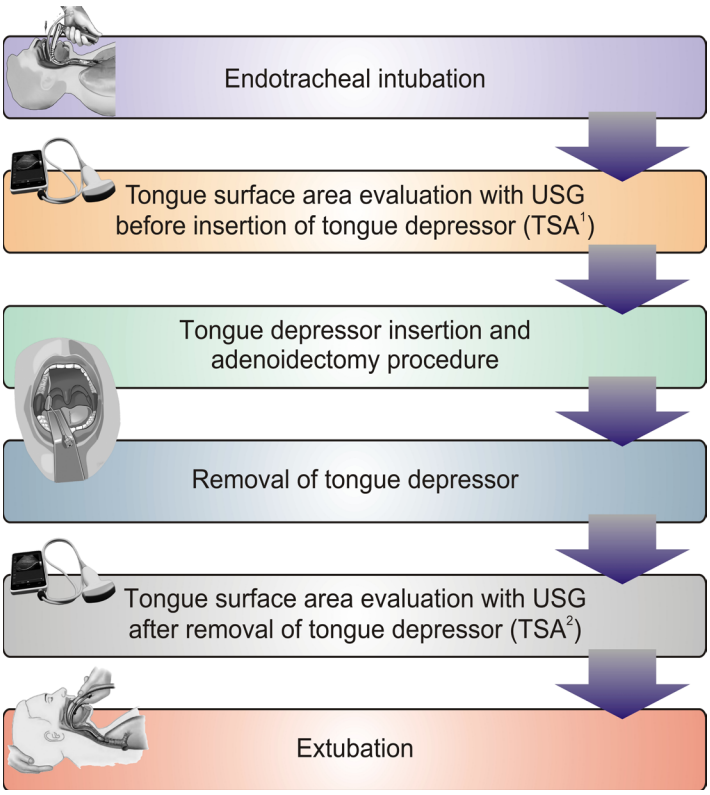


Figure 2. Flowchart of the study.

Secondary outcome: The secondary outcome was the presence of tongue swelling caused by tongue depressor shown with USG. Our hypothesis was that the tongue swelling associated with the tongue depressor could be evidenced by TSA values measured by USG. The difference between TSA^2 and TSA^1 (i.e., TSA^2- TSA^1) was used to describe the tongue swelling for both groups.

Ultrasound Examination

TSA measurements were carried out in the Esaote MyLab (Genoa, Italy) ultrasound device with a convex probe operating at 4 MHz frequency in the coronal plane of the submental midline region. When the patient in the supine neutral position, the probe was placed under the chin without pressing too much, and when the whole tongue image was obtained on the monitor, the image was freezed. The following landmarks were identified to confirm consistent transducer placement for each subject: fascia between the mylohyoid muscle and intrinsic muscles of

the tongue and the interface between the soft palate and air in the oral cavity. Additionally, the image of the tongue was identified as ‘‘oval-shaped,’’ further confirming consistent positioning of the transducer. TSA borders were drawn manually and the TSA was calculated automatically.

Adenoidectomy procedure

The same two otolaryngologists performed all adenoidectomy procedures under general anesthesia; they used the conventional curettage adenoidectomy method, which was carried out blindly by an adenoid curette. The same Crowe–Dawis tongue depressor blade was used to keep the mouth open. Each patient was given standard general anesthesia, which was induced with methylprednisolone (1 mg/kg) (Prednole, Gensenta, Istanbul, Turkey) For each patient hydration was started with a mixed pediatric solution (Biof, Osel, Istanbul, Turkey), which was administered intravenously at a rate of 10 mL/kg/h. Each patient was intubated with an identical type of endotracheal tube that was appropriate for each patient’s age, and the endotracheal tube was set at the center of the mouth. The tongue depressor was placed in the patient’s mouth, and the duration was noted. The tongue depressor was not removed until the surgery was finished. If the tongue depressor was removed or had to be loosened before the surgery, the patient was excluded from the study.

Statistical analysis and sample size

All data are expressed as mean ± standard deviation (SD). A non-parametric Mann–Whitney U-test was used to determine whether the study and control groups differed on each variable. Data analysis was conducted using the Statistical Package for the Social Science software program (SPSS Version 17.0, IBM, Armonk, NY, USA). A P value of < 0.05 indicated statistical significance. We performed a pilot study in 10 patients from the adenoidectomy group to calculate the sample size. In the pilot study, the tongue surface area values before and after the replacement of tonsillar retractor were 1.98 ± 0.29cm² and 2.72 ± 0.28cm² respectively. Assuming an equal SD and to show a difference of 20% between the 2 groups, a 2-sided type I error of 0.05 and a power of 0.95 were applied. According to this calculation, when we included 16 patients per group, a significant difference would be found in terms of tongue surface areas.

Results

No significant difference was seen between the study and control groups in terms of demographics (Table 1). While 19 of the patients in the adenoid group, 17 of the patients in the control group were girls. According to the mean intubation duration no significant difference was revealed between the study (26.2 min), and control (28.8 ± min) groups (P = 0.6).In terms of mean TSA^1 values, there was no significant difference between study and control groups respectively (1.95 ± 0.29cm²) (2.03 ± 0.17cm²) (P = 0.183). The mean TSA^2 values of the study group (2.63 ± 0.22cm²) were higher compared to the control group (2.16 ± 0.24cm²) (P = 0.000).Also, in terms of the tongue swelling values, the mean $TSA^2 – TSA^1$ values of the study group (0.69 ± 0.29 cm²) were higher than the control group (0.12 ± 0.15 cm²) and a significantly difference was noticed between two groups (P = 0.000) (Table 2) (Figure 3).

Table 1. Comparison between the adenoidectomy and control groups in terms of descriptive statistics (Mann–Whitney U test)

	Adenoidectomy(n=34) Mean±SD (min-max)	Control(n=33) Mean±SD (min-max)	P value
Age (Years)	4.8±1.23 (2.50-6.00)	4.5±1.23 (2.5-6.00)	0.108(.914)
Weight (kg)	15.1±3.35 (9.00-23.00)	15.51±3.40 (9.50- 23.50)	-0.729(.466)

Table 2. Comparison between the adenoidectomy and control groups in terms of preoperative and postoperative tongue surface area (TSA^1 and TSA^2 respectively), tongue swelling (TSA^2 - TSA^1), tongue depressor and endotracheal intubation duration.

Parameter (cm²)	Adenoidectomy group (n=34)		Control group (n=33)			p
	Mean	SD	Mean	SD		
TSA^1	1.95	0.29	2.3	0.17	1.282	0.183
TSA^2	2.63	0.22	2.16	0.24	6.192	0.000*
$TSA^2–TSA^1$ (Tongue swelling)	0.69	0.29	0.12	0.15	6.622	0.000*
TongueDepressor Duration	24	3.33				0.6
Endotracheal Intubation Duration			23.8	2.13		

*Comparing adenoidectomy and control group.
Tongue depressor duration: The duration between inserting and removing the tongue depressor in the patient's mouth.
Endotracheal intubation duration: The duration between endotracheal intubation and extubation of the patient.

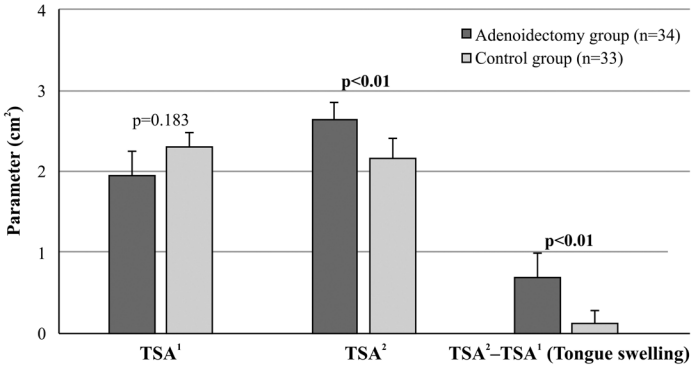


Figure 3. Comparison between the study and control groups in terms of preoperative and postoperative tongue surface area (TSA^1 and TSA^2) values and tongue swelling ($TSA^2 – TSA^1$) values.

Discussion

In our study, we determined that TSA values were increased by the ratio of 34% in adenoidectomy surgeries while the rate of increase was 6% in control group. Although the long-term compression of the tongue during a surgical procedure is thought to be the mechanical reason behind the development of massive tongue swelling, [5] we showed with that non-massive tongue swelling may also occur in short-term surgeries due to the high pressure exerted by the tongue depressor on the tongue in pediatric patients, as previously shown in adult patients who undergo suspension laryngoscopy [8].

At the end of our study, we also thought that there might be other differences between massive and non-massive tongue swelling formations in terms of their characteristics. Although massive tongues swelling can be observed with the naked eye, the non-massive tongues swelling could only be detected by USG. Additionally, when massive tongue swelling occurs, it can immediately cause airway obstruction even in healthy patients, whereas the non-massive tongues welling may cause airway obstruction in patients with certain risk factors. Since, non-massive tongue swelling due to tongue depressor may cause respiratory complications arising from upper airway obstruction, by completely blocking the airway especially in high risk patient groups with an already narrowed upper airway, such as very young age (<2 years), obesity, Obstructive Sleep Apnea Syndrome (OSAS), Down syndrome, craniofacial trauma [4,9,10].

Namely; the tongue swelling does not necessarily have to be massive in order to block the airway completely. Because, although there has been no study on the definition of tongue swelling induced by tongue depressor or its clinical consequences, most of the postoperative respiratory complications after adenotonsillectomy have been known to be due to upper airway obstruction.

In support, in a study conducted by Chorney et al. [11] 16.9% of the patients who underwent adenoidectomy experienced serious postoperative respiratory-related events. The majority of those were children younger than 1.5 years old. This result might have been due to the fact that the tongues of very young children are relatively large and the airway passage has already narrowed during the preoperative period, and the non-massive tongue swelling may be developed in the post-operative period that may completely closed the airway passage.

In another two studies tongue-based obstruction is an important cause of postoperative respiratory complications and that adversely affects airway patency in patients with OSAS [12,13]. Given that the majority of adenoidectomy operations are due to the OSAS and narrowed airway patency, it can be said that the already narrowed airway patency of the patients further constricted due to nonmassive tongue swelling and upper airway obstruction tendency has increased [11]

The OSAS incidence is high in patients with Down syndrome who already have a large tongue in the preoperative period and who already have limited airway passages [14]. In two different studies, it was stated that respiratory complications seen in the post-operative period in children with Down syndrome will occur up to 8 times more than healthy patient group [15,16]. This may be related to the already restricted airway passage being completely closed by non-massive tongues swelling. In line with this, Walker et al. [17] found that the children who underwent adenoidectomy and tonsillectomy surgeries and who were followed up in pediatric intensive care unit for respiratory reasons were those with Down syndrome (9.8%). And also, they stated that tongue size and position could be the determining factors for respiratory events in these pediatric patients.

As reported by Gerkhe et al. [18], all of the patients who had experienced a respiratory complication 3–24 h post adenotonsillectomy surgeries had syndromes that cause the airway to narrow preoperatively. In another study, including patients with craniofacial anomalies or they had been previously subjected to upper airway trauma that causes the preoperative narrowing of airway passage, implicated that respiratory complications were more common in these patients even if they were completely awake in the postoperative period [4]. Brown et al. [19] noted in a research that respiratory-related complications that did not develop in less than 1 h after adenotonsillectomy surgeries but emerged 1–8 h postoperatively constitute one-third of the respiratory complications; however, they did not investigate the causes of these complications.We want to note that the duration of being noticed clinical consequences of non-massive tongue swelling may take up to 2-2.5 hours [20].

In that patients, closure of the narrowed airway passage due to the gradually developing non-massive tongue swelling may be associated with postoperative respiratory complications caused by upper airway obstruction. It is important to note the diagnosis of non-massive tongue swelling by USG in children while undergoing adenoidectomy in order to prevent postoperative respiratory complications caused by upper airway obstruction.

Our study contributed to the current literature from 3 different perspectives. First, we determined that, non-massive tongue edema may occur even in short-term surgeries depending on the pressure applied by the tongue depressor on the tongue. Second, we determined that non-massive tongue edema cannot be seen with the naked eye, but can be detected by USG, and may only have clinical consequences in patients with a narrowed upper airway.Third, we made inferences about the differences between massive and non-massive tongue edema.

Limitation

Our study has some limitations. There is no available study in the literature evaluating TSA values in children. So, we do not know the normal range of TSA values in children and we cannot compare in terms of size. However, we would like to point out that the same trained anesthesist were conducted all measurements in terms of being objective. Low TSA values may be due to the small number of patients. In future studies with more cases in healthy children, the normal values of TSA measured by USG can be revealed. In this study, we measured TSA because it is more practical rather than measuring thickness and width. We could also have more objective results if we could perform the other tongue measurements such as volume, thickness several times in post-anesthesia care unit and ward with 3-dimension USG. Since the cases were children, we did not consider comparing them with CT to avoid radiation. However, comparative studies can be done with MRI in the future. A group of high-risk patients for post-operative upper airway obstruction would demonstrate our clinical results more objectively. The effects of non-massive tongue edema on clinical outcomes need to be examined.

Conclusion

In children who underwent adenoidectomy surgeries, non-massive tongue swelling may have emerged due to the compression exerted by the tongue depressor. Non-massive tongue swelling can be detected by USG and it may positively affect clinical outcomes by alerting the clinician early, in terms of upper airway obstruction especially in high-risk patients in whom used intraoperative

tongue depressors.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
All authors declare no financial support.

Ethical approval
This research was approved by the Selçuk University Medical Faculty Research Ethics Board (No. 2018/331), with ClinicalTrials.gov Identifier: NCT04256590 and it was conducted in accordance with the ethical principles laid down in the Declaration of Helsinki.

References

1. Bhattacharyya N. Ambulatory pediatric otolaryngologic procedures in the United States: characteristics and perioperative safety. Laryngoscope. 2010;120:821-5.
2. Gabriel OT, Oyebanji O. A review and outcome of adenoidectomy performed in resource limited settings. Indian J Otolaryngol Head Neck Surg. 2019;71:1-4.
3. Sjogren PP, Thomas AJ, Hunter BN, et al. Comparison of pediatric adenoidectomy techniques. Laryngoscope. 2018;128:745-9.
4. Rosen GM, Muckle RP, Mahowald MW, et al. Postoperative respiratory compromise in children with obstructive sleep apnea syndrome: can it be anticipated? Pediatrics. 1994;93:784-8.
5. Tanaka N, Ibuki T, Araki A, et al. Airway obstruction caused by massive swelling of the tongue following bilateral tonsillectomy for sleep apnea syndrome. Masui. 2006;55:464-7.
6. Nasr VG, Bitar MA, Chehade JM, et al. Postoperative severe uvular edema following tonsillectomy in a child with a history of obstructive sleep apnea. Paediatr Anaesth. 2008;18:673-5.
7. Wojtczak JA. Submandibular sonography: assessment of hyomental distances and ratio, tongue size, and floor of the mouth musculature using portable sonography. J Ultrasound Med. 2012;31:523-8.
8. Onal M, Colpan C, Elsurer C, et al. Is it possible that direct rigid laryngoscope-related ischemia-reperfusion injury occurs in the tongue during suspension laryngoscopy as detected by ultrasonography: a prospective controlled study. Acta Otolaryngol. 2020;140:583-8.
9. Harris VC, Dalesio NM, Clark J, et al. Postoperative Respiratory Complications and disposition in patients with type 1 laryngeal clefts undergoing injection or repair – A Single Institution Experience. Int J Pediatr Otorhinolaryngol. 2020;131:109844.
10. Ekstein M, Zac L, Schvartz R, et al. Respiratory complications after adenotonsillectomy in high-risk children with obstructive sleep apnea: A retrospective cohort study. Acta Anaesthesiol Scand. 2020;64:292-300.
11. Chorney SR, Dailey JF, Zur KB. Pediatric adenoidectomy in the very young child and indications for postoperative inpatient admission. Int J Pediatr Otorhinolaryngol. 2020;130:109796.
12. Tasli H, Birkent H, Karakoc O, et al. The effect of obesity on transnasal flexible laryngoscopy. J Voice. 2019;23:30216-7.
13. Ishman SL, Chang KW, Kennedy AA. Techniques for evaluation and management of tongue-base obstruction in pediatric obstructive sleep apnea. Curr Opin Otolaryngol Head Neck Surg. 2018;26:409-16.
14. Farhood Z, Isley JW, Ong AA, et al. Adenotonsillectomy outcomes in patients with Down syndrome and obstructive sleep apnea. Laryngoscope. 2017;127:1465-70.
15. Thottam PJ, Choi S, Simons JP, et al. Effect of adenotonsillectomy on central and obstructive sleep apnea in children with down syndrome. Otolaryngol Head Neck Surg. 2015;153:644-8.
16. Goldstein NA, Armfield DR, Kingsley LA, et al. Postoperative complications after tonsillectomy and adenoidectomy in children with Down syndrome. Arch Otolaryngol Head Neck Surg. 1998;124:171-6.
17. Walker P, Whitehead B, Rowley M. Role of paediatric intensive care following adenotonsillectomy for severe obstructive sleep apnoea: criteria for elective admission. J Laryngol Otol. 2013;127:26-9.
18. Gehrke T, Scherzad A, Hagen R,et al. Risk factors for children requiring adenotonsillectomy and their impact on postoperative complications: a retrospective analysis of 2000 patients. Anaesthesia. 2019;74:1572-9.
19. Brown KA, Morin I, Hickey C, et al. Urgent adenotonsillectomy: an analysis of risk factors associated with postoperative respiratory morbidity. Anesthesiology. 2003;99:586-95.
20. Chan MT, Chan MS, Mui KS, et al. Massive lingual swelling following palatoplasty. An unusual cause of upper airway obstruction. Anaesthesia. 1995;50:30-4.

Available online at www.medicinescience.org

ORIGINAL ARTICLE

Medicine Science International Medical Journal

Medicine Science 2021;10(1):18-30

ADME predictions and molecular docking study of some compounds and drugs as potential inhibitors of COVID-19 main protease: A virtual study as comparison of computational results

Harun Uslu[1], Pelin Koparir[2], Kamuran Sarac[3], Arzu Karatepe[4]

[1]Firat University, Department of Medical Services and Techniques, Vocational School of Health Services, Elazig, Turkey
[2]Department of Chemistry, Forensic Medicine Institute, Malatya, Turkey
[3]Bitlis Eren University, Faculty of Art and Sciences, Department of Chemistry, Bitlis, Turkey
[4]Bingol University, Department of Chemistry, Bingol, Turkey

Received 28 September 2020; Accepted 21 October 2020
Available online 20.12.2020 with doi: 10.5455/medscience.2020.09.203

Abstract

Adenoidectomy is one of the most common surgeries performed in children. The tongue depressor is being routinely used during adenoidectomy exerts high mechanical pressure on the tongue. We aimed to discover tongue swelling created by the compression of tongue depressor by using ultrasonography (USG) in pediatric patients who were undertaken adenoidectomy. Thirty-four patients who were undertaken adenoidectomy were involved in the study group. In the control group, 33 patients who were undertaken pediatric surgery were involved. The tongue surface area (TSA) measurement was achieved for two times. In the study group, TSA1 was performed immediately following intubation, prior to the installment of the tongue depressor, TSA2 was performed following the removal of the tongue depressor however prior to extubation. In the control group, TSA1 was performed immediately following intubation, TSA2 was performed prior to extubation. An important correlation was noticed among the severity of tongue swelling (defined as TSA2 - TSA1) (P = 0.000) and tongue depressor. Tongue depressor may provoke tongue swelling in adenoidectomy procedures that can be shown with USG. This tongue swelling seems to be a result of the pressure applied by the tongue depressor. Tongue depressor related tongue swelling may cause respiratory complications in patients with already restricted airway passage even if the patients are fully awake. The tongue swelling in pediatric patients under adenoidectomy surgeries was demonstrated for the first time in the literature by USG.

Keywords: Adenoidectomy; children; complications; tonguedisease; ultrasonography

Introduction

Coronaviruses (CoVs) belong to the Coronavirinae subfamily of the Coronaviridae family, from the order Nidovirales [1]. CoVs are enveloped, positive-strand, large RNA viruses, moreover, they are divided into 4 genera as alpha, beta, delta, and gamma, while only alpha and beta Coronaviruses are known pathogenic for humans [2]. CoVs are significant pathogens for vertebrates and these viruses can infect the gastrointestinal, hepatic, respiratory, and central nervous systems of humans and many wild animals [1, 3, 4]. In new animal studies, it has been found that SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) replicates poorly in pigs, dogs, ducks, and chickens but ferrets and cats allow infection. Experimentally, it has been discovered that cats are susceptible to airborne infections, moreover, cats in Wuhan are reported to be seropositive for SARS-CoV-2 [5, 6].

***Coresponding Author:** Pelin Koparir, Department of Chemistry, Forensic Medicine Institute, Malatya, Turkey, E-mail: mpelin23@hotmail.com

In the last days of 2019, intense pneumonia was reported in the city of Wuhan. Shortly after reporting the outbreak, local Chinese healthcare workers and the Chinese Center for Disease Control (China CDC) determined that the cause of the outbreak was originally a novel coronavirus, called Wuhan Coronavirus or nCov-2019 (as SARS-Cov-2) [7-9]. This viral infection disease has been officially named Coronavirus Disease 2019 (COVID-19) by the World Health Organization (WHO) and, as with other CoVs (SARS (Severe Acute Respiratory Syndrome)-CoV and MERS (Middle East Respiratory Syndrome)-CoV), has been expressed to affect the lower respiratory tract, mostly causing pneumonia. It can also affect the heart, kidney, gastrointestinal tract, and central nervous system, with common symptoms such as cough, fever, and diarrhea [10]. Symptoms range from asymptomatic infections to a lethal form of COVID-19 which is associated with severe pneumonia and acute respiratory distress [11]. According to the World Health Organization data, August 2020 resulted in more than 22,000,000 confirmed cases of COVID-19 with more than ~776,000 deaths. COVID-19 pandemic continues to spread rapidly all over the world. Therefore, drugs and vaccines are in high demand to control this pandemic (https://covid19.who.int/). .

Spike protein is the key for the virus to penetrate the cell via the interaction with Angiotensin-Converting Enzyme 2 (ACE2), which one of the most trend targets for the development of new drugs against SARS-CoV2 due to its crucial role in the transcription and replication of the virus. One of the most important advantages of targeting this protein is that although the mutagenesis rate in viruses is high, the rate here is low because any mutation in this protein can be lethal for the virus [12].

A large number of 3D protein structures for SARS-CoV-2 are available in the Protein Data Bank (http://www.rcsb.org/) and molecular docking studies related to the main protease are increasing in terms of drug screening and protein-inhibitor interactions [13, 14]. More attention was attracted to the phenomenon named repositioning of drugs since the development of the new drug has become more costly in terms of both time and resources [15]. Licensed drugs are more suitable for use in new indications due to their favorable toxicological, pharmacokinetic, and pharmacodynamic properties [16]. In light of all this, it is clear that these approved drugs will be excellent candidates in case of disease emergencies or outbreaks [12]. Binding sites for N3 is well determined in "The crystal structure of COVID-19 main protease in complex with an inhibitor N3" [17]. Potential inhibitor effects with drugs (active metabolite) and synthesized molecules were determined by COVID-19 main protease. The interactions of compounds with the COVID-19 main protease were put forthed via molecular docking studies.

We can define the term drug development as an evaluation of the efficacy and toxicity of novel drug candidates, which includes the target receptor hypothesis for disease and screening of in vitro / in vivo biological activities. With the introduction of early absorption, distribution, metabolism, and elimination (ADME) screening, focusing resources on potential drug candidates has significantly reduced the proportion of compounds that fail in clinical trials and eliminated weak drug candidates in the early stages of drug development [18]. SwissADME free web tool is software used to estimate the absorption, distribution, metabolization, elimination, physicochemical and pharmacokinetic properties of molecules that are more important for clinical research [19, 20].

In this study, it was conducted pharmacokinetics, drug-likeness and medicinal chemistry friendliness with SwissADME web tool [21], molecular modeling studies with Autodock4 [22] software and Autodock Vina [23] software on several FDA approved drugs and 3 different molecules in different chemical structures previously synthesized, so interesting and successful results were achieved.

Material and Methods

ADME Prediction of Ligands

The predictive study of ADME, pharmacokinetics, bioavailability, drug-likeness, and medicinal chemistry friendliness properties of ligands were carried out by using the SwissADME free online tool (http://www.swissadme.ch/). The standard SMILES (Simplified Molecular Input Line Entry System) for each chemical was incorporated in the SwissADME tool for the computational simulation.

Molecular Docking Studies

Ligands were energy-minimized using ChemOffice on Windows 10 operating system. Grid box points were determined according to the size of the ligands. The regular space of the Grid box is determined as 0.375 Å, centered on N3. "The crystal structure of COVID-19 main protease in complex with an inhibitor N3" PDB file (PDB ID: 6LU7) was obtained and was modified using the Maestro (Maestro, Schrödinger, LLC, New York, NY, 2020.). Lamarckian Genetic Algorithm was preferred and standard settings were used for all ligands. Docking scores were obtained using AutoDock 4.2 and AutoDock Vina software.

Results

It has been demonstrated that COVID-19 and severe acute respiratory syndrome (SARS) are characterized by an excessive inflammatory response, moreover, viral load for SARS is not associated with worsening of symptoms [24, 25]. It has been previously reported that approximately 15% of patients with COVID-19 disease experience serious illness and 5% can progress to the critical stage that can lead to rapid death [26]. Effective treatment for SARS-CoV-2 infection is still unproven. Apart from supportive care, specific drugs for this disease continue to be explored [27]. In the USA, the first patient infected with SARSCoV-2 has been reported to be treated with supportive care and intravenous Remdesivir [28]. However, it has been stated that randomized clinical trials are needed to evaluate remdesivir in terms of safety and efficacy in the treatment of COVID-19 [27]. Favipiravir, Hydroxychloroquine, and Remdesivir were identified as promising prodrugs against COVID-19 during the literature review [29-32]. Although it is still included in the treatment protocol of some health institutions, it has been explained in a recent academic study that the death rate of COVID-19 patients treated with Hydroxychloroquine or Chloroquine has increased [33].

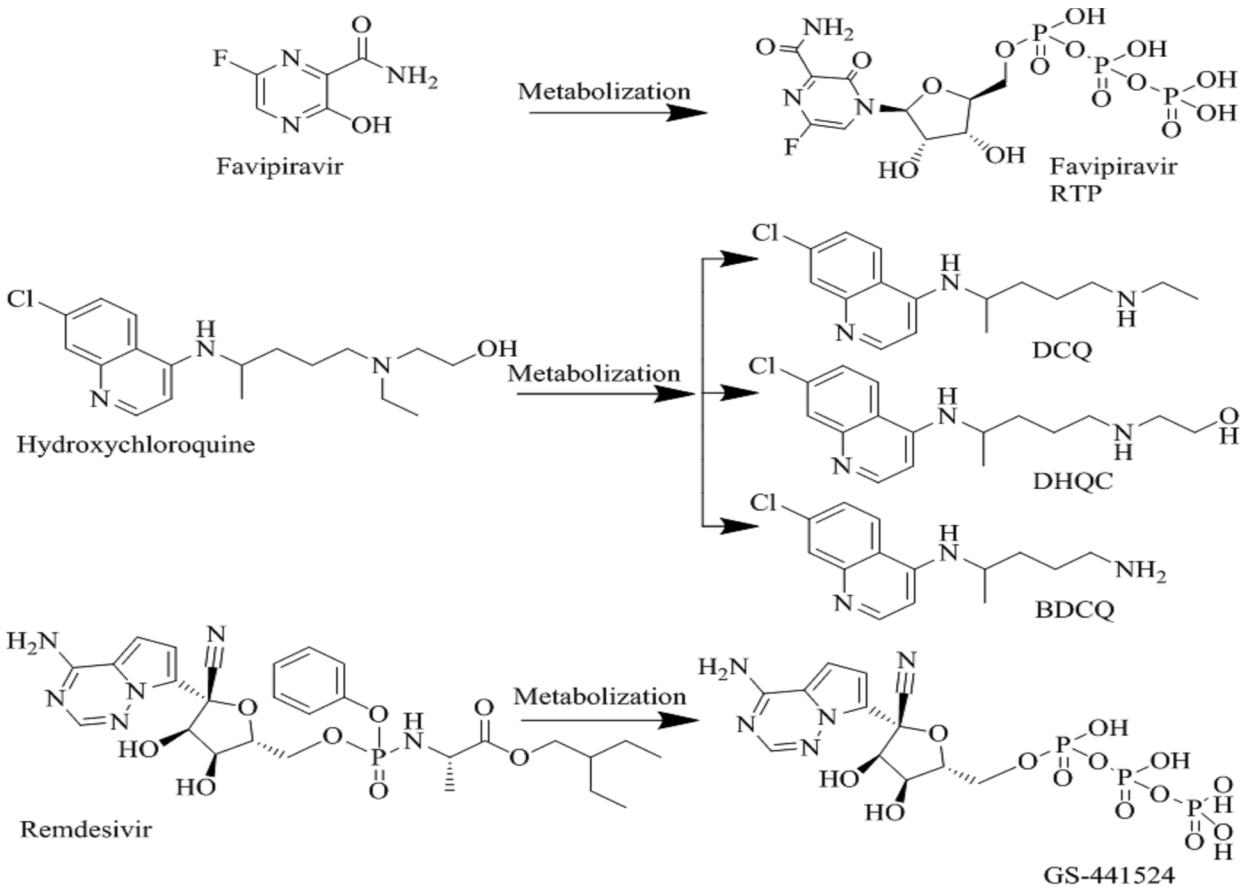
In addition to the base molecules and active metabolites of these prodrugs (Scheme 1), 3 different chemical compounds (pyridine, triazole, thiadiazole, and coumarin ring/rings bearing) were included in silico studies (Scheme 2).

Using the molecular docking approach, the binding interactions of several drug metabolites and other chemical compounds in the active site of the enzyme are understood. Also, here examined the relationships between the chemical structure in these ligands and their efficacy.

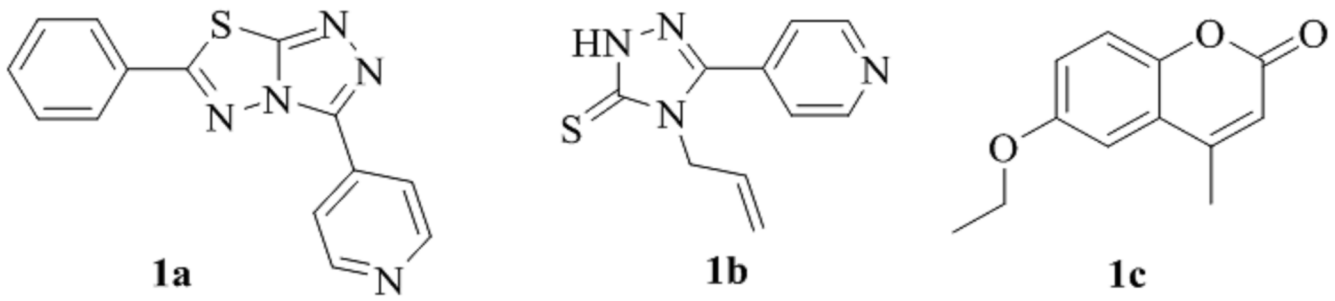
In Silico ADME Prediction

In Silico ADME prediction studies were calculated for compound 1a, compound 1b, compound 1c, Favipiravir, Hydroxychloroquine, Remdesivir, and several active metabolites of these prodrugs (Table 1-4).

Compounds 1a, 1b, 1c, and all prodrugs were found to high for gastrointestinal absorption in terms of pharmacokinetics. There are different results for the blood-brain barrier (BBB). There is a permeation for 1c, Hydroxychloroquine, DCQ, Remdesivir, and GS-441524, but no permeation for all other compounds (Table 1). The fact that Compound 1a does not pass through BBB while



Scheme 1. Molecular structure of Favipiravir [34], Hydroxychloroquine [35], Remdesivir [36], and their some active metabolites



Scheme 2. Molecular structure of 1a [37], 1b [38] and 1c [39].

gastrointestinal absorption is high may indicate low toxic effects.

Water solubility as logS (ESOL) was expressed very soluble for Favipiravir, soluble for all other prodrugs, compounds 1a, 1b, and 1c. Consensus Log Po/w (average of all log P) was expressed negative for Favipiravir and GS-441524, positive for all compounds (Table 2).

Compounds 1a, 1b, 1c, and Hydroxychloroquine were found to comply with all filters and Lipinski rules in terms of drug-likeness, but there were some violations for Favipiravir and Remdesivir. Favipiravir's Ghose filter number of violations is 4: MW<160, WLOGP<-0.4, MR<40, #atoms<20, and Muegge filter number of violations is 1: MW<200. Remdesivir's Lipinski rule number of violations is 2: MW>500, N or O>10, Ghose filter violation number is 3: MW>480, MR>130, #atoms>70, Veber filter violation number is 2: Rotors>10, TPSA>140, Egan filter violation number is 1: TPSA>131.6, Muegge filter number of violations is 3: MW>600, TPSA>150, H-bond acceptor>10 (Table 3.).

Unlike all prodrugs and compound 1b and 1c, compound 1a was found to comply with lead likeness in terms of medicinal chemistry and there were no violations for Structurals Alert. Leadlikeness number of violations for compounds 1b and 1c is 1: MW<250. Among the products and our compounds, the compound with the highest Synthetic Accessibility Score is 1a (Table 4).

Table 1. Comparison between the adenoidectomy and control groups in terms of descriptive statistics (Mann–Whitney U test)

Ligands	Gastrointestinal absorption	Blood-brain permeant	P- glycoprotein substrate	CYP450 1A2 inhibitor	CYP450 2C19 inhibitor	CYP450 2C9 inhibitor	CYP450 2D6 inhibitor	CYP450 3A4 inhibitor	Skin permeation as log Kp (cm/s)
1a	High	No	No	Yes	Yes	No	No	No	-6.22
1b	High	No	No	Yes	No	No	No	No	-6.77
1c	High	Yes	No	Yes	No	No	No	No	-6.01
Favipiravir	High	No	No	No	No	No	No	No	-7.66
Favipiravir RTP	High	No	Yes	No	No	No	No	No	-13.59
Hydroxychloroquine	High	Yes	Yes	Yes	No	No	Yes	Yes	-6.23
DCQ	High	Yes	No	Yes	Yes	No	Yes	Yes	-5.84
DHQC	Low	No	Yes	No	No	No	No	Yes	-8.62
BDCQ	Low	No	No	No	No	No	No	No	-13.27
Remdesivir	High	Yes	No	Yes	No	No	Yes	No	-5.81
GS-441524	High	Yes	No	Yes	Yes	No	Yes	Yes	-5.38

Favipiravir RTP: Favipiravir Ribosyl triphosphate, GS-441524: Remdesivir Active Metabolite, DCQ: Desethylchloroquine, DHQC: Desethylhydroxychloroquine, BDCQ: Bisdesethylhydroxychloroquine.

Table 2. Bioavailability prediction of all ligands

Ligands	Bioavailability score	Water solubility as logS (ESOL)	iLOGP	XLOGP3	WLOGP	MLOGP	SILICOS-IT	Consensus Log Po/w
1a	0.55	Soluble as -3.92	2.39	2.51	2.91	2.63	3.00	2.69
1b	0.55	Soluble as -2.30	1.79	1.21	2.19	0.55	3.16	1.78
1c	0.55	Soluble as -2.83	2.57	2.16	2.50	1.91	3.25	2.48
Favipiravir	0.55	Very Soluble as -0.80	0.39	-0.56	-0.57	-1.30	0.69	-0.27
Favipiravir RTP	0.11	Highly Soluble as 0.94	-1.24	-5.72	-2.46	-4.91	-5.08	-3.88
Hydroxychloroquine	0.55	Soluble as -3.91	3.58	3.58	3.59	2.35	3.73	3.37
DCQ	0.55	Soluble as -3.95	3.43	3.80	3.89	2.73	3.98	3.57
DHQC	0.55	Soluble as -3.31	3.00	2.75	2.86	1.88	3.38	2.77
BDCQ	0.55	Soluble as -3.40	2.64	2.92	3.24	2.24	3.14	2.83
Remdesivir	0.17	Moderately Soluble as -4.12	3.40	1.91	2.21	0.18	-0.05	1.53
GS-441524	0.11	Highly Soluble as 0.50	-0.99	-5.25	-1.61	-3.89	-5.27	-3.40

Table 3. Druglikeness prediction of all ligands as number of violations

Ligands	Lipinski rule	Ghose filter	Veber filter	Egan filter	Muegge filter
1a	Yes: 0	Yes: 0	Yes: 0	Yes: 0	Yes: 0
1b	Yes: 0	Yes: 0	Yes: 0	Yes: 0	Yes: 0
1c	Yes: 0	Yes: 0	Yes: 0	Yes: 0	Yes: 0
Favipiravir	Yes: 0	No: 4	Yes: 0	Yes: 0	No: 1
Favipiravir RTP	No: 3	No: 2	No: 1	No: 1	No: 4
Hydroxychloroquine	Yes: 0	Yes: 0	Yes: 0	Yes: 0	Yes: 0
DCQ	Yes: 0	Yes: 0	Yes: 0	Yes: 0	Yes: 0
DHQC	Yes: 0	Yes: 0	Yes: 0	Yes: 0	Yes: 0
BDCQ	Yes: 0	Yes: 0	Yes: 0	Yes: 0	Yes: 0
Remdesivir	No: 2	No: 3	No: 2	No: 1	No: 3
GS-441524	No: 3	No: 2	No: 1	No: 1	No: 4
DCQ	Yes: 0	Yes: 0	Yes: 0	Yes: 0	Yes: 0
DHQC	Yes: 0	Yes: 0	Yes: 0	Yes: 0	Yes: 0
BDCQ	Yes: 0	Yes: 0	Yes: 0	Yes: 0	Yes: 0
Remdesivir	No: 2	No: 3	No: 2	No: 1	No: 3
GS-441524	No: 3	No: 2	No: 1	No: 1	No: 4

Table 3. Medicinal chemistry prediction of all ligands

Ligands	Leadlikeness	PAINS Structural Alert	Brenk Structural	Synthetic Accessibility Score
1a	Yes: 0	0	0	2.89
1b	No: 1	0	2	2.16
1c	No: 1	0	1	2.57
Favipiravir	No: 1	0	0	2.08
Favipiravir RTP	No: 2	0	1	4.98
Hydroxychloroquine	No: 2	0	0	2.82
DCQ	No: 1	0	0	2.54
DHQC	No: 1	0	0	2.60
BDCQ	Yes: 0	0	0	2.35
Remdesivir	No: 2	0	1	6.33
GS-441524	No: 2	0	1	4.82
Remdesivir	No: 2	0	1	6.33
GS-441524	No: 2	0	1	4.82

Molecular Docking Studies

According to the X-ray crystallographic structure of COVID-19 main protease in complex with an inhibitor N3 (PDB ID:6LU7), the main binding site has been determined around small molecules as N3 in the receptor. It has been declared that N3 interacts with the active site as binding sites. It has been previously established that N3 interacts with PHE140A, ASN142A, GLY143A, CYS145A, HIS163A, HIS164A, GLU166A, GLN189A, THR190A residues via H-bonds. The covalent bond between N3 and C145A has been reported [17]. Similar H-bonds interactions were observed on all molecules with molecular docking studies except for compound 1a and compound 1c (Table 5). Docking studies were performed for the compound 1a, compound 1b, compound 1c, and several metabolites of all prodrugs. Interaction modes for compounds 1a, 1b, 1c (Figure 1, Figure 3), and metabolites of Favipiravir, Hydroxychloroquine, Remdesivir (Figure S2-S6.) with enzyme active sites were determined (Table 5). Ligands binding types and residues were produced showed by Maestro software (Figure 1, Fig. 2, Figure 3, and Figure. S1-S7) (Maestro, Schrödinger, LLC, New York, NY, 2020.). These compounds' binding modes were similar to N3 (Fig. 1, Fig. S7). The interactions of all compounds, that molecular docking is performed, can be examined in detail with the figures in the Supporting Information Material.

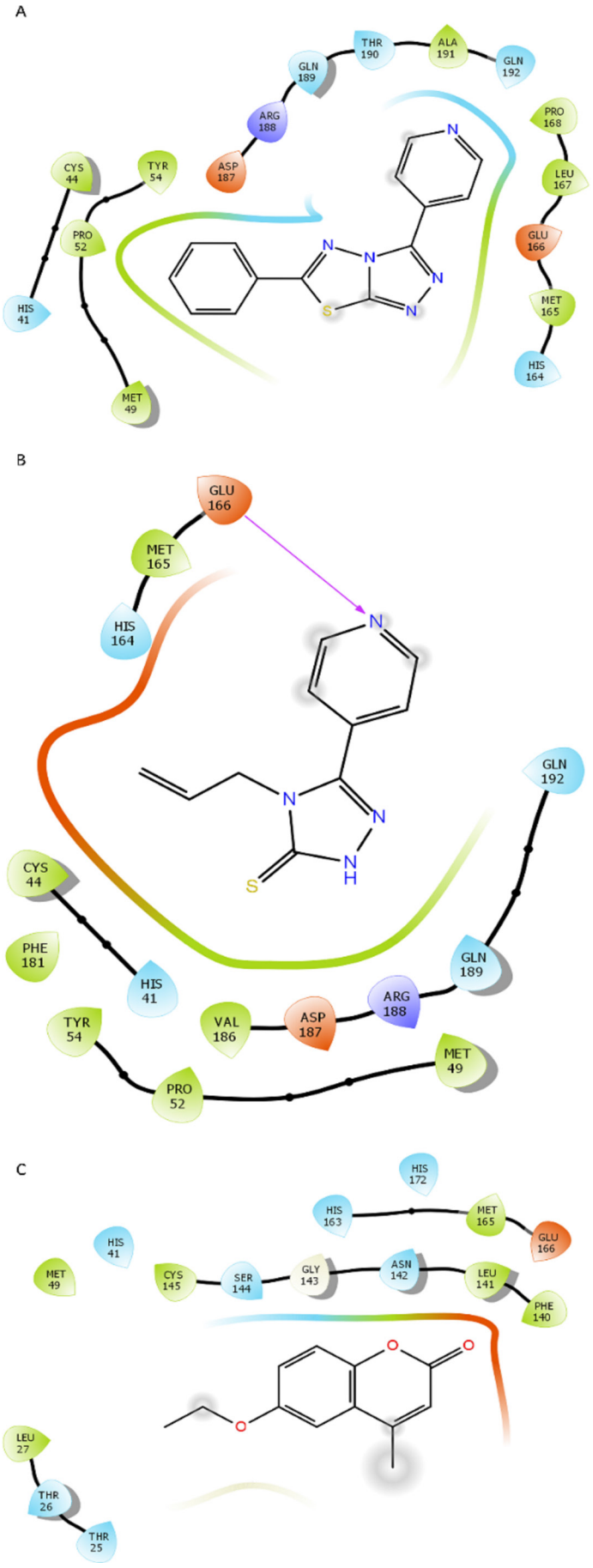


Figure 1. 2D interactions diagram for our compounds (A:1a, B:1b, C:1c) at the active site of 6LU7

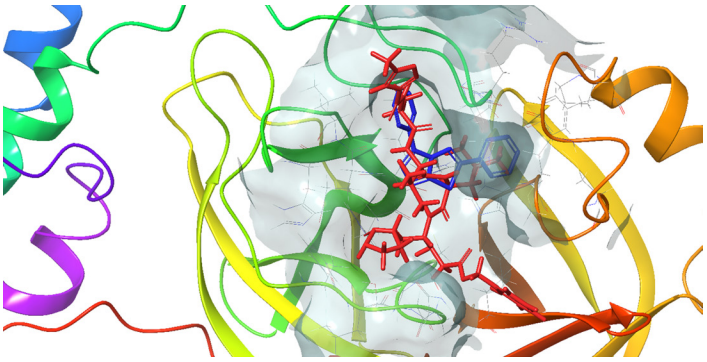


Figure 2. Compounds 1a (blue) and N3 (red) are presented in the COVID-19 main protease (PDB ID: 6LU7) binding cavity (molecular surface rendered in turquoise)

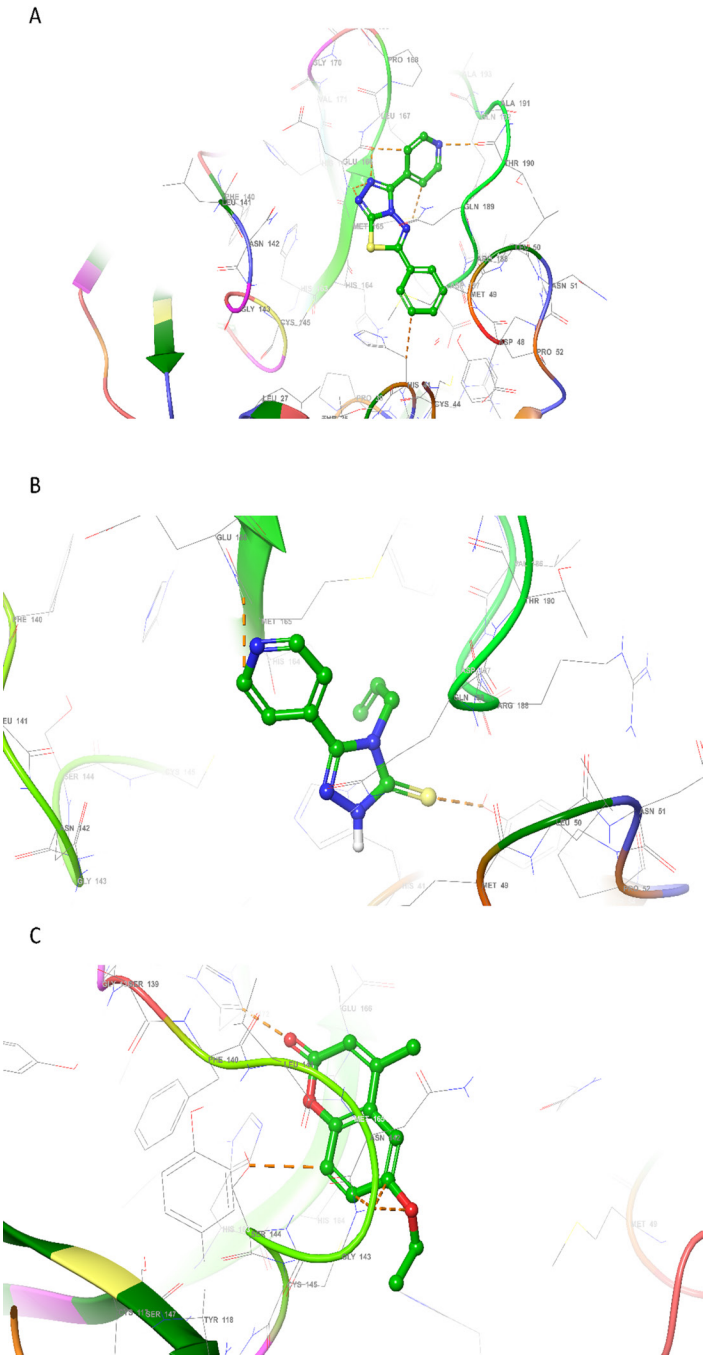


Figure 3. 3D interactions for our compounds (A:1a, B:1b, C:1c) at the binding cavity of 6LU7

Table 5. Molecular docking binding scores of some compounds, within the COVID-19 main protease in complex with an inhibitor N3 (PDB ID: 6LU7) active site. Residues participating H-bonds with the compounds are shown

Compound	Autodock Result			Vina Result
	H-bonds	Estimated Inhibition Constant, Ki	Best Docking Score Estimated Free Energy of Binding (kcal/mol)	Best Docking Score
1a	-	1.04 µM	-8.16	-7.3
1b	Glu166.	128.59 µM	-5.31	-5.5
1c	-	29.21 µM	-6.19	-5.9
Favipiravir RTP	Asn142, Gly143, Ser144, Cys145, Gln192.	1.13 mM	-4.02	-7.4
DCQ	Glu166.	6.23 µM	-7.10	-6.0
DHQC	Thr190.	7.07 µM	-7.03	-6.1
BDCQ	Asn142, Glu166.	2.87 µM	-7.56	-5.8
GS-441524	Cys145, Glu166.	702.64 µM	-4.30	-7.3

Favipiravir RTP: Favipiravir Ribosyl triphosphate, GS-441524: Remdesivir Active Metabolite, DCQ: Desethylchloroquine, DHQC: Desethylhydroxychloroquine, BDCQ: Bisdesethylhydroxychloroquine, mM: millimolar, µM: micromolar

Discussion

In particular, the reason for the low docking scores of active metabolites with triphosphate may be the reduction of the Autodock4 algorithm power by increasing the number of rotating bonds. On the other hand, there was no such low level for Autodock Vina docking scores [40]. The results of molecular docking studies were exhibited to be convenient for the results of the ADME predictions studies. When Autodock4 docking scores were examined, it was observed that the results of hydroxychloroquine metabolites, which are relatively small among our compounds and prodrug metabolites compared to others, and which do not contain triphosphate so contain less rotatable bonds, are closer.

Conclusion

A COVID-19 main protease inhibitor activities of several promising drugs with them active metabolites and some compounds in different structures that we had previously synthesized, in silico ADME prediction and molecular docking studies, were evaluated. In silico ADME prediction studies showed that the compounds 1a, 1b, and 1c were drug-likeness in terms of most of the physicochemical parameters and they possessed generally favorable pharmacokinetic properties. When the number of H-bond acceptors (1a: 4, 1b: 2, 1c: 3) is evaluated, it can be said to be related to the docking score (1a: -8.16/-7.3, 1b: -5.31/-5.5, 1c: -6.19/-5.9). Molecular docking studies exhibited the interaction mode of all ligands with COVID-19 main protease including hydrophobic interactions and/or hydrogen bonds. It can be expected that the activity will increase as the number of groups that will make H-bond in these previously synthesized compounds bearing the nitrogen atom and carbonyl or ether structure in the ring. When the ADME predictions especially lead-likeness with drug-likeness and docking scores were evaluated, Compound 1a continues to show hope as a COVID-19 main protease inhibitor agent, suggesting that this aspect should be improved.

Acknowledgments
Thanks to the free software and internet tools manufacturers and developers used in this study.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
The author declared that this study has received no financial support.

Ethical approval
No ethical approval is needed for this research.

References

1. Chen Y, Liu Q, Guo D. Emerging coronaviruses: Genome structure, replication, and pathogenesis, J Med Virol. 2020;92:418-23.
2. De Wilde AH, Snijder EJ, Kikkert M, et al. Host factors in coronavirus replication, roles of host gene and non-coding RNA expression in virus infection. Springer. 2017;1-42.
3. Wang LF, Shi ZL, Zhang SY, et al. Review of bats and SARS, Emerg Infect Dis. 2006;12:1834-40.
4. Ge XY, Li JL, Yang XL, et al. Isolation and characterization of a bat SARSlike coronavirus that uses the ACE2 receptor, Nature. 2013;503:535.
5. Shi J, Wen Z, Zhong G, et al. Susceptibility of ferrets, cats, dogs, an d other domesticated animals to SARS–coronavirus 2, Science. 2020;7015.

6. Zhang Q, Zhang H, Huang K, et al. SARS-CoV-2 neutralizing serum antibodies in cats: a serological investigation. Bio Rxiv. 2020;021196.
7. Qiu-Hua Y. Li HM, Wang N, et al. New coronavirus-infected pneumonia engulfs wuhan, span style='display:none'>8 Asian Toxicol Res. 2020:2;1-7.
8. Chen X. Xu P, Wang J, et al. Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission, Science China. Life Sci. 2020:23;457-60.
9. Guarner J. Three emerging coronaviruses in two decades. Am J Clin Pathol. 2020;153:420-1.
10. Liu C, Zhou Q, Li Y, et al. Research and development on therapeutic agents and vaccines for COVID-19 and related human coronavirus diseases. ACS Cent Sci. 2020:6;315-31.
11. Uddin M, Mustafa F, Rizvi TA, et al. SARS-CoV-2/COVID-19: Viral genomics, epidemiology, vaccines, and therapeutic interventions. Viruses. 2020:12;526.
12. Serdar D, Busecan A, Berna D, et al. Screening of clinically approved and investigation drugs as potential inhibitors of COVID-19 main protease. A Virtual Drug Repurposing Study. 2020.
13. Li G, De Clercq E. Therapeutic options for the 2019 novel coronavirus (2019-nCoV), Nature reviews. Drug discovery. 2020:19;149-50.
14. Khaerunnisa S, Kurniawan H, Awaluddin R, et al. Soetjipto, potential inhibitor of COVID-19 main protease (Mpro) from several medicinal plant compounds by molecular docking study, Prepr. Online: 13 March 2020.
15. Corsello SM, Bittker JA, Liu Z, et al. The drug repurposing hub: a nextgeneration drug library and information resource, Nature medicine. 2017:23;405-8.
16. Adams CP, Brantner VV. Estimating the cost of new drug development: is it really $802 million? Health Affairs. 2006:25;420-8.
17. Jin Z, Du X, Xu Y, et al. Structure of Mpro from COVID-19 virus and discovery of its inhibitors. Nature. 2020.
18. Kaitin, KI. Obstacles and opportunities in new drug development, Clin Pharmacol Ther. 2008:83;210-2.
19. Pires DEV, Blundell TL, Ascher DB, pkCSM: Predicting small-molecule pharmacokinetic and toxicity properties using graph-based signatures. J Med Chem. 2015:58:4066-72.
20. Mishra S, Dahima R. In vitro adme studies of tug-891, a gpr-120 inhibitor using swiss adme predictor, J Drug Delivery Therapeutics. 2019:9-2:366-9.
21. Daina A, Michielin O, Zoete V. SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules, Scientific Reports. 2017:7;42717.
22. Morris GM, Huey R, Lindstrom W, et al. AutoDock4 and AutoDockTools4: Automated docking with selective receptor flexibility, J Comput Chem. 2009:30;2785-91.
23. Trott O, Olson AJ. AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading, J Comput Chem. 2010:31;455-61.
24. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020:395;497-506.
25. Peiris JSM, Chu CM, Cheng VCC, et al. Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. Lancet . 2003:361;1767-72.
26. Yeleswaram S, Smith P, Burn T, et al. Inhibition of cytokine signaling by ruxolitinib and implications for COVID-19 treatment, Clin Immunol. 2020:108517.
27. Chen L, Xiong J, Bao L, Shi Y. Convalescent plasma as a potential therapy for COVID-19, Lancet Infect Dis. 2020:20;398-400.
28. Holshue ML, DeBolt C, Lindquist S, et al. First case of 2019 novel coronavirus in the United States, N Engl J Med. 2020;382:929-36.
29. Cortegiani A, Ingoglia G, Ippolito M, et al. A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19, J Crit Care. 2020;57:279-83.
30. Colson P, Rolain JM, Raoult D. Chloroquine for the 2019 novel coronavirus SARS-CoV-2, Int J Antimicrobial Agents. 2020:55;105923.
31. Cai Q, Yang M, Liu D, et al. Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study, Engineering. 2020;6:1192-8.
32. Al-Tawfiq JA, Al-Homoud AH, Memish ZA. Remdesivir as a possible therapeutic option for the COVID-19, Travel Med Infect Dis. 2020;34:10161.
33. Mehra MR, Desai SS, Ruschitzka F, et al. Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. Lancet. 2020.
34. Jin Z, Smith LK, Rajwanshi VK, et al. The ambiguous base-pairing and high substrate efficiency of T-705 (Favipiravir) Ribofuranosyl 5'-triphosphate towards influenza A virus polymerase, PLoS One. 2013:8;68347.
35. Williams SB, Patchen LC, Churchill FC. Analysis of blood and urine samples for hydroxychloroquine and three major metabolites by highperformance liquid chromatography with fluorescence detection. J Chromatogr.1988;433:197-206.
36. Murphy BG, Perron M, Murakami E, et al. The nucleoside analog GS-441524 strongly inhibits feline infectious peritonitis (FIP) virus in tissue culture and experimental cat infection studies, Vet Microbiol. 2018:219;226-33.
37. Cansız A, Cetin A, Orek C, et al. 6-Phenyl-3-(4-pyridyl)-1,2,4-triazolo-[3,4-b][1,3,4]thiadiazole: Synthesis, experimental, theoretical characterization and biological activities, Spectrochim Acta A Mol Biomol Spectrosc. 2012;201297:606-15.
38. Cansız A, Orek C, Koparir M, et al. 4-Allyl-5-pyridin-4-yl-2,4-dihydro-3H-1,2,4-triazole-3-thione: Synthesis, experimental and theoretical characterization, Spectrochim Acta A Mol Biomol Spectrosc. 2012:9;1136-45.
39. Celikezen FC, Orek C, Parlak AE, et al. Synthesis, structure, cytotoxic and antioxidant properties of 6-ethoxy-4-methylcoumarin, J Molecular Structure. 2020:1205;127577.
40. Dhanik A, McMurray JS, Kavraki LE. DINC: a new AutoDock-based protocol for docking large ligands, BMC Struct Biol. 2013:13 (Suppl 1);11.

Supplemental

Supporting Information: Computational Studies Results

ADME Predictions and Molecular Docking Study of Some Compounds and Drugs as Potential Inhibitors of COVID-19 Main Protease: A Virtual Study as Comparison of Computational Results

Harun Uslu, Pelin Koparir, Kamuran Sarac and Arzu Karatepe

Correspondence to: Pelin KOPARIR (E-mail: mpelin23@hotmail.com)

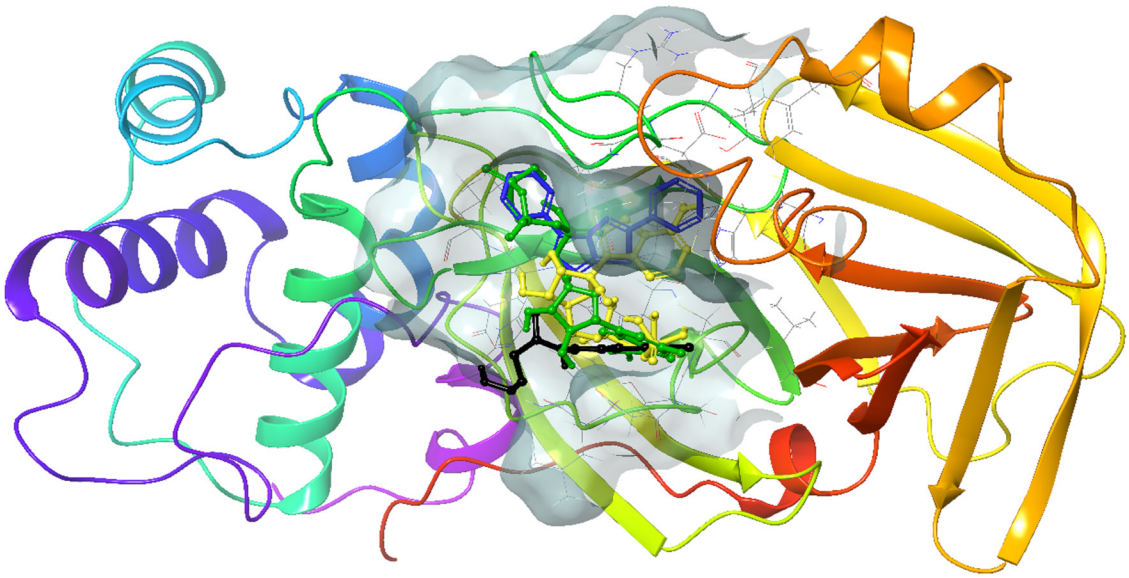


Figure. S1. Compounds 1a (blue), GS-441524 (yellow), Favipiravir RTP (green) and BDCQ (black) are presented in the COVID-19 main protease (PDB ID: 6LU7) binding cavity (molecular surface rendered in turquoise).

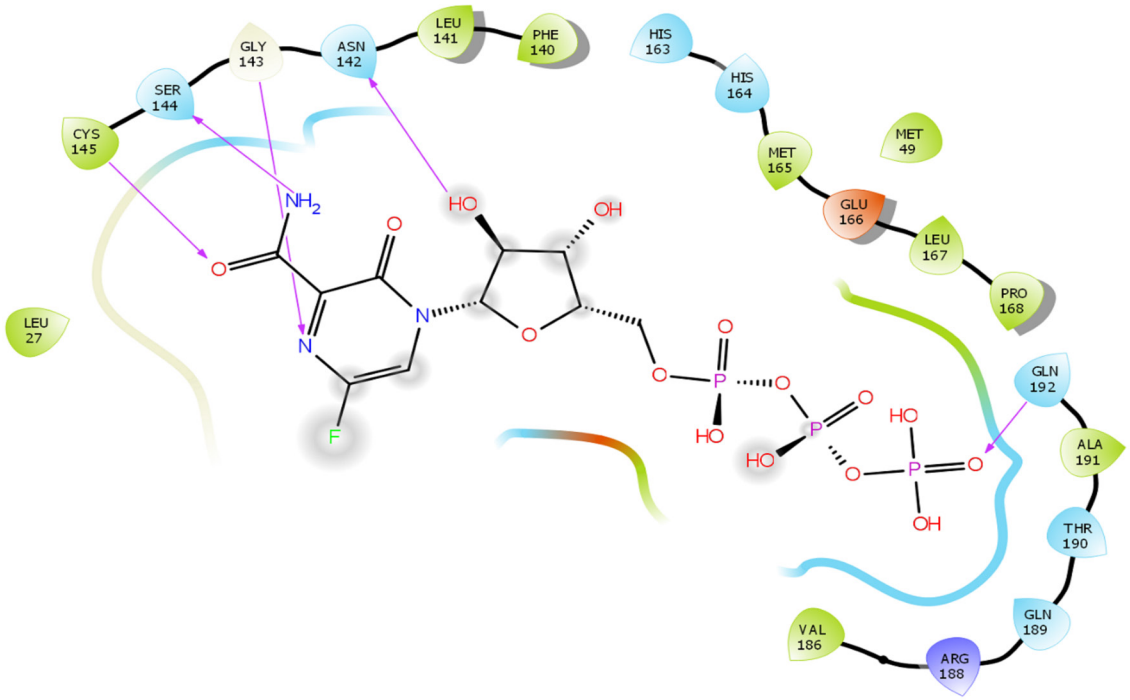


Figure. S2. 2D interactions diagram for Favipiravir RTP at active site of 6LU7

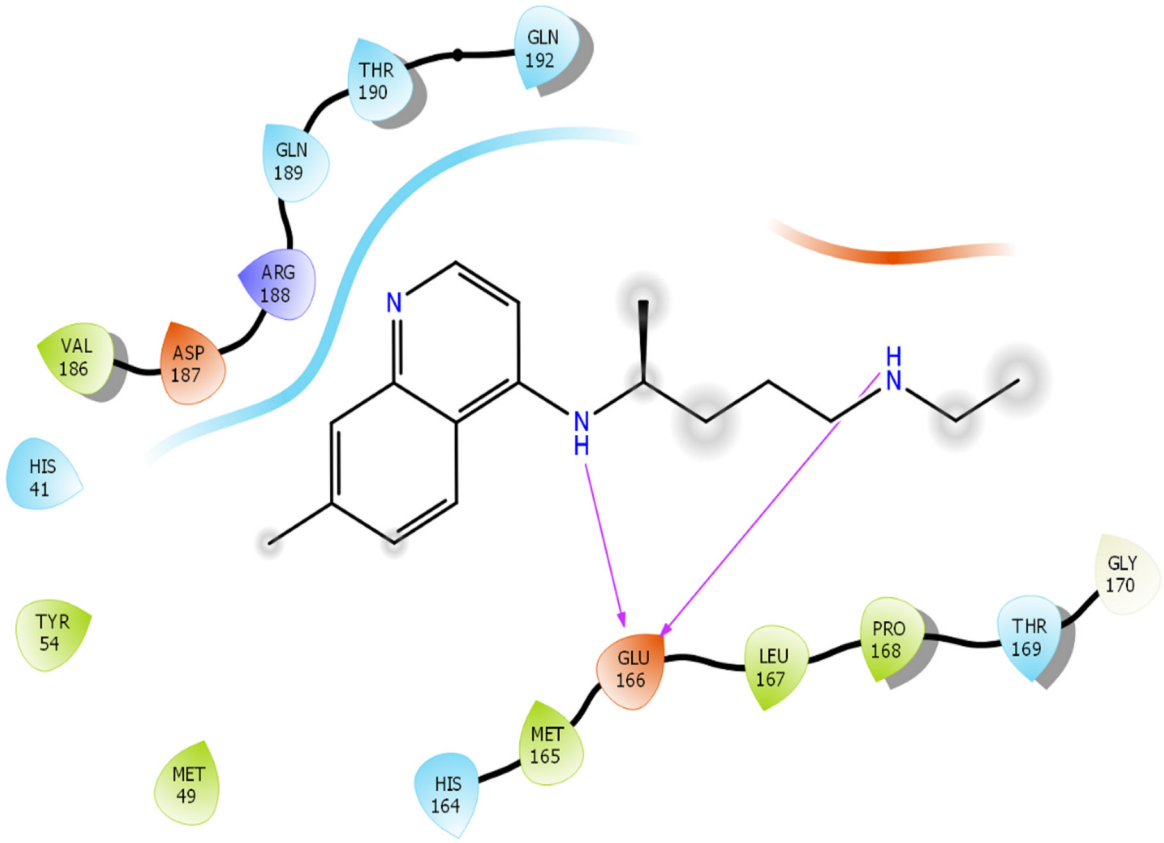


Figure. S3. 2D interactions diagram for DCQ at active site of 6LU7

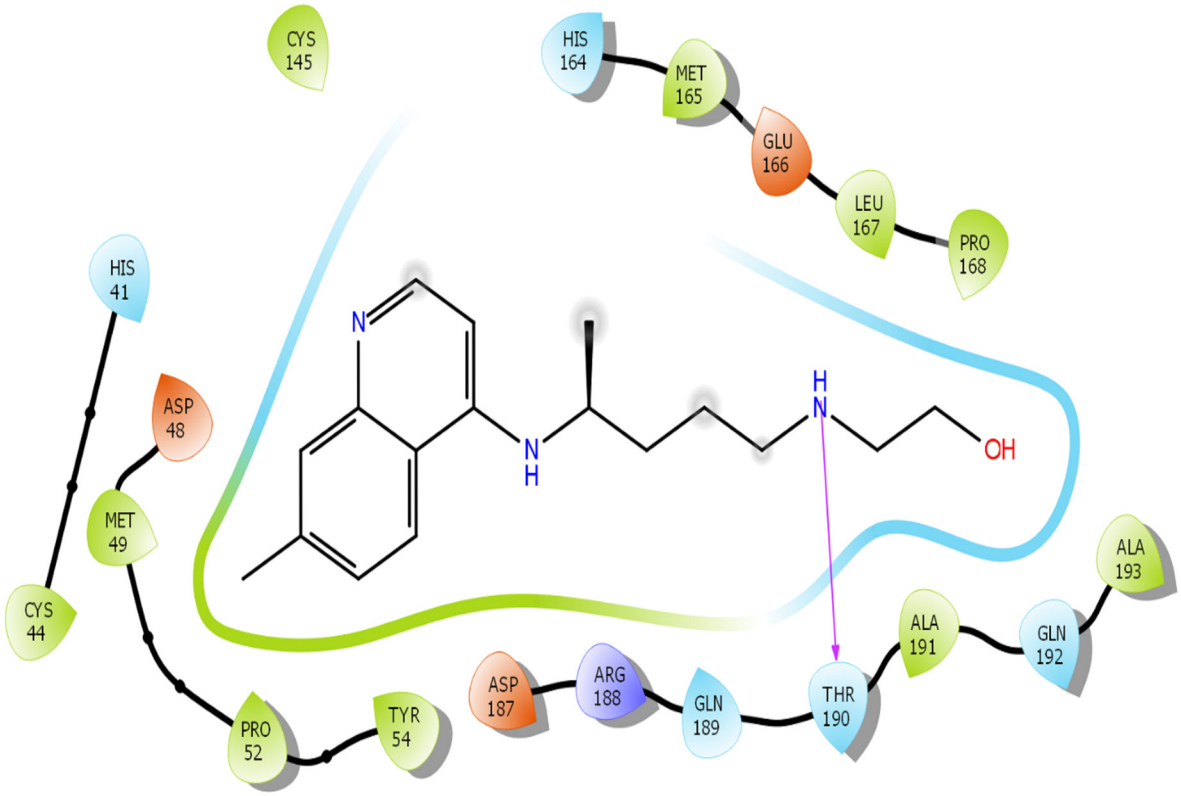


Figure. S4. 2D interactions diagram for DHQC at active site of 6LU7

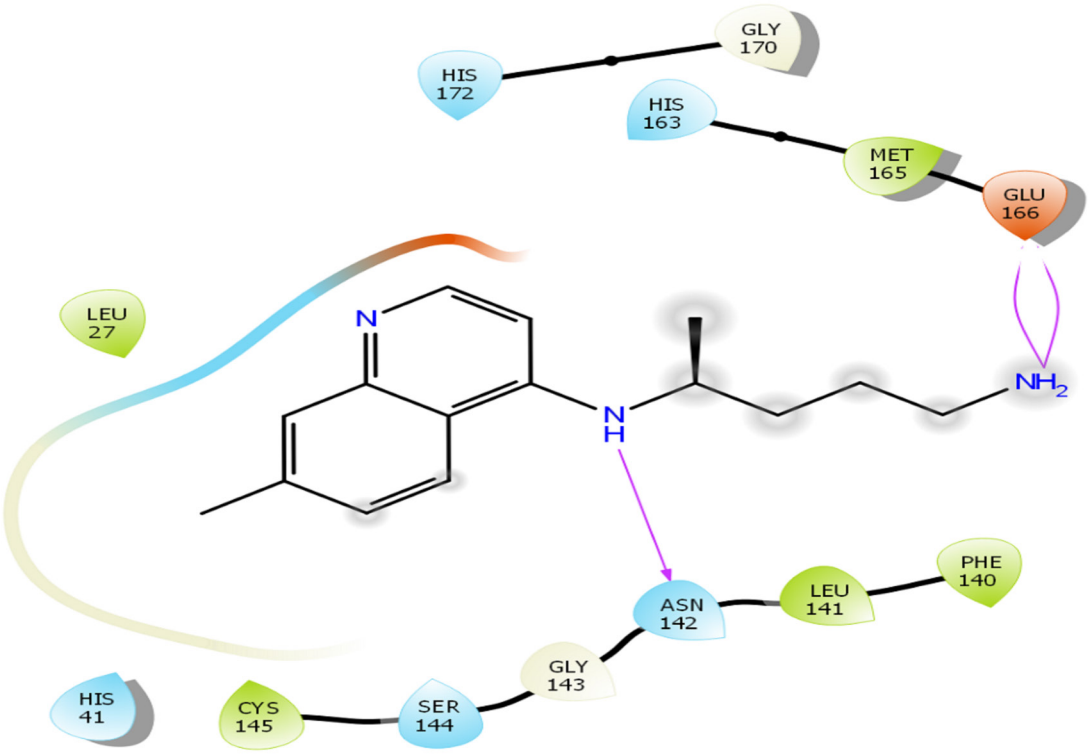


Figure. S5. 2D interactions diagram for BDCQ at active site of 6LU7

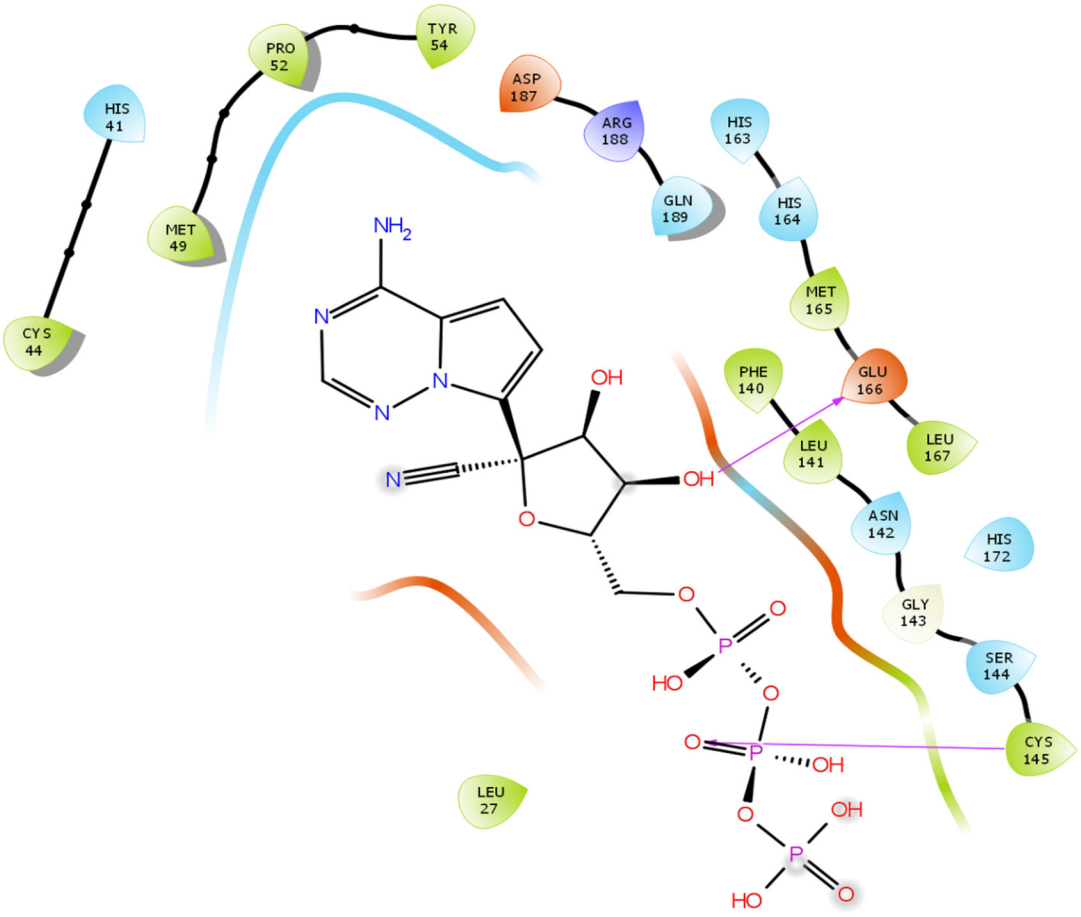


Figure. S6. 2D interactions diagram for GS-441524 at active site of 6LU7

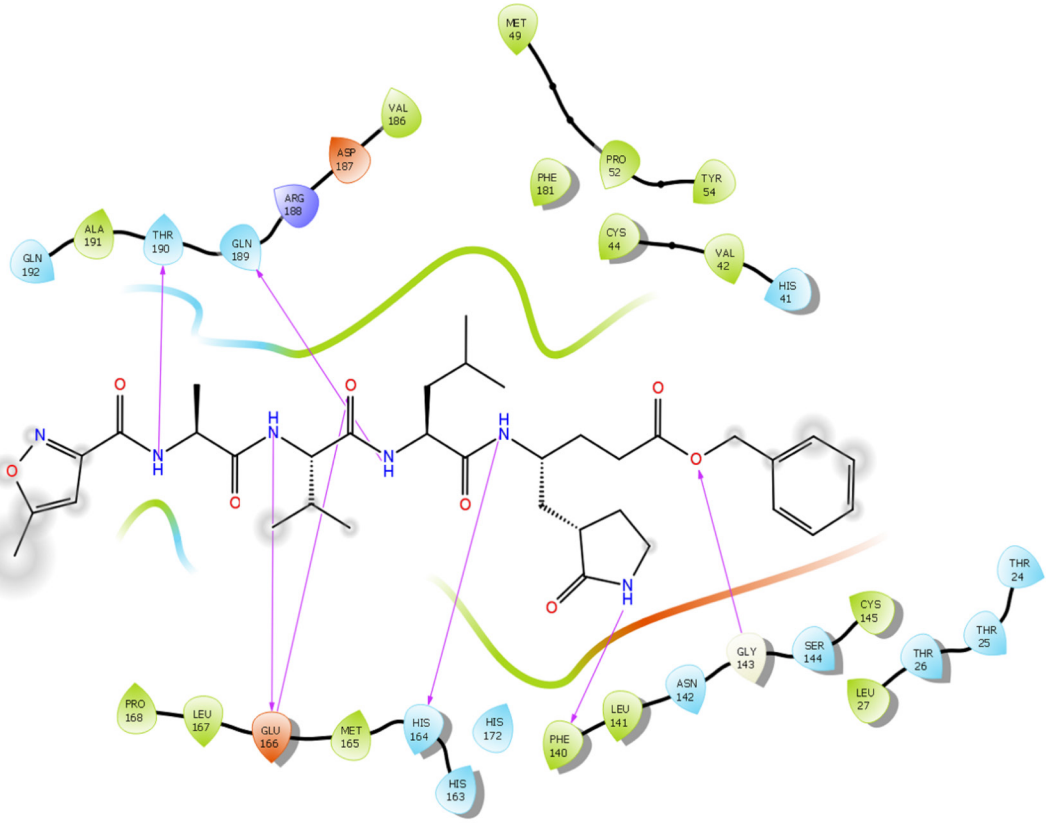


Figure. S7. 2D interactions diagram for N3 at active site of 6LU7

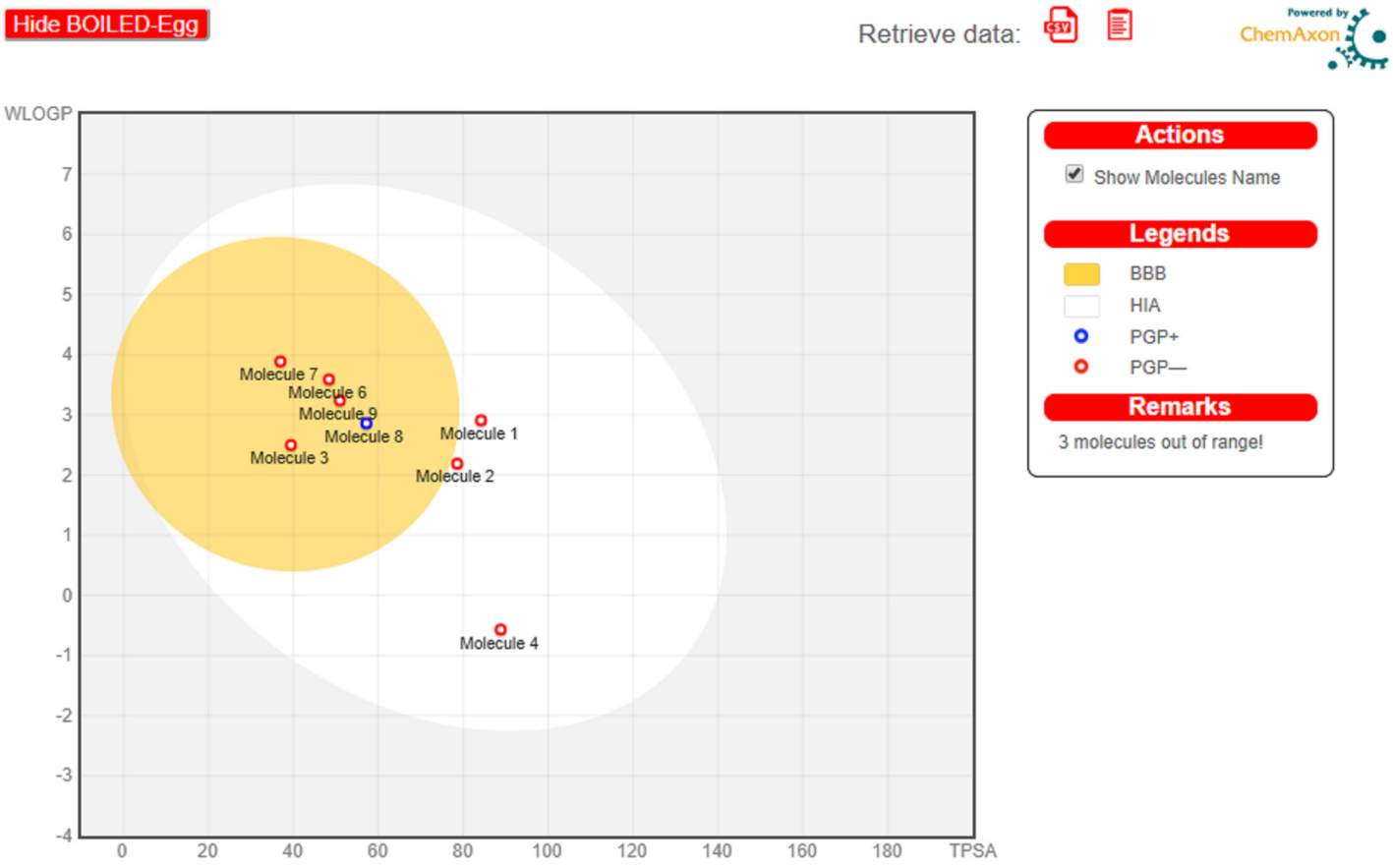


Figure. S8. BOILED-Egg for all ligans

Table S1. Number of Compounds for ADME Predictions (SwissADME)

1a	Molecule 1
1b	Molecule 2
1c	Molecule 3
Favipiravir	Molecule 4
Favipiravir RTP	Molecule 5
Hydroxychloroquine	Molecule 6
DCQ	Molecule 7
DHQC	Molecule 8
BDCQ	Molecule 9
Remdesivir	Molecule 10
GS-441524	Molecule 11

Available online at www.medicinescience.org

ORIGINAL ARTICLE

Medicine Science International Medical Journal

Medicine Science 2021;10(1):31-5

The effects of comorbidity factors on the prognosis in geriatric sepsis patients in the intensive care unit

Ozkan Gorgulu[1], Mehmet Nuri Kosar[2]

[1]*Antalya Training and Research Hospital, Department of Anesthesiology and Reanimation, Antalya, Turkey*
[2]*Antalya Training and Research Hospital, Department of General Surgery, Antalya, Turkey*

Received 10 July 2020; Accepted 21 August 2020
Available online 20.11.2020 with doi: 10.5455/medscience.2020.07.133

Abstract

Mortality rates in geriatric sepsis patients are very high in the intensive care unit. The aim of our study is to evaluate the prognosis of geriatric patients diagnosed with sepsis according to age groups in the intensive care unit. The data of 189 geriatric patients were reviewed retrospectively. Elixhauser Comorbidity index was calculated. The patients were divided into three different age groups young-old (65-74 years), middle-old (75-84 years) and oldest-old (85 years and above). The prognosis was evaluated in patients with Elixhauser Comorbidity index score ≥ 10. The mean length of ICU stays of those aged over 85 years (21.10±23.75) and 75-84 years (17.45±20.59) was compared with that of 65-74-year-old patients (10.23±12.19). Young elderly patients had shorter lenght of ICU stay than other groups (95% confidence interval) (p=0,01 p<0,05). It was found that in terms of length of ICU stay and age did not affect prognosis in the sepsis patients in 3 different geriatric age groups (p>0.05). Oldest-old and middle-old patients' length of stay in the intensive care unit for a longer period than young-old patients. Mortality rate in geriatric sepsis patients with Elixhauser Comorbidity Index greater than 10 is over 70%, but ICU stay did not affect 30-day mortality.

Keywords: Geriatrics, sepsis, Intensive care units, mortality, comorbidity

Introduction

The World Health Organization defined patients aged ≥65 years as geriatric patients. Aging brings many functional and physiological deterioration, while a weakened immune system becomes susceptible to infections, such as bacteremia and sepsis [1,2], a major cause of morbidity and mortality in the geriatric age group [2]. Although a consensus on the definition of sepsis with regard to the host response to infection is available, the complexity of this response and the affected patient groups means that establishing accepted definitions of sepsis is difficult [3]. The prevalence of sepsis in geriatric patients admitted to intensive care units (ICUs) is quite high, and its prognosis varies depending on the underlying pathogen and severity of organ failure [4]. As the length of ICU stay of geriatric patients increases, they become susceptible to nosocomial infections [5]. The most common causes of nosocomial infections are urinary, nasogastric, and central venous catheters [5]. The most common tissue sources for bacteremia are the urogenital system and lungs [6,7].

***Coresponding Author:** Filiz Araz, Baskent University, Adana Dr. Turgut Noyan Training and Research Hospital, Gastroenterology, Adana, Turkey,
E-mail: filizaraz2@hotmail.com

In geriatric age groups, the most common cause of sepsis in ICUs appears to be gram-negative bacteria [8]. Geriatric patients admitted in the ICU commonly had sepsis, which has an effect on mortality [9]. Severe sepsis increases the morbidity and mortality by creating a global tissue hypoperfusion and oxidative damage [10]. The key to preventing sepsis in geriatric patients is rapid diagnosis and aggressive resuscitation [2]. This study aimed to analyze the length of ICU stay and investigate the 30-day mortality rate in geriatric patients diagnosed with sepsis in the ICU.

Material and Methods

Study Population

This study was conducted from 2008 to 2018 in accordance with the Helsinki Declaration after obtaining approval from the Ethics Committee of the Institution (Approval Date/ Protocol No: 07.11.2019-24/6). This is a single-center retrospective descriptive study conducted by scanning the electronic patient data system (SARUS) data of 6501 geriatric patients treated in the ICU of our Level 3 hospital. During the study period, among the 273 patients with sepsis followed up in the ICU, 189 (69.2%) were diagnosed with geriatric sepsis, aged ≥65 years (mean±SD: 76.68±7.09) (65-95), 50.8% (96) of them were women, and the mean length of ICU

stay was 14.87±18.44 (1-81) days.

Assessments

Patients included in the study (n=189) were divided into three geriatric age groups: young-old (65-74), middle-old (75-84), and oldest-old (≥85 years). Diagnostic criteria for sepsis; 1-Fever > 38.3 degrees C or Hypothermia < 36 degrees C core temperature 2-Change in mental status 3-White blood cell count > 12.000 or less than 4.000 4-Arterial hypoxemias (paO2 / FiO2<300). 5-Acute drop in urine output (<0.5ml/kg/hr for at least 2 hours despite fluid resuscitation, or about 35ml/hour for a 70kg person) 6-Creatinine increase > 0.5mg/dL 7-INR > 1.5 9-Platelet count < 100,000 8-Hypotension (systolic blood pressure <90mm Hg or fallen by >40 from baseline, mean arterial pressure < 70mm Hg). 9-High bilirubin values (total bilirubin >4mg/dL) 10-Glasgow coma score (GCS) <10. In the presence of infection, patients with two or more of these criteria were diagnosed as sepsis. The Elixhauser Comorbidity Index criteria include the following diseases (range -19 [less likely for in-hospital death] to 89 [more likely for in-hospital death]).

Elixhauser Comorbidity Index Score

Comorbidity Values and percentage rate

1. Congestive heart failure 7 points or 75.9%
2. Cardiac arrhythmias 5 points or 77.8%
3. Valvular disease -1 points or 83.3%
4. Pulmonary circulation disorders 4 points or 78.7%
5. Peripheral vascular disorders 2 points or 80.6%
6. Hypertension 0 points or 82.4%
7. Paralysis 7 points or 75.9%
8. Neurodegenerative disorders 6 points or 76.9%
9. Chronic pulmonary disease 3 points or 79.6%
10. Diabetes 0 points or 82.4%
11. Hypothyroidism 0 points or 82.4%
12. Renal failure 5 points or 77.8%
13. Liver disease 11 points or 72.2%
14. Peptic ulcer disease, no bleeding 0 points or 82.4%
15. AIDS/HIV 0 points or 82.4%
16. Lymphoma 9 points or 74.1% 17. Metastatic cancer 12 points or 71.3%
18. Solid tumor without metastasis 4 points or 78.7%
19. Rheumatoid arthritis/collagen vascular diseases 0 points or 82.4%
20. Coagulopathy 3 points or 79.6%
21. Obesity -4 points or 86.1%
22. Weight loss 6 points or 76.9%
23. Fluid and electrolyte disorders 5 points or 77.8%
24. Blood loss anemia -2 points or 84.3%
25. Deficiency anemia -2 points or 84.3%
26. Alcohol abuse 0 points or 82.4%
27. Drug abuse -7 points or 88.9%
28. Psychosis 0 points or 82.4%
29. Depression -3 points or 85.2%

The Elixhauser Comorbidity Index score was calculated to adjust the effects of comorbidities on clinical outcomes. Mortality and length of ICU stay were analyzed. The study included geriatric patients diagnosed with sepsis and with an Elixhauser Comorbidity Index of >10 point. Geriatric patients without sepsis and non-geriatric patients aged <65 years were excluded from the study.

Statistical analysis

Frequency and percentage values were calculated to analyze data related to the descriptive statistics of the groups. Chi-square analysis (Fisher's exact test) was performed to analyze the diagnoses received according to patient characteristics. The Bonferroni method was used to identify the group with differences among the three groups. In this study, the correlation analysis was performed to analyze the correlation between age and length of stay (days) according to age groups. Analysis of variance test was performed to analyze whether the mean length of stay differs according to age groups, and the Sidak binary comparison test was performed to determine differences among groups. In this study, an independent sample t-test was performed to analyze the difference in the length of hospital stay according to mortality rate. Bar charts were drawn to present data. In the study, p-values of <0.05 were considered statistically significant. Analyses were performed using the SPSS 22.0 software package.

Power analysis

The study consisted of patients aged >65 years diagnosed with sepsis and hospitalized in the ICU between 01/01/2008 and 31/12/2018 in a tertiary care hospital. The group of patients included in this study would provide 0.90 sampling power at an effect size of 0.40 (in studies, 0.70 sampling power and an effect size of <0.10 is expressed as small, 0.25 as medium, and 0.40 as large effect size). In summary, this study has sufficient power and level of effect size. The power level and effect size calculated in this study were determined using the G* Power Version 3.1.7.

Results

Rates in the geriatric sepsis groups were different from that of other geriatric diagnostic groups. The incidence of sepsis in geriatric patients hospitalized in the intensive care unit: 84(3.2%) young-old, 72(2.7%) middle-aged, and 33(3.0%) elderly (p=0.01 p<0.05). Among the 189 patients admitted in the ICU, 93(49.2%) were men and 96(50.8%) were women. The number of patients in three study groups was as follows: 84(44.5%) young-old (69.92±2.48), 72(38.0%) middle-aged (79.62±2.28), and 33 (17.5%) elderly (87.57±2.57). Among them, 144(76.2%) died, whereas 45(23.8%) were discharged from the ICU (Table 1). The length of hospital stays (days) of patients hospitalized in the ICU diagnosed with sepsis varied according to age groups. In the study, the mean length of hospital stay of patients aged >85 (21.10±23.75)

and 75-84(17.45±20.59) years was statistically higher than that of patients aged 65-74 (10.23±12.19) (95% confidence interval) (p=0.01, p<0.05) (Table 2). Mortality rates of patients did not vary according to age groups: 77.0%(65) aged 65-74 years, 76.8%(56) aged 75-84 years, and 69.6%(23) aged ≥85 years died (p=0.67, p>0.05) (Figure 1). In the age group 65-74, 75-84, ≥85 years, age and length of hospital stay were not correlated with the prognosis (r=-0.06, p=0.59, p>0.05; r=-0.09, p=0.45, p>0.05; and r=-0.05, p=0.78, p>0.05, respectively). In the age group 65-74, 75-84, and ≥85 years who were discharged, age and length of hospital stay were not correlated with prognosis (r=-0.03, p=0.91, p> 0.05; r=-0.02, p=0.96, p>0.05; and r=-0.01, p=0.99, p>0.05, respectively). In the age group 65-74, 75-84, and ≥85 years who died, age and length of hospital stay were not correlated with prognosis (r=-0.04, p=0.74, p> 0.05; r=-0.05, p=0.72, p>0.05; and r=0.05, p=0.73, p>0.05, respectively) (Figure 2). The difference between the prognosis and length of hospital stay was not significant in the geriatric group aged 65-74 (p=0.29, p>0.05), 75-84 (p=0.06, p>0.05), and >85 (at 95% confidence interval) (p=0.09, p>0.05) years (Figure 3).

Table 1. Demographic characteristics of patients

Gender	**n**	**%**
Male	93	49.2
Female	96	50.8
Age	**n**	**%**
65-74 years of age	84	44.4
75-84 years of age	72	38.1
85 years of age and above	33	17.5
Mean Age by Age Group	**Mean age**	**s.d.**
65-74 years of age	69.92	2.48
75-84 years of age	79.62	2.28
Above 85 years of age	87.57	2.57
Survival	**n**	**%**
Exitus	144	76.2
Survived	45	23.8

Table 2. Length of stay by age groups

Measurement	**Group**	**n**	**x**	**s.d.**	**Confidence Interval 95%**		**p**
					Below	**Above**	
Length of stay	65-74 years of age	84	10.23	12.19	7.47	13.00	%
	75-84 years of age	72	17.45	20.59	12.39	22.52	44.4
	Above 85 years of age	33	21.10	23.75	12.23	29.97	38.1

** Analysis of variance was carried out. * Indicates a significant difference

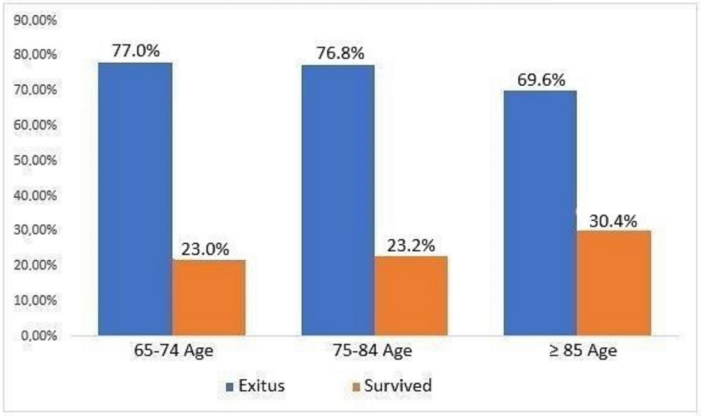


Figure 1. Mortality and survival rates in patients with sepsis

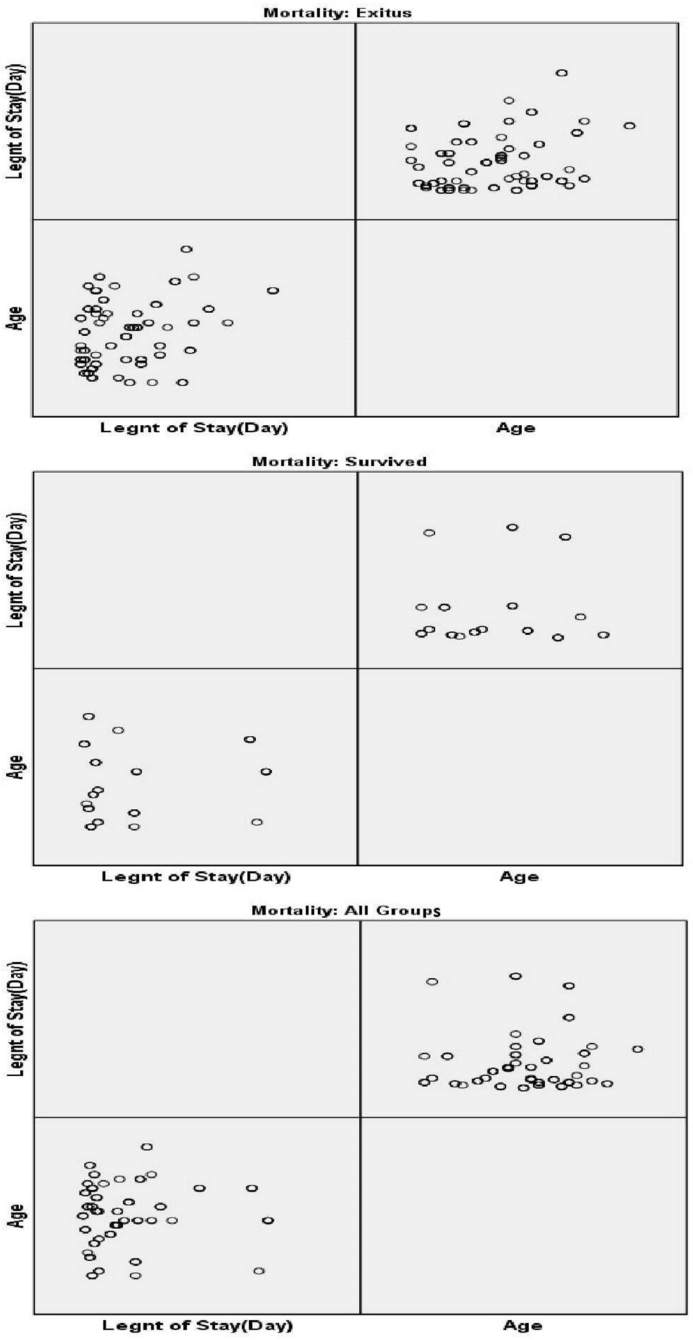


Figure 2. Correlation of age length of hospital stay with prognosis

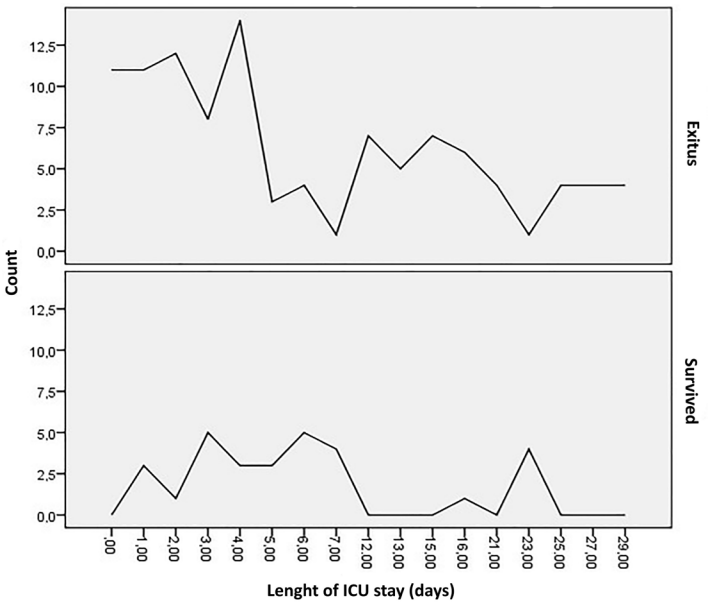


Figure 3. Correlation between length of ICU stay and prognosis

Discussion

The incidence of sepsis in geriatric ICU patients varies between 3.0% and 3.2%. The fact that 189(69.2%) of 273 patients diagnosed with sepsis in the ICU from 2008 to 2018 were in the geriatric age group shows the significance of sepsis in the geriatric age group in ICU patients. There are many scoring systems such as qSOFA, EWS, SIRS [11], APACHE II [12] that evaluate the lenght of hospital stay and mortality rates of patients diagnosed with sepsis in the intensive care unit. Because the Elixhauser Comorbidity Index is comprehensive, it can make better estimates than other scoring systems in evaluating in the lenght ICU stay and mortality rate due to the increase in the rate of multimorbidity in geriatric age groups. The mortality rate is very high in three different geriatric age groups diagnosed with sepsis according to the Elixhauser Comorbidity Index of >10 in the ICU. The fact that the 30- day mortality rate of three different geriatric age groups diagnosed with sepsis in the ICU is >70% indicates that sepsis should be diagnosed and treated aggressively in the ICU. In a prospective study evaluating elderly and young adults in the ICU, the 28-day mortality rate was found to be 24.8% [10]. Mortality due to sepsis increases twofold in geriatric patients aged >70 years as compared to patients aged <70 years [13,14]. While aging is associated with weakened immune system [1,2], elderly patients diagnosed with sepsis are thought to increase immune system suppression and mortality by increasing susceptibility to secondary infections [9]. In an international prospective study, hospital-and ICU-acquired infections have been microbiologically documented as the more common cause of sepsis than community-acquired infections [15]. In another study conducted in the geriatric unit, venous catheters, immobilization, swallowing disorders, and nosocomial infections occurring in elderly patients hospitalized due to cancer have been associated with mortality [5]. In another study, three comorbidities were associated with mortality in geriatric patients aged >65 years, indicating coagulopathy, fluid electrolyte disorder, peripheral vascular diseases, and chronic lung diseases [16]. High mortality due to sepsis increases with additional factors, such as winter season, immobilization, chronic heart failure, and respiratory failure [17]. These factors, which lead to increased mortality, are commonly observed in the geriatric age groups. In our study, geriatric patients aged >75 years diagnosed with sepsis were generally considered to have a significantly prolonged length of ICU stay. Although the presence of a significant correlation between advanced age and prolonged length of ICU stay suggested to contribute to increased secondary infections and mortality in geriatric intensive care patients [9], the length of ICU stay does not have an increasing effect on mortality [17]. In our study, the length of ICU stay among three different geriatric age groups diagnosed with sepsis did not have an effect on prognosis, although it increased with age. In a retrospective observational study including male patients aged >50 years, the incidence of sepsis has been found to increase between 2007 and 2016, whereas the in-hospital mortality rate, length of hospital stay, and admission rate to the ICU decreased [18]. In a prospective cohort study on geriatric ICU patients diagnosed with sepsis, the 1-month mortality rate of 60% [19] necessitated early diagnosis, aggressive treatment, and early intensive care support, especially in geriatric age groups.

Conclusion

The incidence of sepsis in geriatric patients hospitalized in the intensive care unit and 30-day mortality rate are extremely high in geriatric patients admitted to the ICU. The mortality rate of geriatric sepsis patients with Elixhauser Comorbidity Index of >10 is >70%. In geriatric patients diagnosed with sepsis, the length of ICU stay increases with age; however, age and length of ICU stay have no effect on the 30-day mortality.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
All authors declare no financial support.

Ethical approval
This study was conducted in accordance with the ethical principles stated in the "Declaration of Helsinki" and permission was obtained from Ethics Committee of Antalya Training and Research Hospital for the use of patient data for publication purposes (07.11.2019-24/6).

References

1. Esme M, Topeli A, Yavuz BB et al. Infections in the Elderly Critically-Ill Patients. Front Med (Lausanne). 2019;6:118.
2. Yahav D, Schlesinger A, Shaked H et al. Clinical presentation, management and outcomes of Staph aureus bacteremia (SAB) in older adults. Aging Clin Exp Res. 2017;29:127–33.
3. Vincent JL, Korkut HA. Defining sepsis. Clin Chest Med. 2008;29:585-90.
4. Vasilevskis EE, Chandrasekhar R, Holtze CH et al. The cost of ICU delirium and coma in the intensive care unit patient. Med Care. 2018;56:890 –7.
5. Buetti N, Timsit JF. Management and prevention of central venous catheter-related infections in the ICU. Semin Respir Crit Care Med. 2019;40:508–23.
6. Pletz MW, Weis S, Forstner C et al. Urologe A. 2018;57:79–92.
7. De Freitas Caires N, Gaudet A, Portier L et al. Endocan, sepsis, pneumonia, and acute respiratory distress syndrome. Crit Care. 2018;26;22:280.
8. Leibovici-Weissman Y, Tau N, Yahav D. Bloodstream infections in the elderly: what is the real goal?. Aging Clin Exp Res. 2019
9. van Vught LA, Klein Klouwenberg PM, Spitoni C et al. Incidence, Risk Factors, and Attributable Mortality of Secondary Infections in the Intensive Care Unit After Admission for Sepsis. JAMA. 2016;315:1469-79.
10. Yin M, Liu X, Chen X et al. Ischemia-modified albumin is a predictor of

short-term mortality in patients with severe sepsis. J Crit Care. 2017;37:7-12.

11. Siddiqui S, Chua M, Kumaresh V et al. A comparison of pre ICU admission SIRS, EWS and q SOFA scores for predicting mortality and length of stay in ICU. J. Crit. Care. 2017;41:191–3.

12. Basile-Filho A, Lago AF, Menegueti MG et al. The use of APACHE II, SOFA, SAPS 3, C-reactive protein/albumin ratio, and lactate to 19 predict mortality of surgical critically ill patients: A retrospective cohort study. Med (Baltim). 2019;98:e16204.

13. Warmerdam M, Stolwijk F, Boogert A et al. Initial disease severity and quality of care of emergency department sepsis patients who are older or younger than 70 years of age. PLoS One. 2017;12:e0185214.

14. de Groot B, Stolwijk F, Warmerdam M, et al. The most commonly used disease severity scores are inappropriate for risk stratification of older emergency department sepsis patients: an observational multi-centre study. Scand J Trauma Resusc Emerg Med. 2017;25:91.

15. Le G Jr, Alberti C, Brun BC. Epidemiology of infection and sepsis in intensive care unit patients. Bull Acad Natl Med. 2004;188:1115-25.

16. Ho VP, Schiltz NK, Reimer AP et al. High-Risk Comorbidity Combinations in Older Patients Undergoing Emergency General Surgery. J Am Geriatr Soc. 2019;67:503-10.

17. Degoricija V, Sharma M, Legac A et al. Survival analysis of 314 episodes of sepsis in medical intensive care unit in university hospital: impact of intensive care unit performance and antimicrobial therapy. Croat Med J. 2006;47:385-97.

18. Oh SY, Cho S, Kim GH et al. Incidence and outcomes of sepsis in Korea: A nationwide cohort study from 2007 to 2016. Crit Care Med. 2019;47:e993-e8.

19. Rowe T, Araujo KL, Van Ness PH et al. Outcomes of older adults with sepsis at admission to an intensive care unit. Open Forum Infect Dis. 2016;3:ofw010.

Available online at www.medicinescience.org

ORIGINAL ARTICLE

Medicine Science International Medical Journal

Medicine Science 2021;10(1):36-9

Effect of montelukast treatment on adenoid hypertrophy and sleep quality in pediatric patients

Isil Cakmak Karaer[1], Ayla Cimen[2]

[1]Malatya Traning and Research Hospital, Clinic ENT, Malatya, Turkey
[2]Malatya Traning and Research Hospital, Clinic of Radiology, Malatya, Turkey

Received 05 October 2020; Accepted 11 October 2020
Available online 13.10.2020 with doi: 10.5455/medscience.2020.10.207

Abstract

Adenoid vegetation is part of lymphoid tissue located in the upper respiratory tract. When adenoid tissue becomes hypertrophied, it may cause narrowing of the respiratory tract and complications. Generally, treatment of adenoid hypertrophy is surgical; however, currently reducing the size of adenoid hypertrophy with the leukotriene receptor blocker of montelukast is evaluated among treatment choices apart from surgery. The aim of the study was to assess whether montelukast treatment is an alternative to surgical treatment or not. The study included a total of 50 pediatric patients. Adenoid tissue size was evaluated endoscopically and radiographically. Patients were divided into two groups based on closure of the nasopharynx by adenoid tissue. Group 1 comprised adenoid hypertrophy cases with the choana blocked by less than 50%, with Group 2 comprising children with adenoid hypertrophy and more than 50% closure of the choana. All patients began 5 mg montelukast treatment for 12 weeks. Patients had the pediatric sleep questionnaire applied before and after treatment. Tests and radiographic results were compared. In both groups, it was identified that montelukast treatment had no effect on adenoid tissue size (p=0.286, 0.304, respectively). Contrary to this, patients in Group 1 were identified to have statistically significant improvement in sleep quality with montelukast treatment (p=0.006). In Group 2 patients, there was no such improvement in sleep quality identified (p=0.91). Montelukast treatment increased sleep quality in children with less than 50% obstruction of the choana.

Keywords: Adenoid hypertrophy, children, montelukast, sleep quality

Introduction

Adenoid hypertrophy refers to the lymphoid tissue belonging to the Waldeyer ring located in the nasopharynx being larger than normal [1]. Adenoid hypertrophy is generally a clinical situation encountered in the childhood period. It may cause many different problems like difficulty with nasal respiration, reduced sleep quality, obstructive sleep apnea (OSAS), recurrent otologic and upper respiratory tract complaints, maxillofacial anomalies, hyperactivity, learning difficulties, growth and development regression or cardiac problems [2]. Generally, families attend the clinic with complaints of disrupted sleep quality initially [3, 4]. Adenoidectomy is most common surgical procedure performed in pediatric otolaryngological practice. Risk of anesthesia, pain, an altered voice and adenoid regrowth is common risk of adenoidectomy. Bleeding, dental trauma and minor injuries to the lips can occur following adenoidectomy [5].

***Coresponding Author:** Isil Cakmak Karaer, Malatya Traning and Research Hospital, Clinic ENT, Malatya, Turkey
E-mail: drisil_cakmak@yahoo.com

The effect of leukotrienes, with very important place in inflammation in the respiratory system, may reduce with leukotriene receptor blockers. Montelukast is a leukotriene receptor blocker used orally for asthma and allergic rhinitis treatment that is effective, reliable and has few side effects [6,7]. Studies in recent times have identified leukotriene receptor 1 and 2 in lymphoid tissue and there are publications in the literature stating that montelukast treatment may be an alternative to surgical treatment for adenoid hypertrophy [8-10].

Our aim in this study was to research the effect of montelukast treatment on adenoid tissue size and whether it is an alternative to adenoidectomy in pediatric patients with adenoid hypertrophy diagnosis.

Material and Methods

The study included a total of 50 pediatric patients. The study was performed on patients attending the ENT clinic in Malatya Education Research Hospital with snoring complaints. Permission was granted by Malatya ethics committee. The study included 25 female and 25 male patients with adenoid hypertrophy diagnosis on lateral neck radiography aged from 4 to 11 years. Those with systemic diseases,

using systemic medication or nasal topical corticosteroid treatment, with nutritional and medication allergies, with history of allergic rhinitis, with tonsillar hypertrophy, with obesity, any acute or chronic respiratory tract infection or asthma diagnosis, with maxillofacial deformities or neurological diseases were excluded from the study. All patients were examined by the same otolaryngologist (I.K.). Firstly, endoscopic nasal examination was performed, and patients were classified according to adenoid tissue size [11].

Patients were divided into two groups as

Group 1: 25 patients with adenoid hypertrophy obstructing less than 50% of the choana on lateral radiography

Group 2: 25 patients with adenoid hypertrophy obstructing more than 50% of the choana on lateral radiography

All radiological images were evaluated by the same radiology expert (A.C.) blinded to the patient names and film dates. Adenoid tissue size was evaluated with lateral neck radiography. Using the method described by Fujioka et al., the adenoid/nasopharyngeal ratio (A/N-R) was identified . Adenoid depth was determined by drawing a perpendicular line from a line drawn along the straight part of the anterior margin of basiocciput to a point of maximal convexity of adenoid. Nasopharyngeal depth was determined by drawing a line from the anterior inferior edge of sphenobasioccipital synchondrosis to the posterior superior margin of the hard palate. A/N-R was then determined by dividing adenoidal depth with nasopharyngeal depth. [12.

After all patients were diagnosed, the pediatric sleep questionnaire (PSQ) was applied. The PSQ is a test that can be applied to children aged from 2 to 18 years. The PSQ is a 22-item questionnaire showing sleep-related breathing disorders used in clinical trials to evaluate sleep-related breathing disorders.. It questions the frequency of snoring during sleep in children, presence of apnea, respiratory difficulties during sleep, daytime sleepiness, attention deficit and hyperactivity presence [13]. Responses are “yes” = 1, “no” = 0, and “don't know” = missing. The mean response on nonmissing items is the score, which can vary from 0 to 1. Pediatric sleep-related breathing disorder was defined as a positive mean PSQ score ≥ 0.33.

Patients with complete examination began 5 mg/day montelukast. After 12 weeks of regular treatment, patients again had the PSQ test applied and lateral neck radiography taken. Outcomes before and after treatment were compared. No drug side effects were seen during treatment.

Statistical analysis

All analyses were conducted using SPSS 15.0 (SPSS® for Windows 15.0, Chicago, USA). Normal distribution of parameters was identified by using the Kolmogorov-Smirnov test. Parameters with normal distribution are given as mean+SD and parameters with abnormal distribution are given as median (IQR). The Wilcoxon signed rank test was used to compare parameters before and after treatment. A two-tailed $p<0.05$ was considered statistically significant.

Results

The mean age of patients in Group 1 was 7.2 ± 1.9 years, while the age of patients in Group 2 was 6.7±2.2 years. There was no statistically significant difference between the two groups in terms of age. The mean body mass index (BMI) for patients in Group 1 was 17.1±0.7 , while the BMI of patients in Group 2 was 17.8±0.4. There was no statistically significant difference between the two groups in terms of BMI.

The mean A/N-R was 0.47 (0.42-0.49) in Group 1 before treatment, while after treatment the mean A/N-R was 0.46 (0.42-0.56). There was no statistically significant difference identified between the A/N-R ratio before and after treatment (p=0.286). The PSQ total value in Group 1 was 0.33 (0.23-0.50) before treatment, while after treatment the total value was 0.29 (0.10-0.42). In Group 1, it was identified that sleep quality statistically significantly increased after treatment (p=0.006) (Table 1).

Table 1. Clinical characteristics and radiological results of patients with less than 50% adenoid hypertrophy (Group 1)

	Pretreatment n=25	**Posttreatment** n=25	**p**
Age (y)	7.2±1.9		NS
BMI (kg/m²)	17.1± 0.7		NS
Female/Male	15/10		
A/N-R	0.47 (0.42-0.49)	0.46(0.42-0.56)	0.286
PSQ-T	0.33 (0.23-0.50)	0.29(0.10-0.42)	0.006*

BMI: Body mass index, NS: not significant, A/N-R: adenoid/nasopharyngeal ratio, PSQ-T: Pediatric Sleep Questionnaire Test - Total value

The mean A/N-R was 0.73 (0.61-0.82) in Group 2 before treatment, while the mean A/N-R was 0.73 (0.61-0.80) after treatment. There was no statistically significant difference identified between the adenoid sizes before and after treatment (p=0.304). The PSQ total value in Group 2 was 0.37 (0.30-0.46) before treatment, while the PSQ total value was 0.37 (0.33-0.50) after treatment. In Group 2, there was no statistically significant difference identified in terms of sleep quality before and after treatment (p=0.91) (Table 2).

Table 2. Clinical characteristics and radiological results of patients with more than 50% adenoid hypertrophy (Group 2)

	Pretreatment n=25	**Posttreatment** n=25	**p**
Age (y)	6.7± 2.2		NS
BMI (kg/m²)	17.8 ± 0.4		NS
Female/Male	12/13		
A/N-R	0.73 (0.61-0.82)		0.304
PSQ-T	0.73 (0.61.5-0.80)		0.91

BMI: Body mass index, NS: not significant, A/N-R: adenoid/nasopharyngeal ratio, PSQ-T: Pediatric Sleep Questionnaire Test - Total value.

Discussion

The results of this study show that in the group with adenoid tissue size less than 50%, montelukast treatment did not cause a statistically significant change in adenoid tissue size, but the patients in this group were identified to have a statistically significant improvement in sleep quality after montelukast treatment. In the group with adenoid tissue size of more than 50%, montelukast treatment was not identified to cause statistically significant changes in adenoid tissue size and sleep quality.

A study by Goldbart et al. divided 46 non-severe OSAS (obstructive apnea/hypopnea index [AHI] <10) children into two groups. While 23 children were administered placebo, 23 children were given montelukast treatment for 12 weeks. Different to our study, children receiving montelukast treatment were observed to have adenoidal/ nasopharyngeal ratio fall from 0.81±0.04 to 0.57±0.04 compared to those not receiving treatment. Additionally, the sleep apnea test scores of children were found to fall significantly compared to the controls receiving placebo. However, no variations were identified in the placebo group [9]. Shokouhi et al. in a study of 60 pediatric patients with adenoid hypertrophy identified 76% reduction in adenoid size in the group receiving 12 weeks montelukast treatment and 3% reduction in adenoid size in the group receiving placebo. The group receiving montelukast treatment were not identified to have a statistically significant improvement in sleep quality. The authors showed montelukast treatment was an alternative to surgery [10].

Another study divided 120 patients into 4 groups. The 1st group only received corticosteroids, the 2nd group received only montelukast, the 3rd group received corticosteroid+montelukast treatment and the 4th group received placebo. Patients with 3 months of montelukast treatment had adenoidal/nasopharyngeal measurements compared before and after treatment. After montelukast treatment they identified a 22.51% reduction in adenoid size. However, a topic noted in this study was that the reduction in adenoid tissue size in the placebo group was 12.46%. Additionally, it was reported that corticosteroid+montelukast treatment was more effective than montelukast treatment alone [14].

Another study administered montelukast treatment for 16 weeks to 26 patients with moderate OSAS (1< AHI <5) diagnosis. In this study, adenoid tissue size regressed from 0.76±0.03 to 0.56±0.03 with montelukast treatment. Further, they observed improvements in peak end-tidal carbon dioxide levels in patients after montelukast treatment. However, they did not observe any significant change in sleep quality scores of patients after montelukast treatment. The authors of this study emphasized that the combined use of leukotriene 1 and 2 receptor blockers will be more effective than the use of montelukast alone [15].

In our study, only montelukast was used as leukotriene blocker and patients were given the standard dose of 5 mg/day. Another study of 52 pediatric patients with AHI<10 investigated the effects of leukotriene receptor blockers on cell culture, proliferation assay, immunohistochemistry and cytokine assays using adenotonsillectomy material from patients. In conclusion, montelukast was the most effective leukotriene receptor blocker; however, the antiproliferative effect on lymphoid tissue increased in dose-linked manner and the efficacy was determined to increase further when used in combination with other leukotriene receptor blockers [16].

The results of our study can be said to show montelukast treatment alone does not affect adenoid tissue size at standard doses. However, in pediatric patients with low adenoid tissue size, montelukast treatment has a positive effect on sleep quality. This situation may be explained by lymphoid tissue previously shown in pediatric patients with OSAS complaints being different to lymphoid tissue growing linked to chronic infection, but more due to the leukotriene receptor ratio [8]. The reduction in inflammation in adenoid tissue may have increased the patients' sleep quality.

Although there are similar studies [17-19] this study is show that montelukast therapy on improving sleep quality in small adenoid size and prevent postoperative complications. In clinical practice, these study results show that if patients have adenoid tissue obstructing less than 50% of the choana, montelukast treatment may be an alternative to surgical treatment for OSAS due to adenoid hypertrophy. Contrary to this, in children with adenoid hypertrophy obstructing more than 50% of the choana, montelukast treatment for 12 weeks at standard dose does not appear to be an alternative to surgical treatment. However, there is a need for more advanced research administering montelukast treatment for longer durations. and at higher doses to more patients. Additionally the number of patients in the study can be more .

Acknowledgements

The authors declare that there are no conflicts of interest.There is no financial support or funding in this study. I.C.K designed and performed experiments, analyzed data and wrote the paper; I.C.K. collected and analyzed data. All authors contributed equally to this work. I.C. reviewed data from all sites and provided interpretive analysis; A.C. provided the Supplementary Digital Content and analyzed data. All authors discussed the results and implications and commented on the manuscript at all stages. This paper was not presented at any meeting formerly. This paper checked by native English speaker prior to submission

Conflict of interests

The authors declare that they have no competing interests.

Financial Disclosure

The financial support no have.

Ethical approval

This study was approved by the Institutional Ethics Committee and conducted in compliance with the ethical principles according to the Declaration of Helsinki. number of Ethics protocol number 2020/20.

References

1. Mnatsakanian A, Sharma S. Anatomy , Head and Neck, Adenoids. Treasure Island (FL). SourceStatPearls, StatPearls Publishing; 2019.
2. Scadding G. Non-surgical treatment of adenoidal hypertrophy: the role of treating IgE-mediated inflammation. Pediatr Allergy Immunol. 2010;21:1095–106.
3. Major MP, Flores-Mir C, Major PW. Assessment of lateral cephalometric diagnosis of adenoid hypertrophy and posterior upper airway obstruction: a systematic review. Am J Orthod Dentofac Orthop. 2006;130:700–8.
4. Caylakli F, Hizal E, Yilmaz I ,et al. Correlation between adenoid-nasopharynx ratio and endoscopic examination of adenoid hypertrophy: a blind, prospective clinical study. Int J Pediatr Otorhinolaryngol. 2009;73:1532-5.
5. Benjamin JM, Gunjan G. Adenoidectomy. Treasure Island (FL). StatPearls Publishing; 2020.6. National Heart, Lung, and Blood Institute. National asthma education and prevention program; expert panel report 3: guidelines for the diagnosis and management of asthma. 2007.

6. Berlucchi M, Salsi D, Valetti L, et al. The role of montelukast in the treatment of adenoidal hypertrophy in the pediatric age group: preliminary results of a prospective, randomized study. Pediatrics 2007;119:1392–7.

7. Goldbart AD, Goldman GL, Li RC, Brittian KR, et al. Differential expression of cysteinyl leukotriene receptors 1 and 2 in tonsils of children with obstructive sleep apnea and recurrent infection. Chest. 2004;126:13–8.

8. Goldbart AD, Greenberg-Dotan S, Tal A. Montelukast for children with obstructive sleep apnea: a double-blind, placebo controlled study. Pediatrics 2012;130:575-80.

9. Shokouhi F, Jahromi AM, Majidi MR, et al. Montelukast in adenoid hypertrophy: its effect on size and symptoms. Iranian Journal of Otorhinolaryngology. 2015;27:443-8.

10. Cassano P, Gelardi M, Cassano M, et al. Adenoid tissue rhinopharyngeal obstruction grading based on fiberendoscopic findings: a novel approach to therapeutic management. Int J Pediatr Otorhinolaryngol. 2003;67:1303-9.

11. Fujioka M, Young LW, Girdany BR. Radiographic evaluation of adenoidal size in children: adenoidal-nasopharyngeal ratio. AJR Am J Roentgenol. 1979;133:401–4.

12. Yuksel H, Sogut A, Yılmaz O, et al. Reliability and validity of the Turkish version of the pediatric sleep questionnaire: a tool for prediction of sleep related breathing disorder. Tüberküloz ve Toraks Dergisi. 2011;59:236-41.

13. Tuhanıoğlu B, Erkan SO. Evaluation of the effects of montelukast, mometasone furoate, and combined therapyon adenoid size: a randomized, prospective, clinical trial with objective data. Turk J Med Sci. 2017;47:1736-43.

14. Goldbart AD, Goldman JL, Veling MC, et al.Leukotriene Modifier Therapy for Mild Sleep-disordered Breathing in Children. Am J Respir Crit Care Med. 2005; 172:64-370.

15. Dayyat E, Serpero LD, Kheirandish-Gozal L, et al.Leukotriene Pathways and In Vitro Adenotonsillar Cell Proliferation in Children With Obstructive Sleep Apnea Chest. 2009;135:1142-9.

16. Kumar J. Clinical Outcomes of Montelukast Sodium in Children with Adenoid Hypertrophy. Biomed J Sci & Tech Res 27-2020. BJSTR. MS.ID.004438.

17. Kheirandish-Gozal L, Bandla H. P. R, Gozal D. Montelukast for Children with Obstructive Sleep Apnea: Results of a Double-Blind, Randomized, Placebo-Controlled Trial. Ann Am Thorac Soc. 2016;13:1736–41.

18. Kar M, Altıntoprak N, Muluk BN, et al. Antileukotrienes in adenotonsillar hypertrophy: a review of the literature. European Archives of Oto-Rhino-Laryngology. 2016;273:4111–7.

Available online at www.medicinescience.org

ORIGINAL ARTICLE

Medicine Science International Medical Journal

Medicine Science 2021;10(1):40-5

Being a medical pathology expert in the COVID-19 pandemic

Havva Erdem, Muruvvet Akcay Celik

Ordu University Faculty of Medicine, Deparment of Pathology, Ordu, Turkey

Received 09 September 2020; Accepted 02 December 2020
Available online 29.12.2020 with doi: 10.5455/medscience.2020.09.181

Abstract

The aim of the study is to reveal the risk of COVID-19 among pathologists and to examine their views, concerns along with measures to be taken in dealing with COVID-19. The research was carried out in Turkey with online survey method, on 176 participants. According to the findings of the study, participants who served one-on-one to a COVID-19 patient was 47.16%. Number of participants assigned in the polyclinic and clinical processes of coronavirus patients; 63.6%. 24 participant (13.6%) stated that their frozen cases decreased. Substantially, there was a use of protective equipment (88.6%). Cytological specimens were seen to continue 93.7%. There was a competence of 88.6% in terms of protective equipment. It was determined that the anxiety levels of the participants did not change according to age groups, according to the hospital type, working pandemic outpatient clinic and gender variables ($p > 0.05$). As a result, medical pathologists actively continue their routine services during the pandemic process and also support their other colleagues by working actively in the COVID-19 outpatient clinic. As always, solidarity with our colleagues continues.

Keywords: COVID 19, pathologist, pathology laboratory, protection

Introduction

A pandemic happens when a large number of communities have not developed immunity against the presence of a new virus. Pandemia; it means a large number of diseases and deaths. With the increase in global transportation and urbanization, the pandemic caused by a new virus can affect the whole world instantly. This has led to the deaths of millions of people, social tremors, and profound economic losses [1].

Four stages are observed during a pandemic. These; start, increase, peak, decrease periods. It is said that there may be a second wave after the decrease period [1].

In Wuhan, China, a set of cases of pneumonia the new 2019 coronavirus (2019-nCoV), caused by betacoronavirus, has been identified. On December 31, 2019 Chinese health officials came up with the notification of a set of acute respiratory diseases in people related to the Hunan Seafood and Animal Market in Wuhan city, Hubei Province, in the center of China. Then it started to spread rapidly in China and many other countries [2].

***Coresponding Author:** Havva Erdem, Ordu University Faculty of Medicine, Deparment of Pathology, Ordu, Turkey
E-mail: drhavvaerdem@gmail.com

As of April 29, there were 3.089.013 cases, 217.551 deaths, 888.091 cases of improvement worldwide. As of now, coronavirus cases have been seen in 210 countries. In Turkey 117.589 total cases, 3.081 total number of death, 44040 total number of healed. Healthcare workers who become infected, 10-11% in the world and between 6.4-6.5% in Turkey [3].

The outbreak of COVID-19 worldwide has become a clinical threat to the general population and health professionals. However, information about this new virus is currently limited. In addition, insufficient personal protection of healthcare workers, long exposure to many infected patients (increased virus load), abnormal increase in workload and lack of personal protective equipment further increase the risk of infection for healthcare professionals [2,4].

Research has reported that these healthcare professionals are afraid f getting infected and infection to their families, friends and colleagues, they feel uncertainty and stigma, think of withdrawal or resignation, and experience high levels of stress, anxiety, and depression [5].

Despite all the psychological burden in this pandemic environment, both pathologists, technicians and other workers continue to work and do well.

Periodical algorithms and guidelines are published by the Ministry

of Health of the Republic of Turkey on methods of working environment security and protection from COVID-19 [6,7].

In this context, depending on the circular issued by the Ministry and the attitude of surgeons, and since many of the hospitals were converted to pandemic hospitals, the number of cases decreased significantly.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is highly contagious and can be fatal, so pathologists and lab workers should be very careful while working on fresh tissues [8].

For the extraordinarily fast spread of pandemic and frequent changes in information about it, protection precautions come first because there is currently no vaccine against COVID-19.

The shift system is recommended as part of COVID-19 measures. In addition to protective equipment such as mask, goggles, apron and visor, disinfection is important as protection equipment.

In addition, cooperation and mutual tolerance are required with other colleagues during the pandemic period. Thus, tolerance can be shown against possible defects. It is important to address the fact that this outbreak will inevitably cause stress, fear and anxiety on pathologists, laboratory staff, and students.

Therefore, in this study the role of fighting with COVID-19 medical pathology specialists in Turkey, working conditions in a pandemic environment, attitudes towards pandemic and risk environments and in different environments was carried out to demonstrate that affect their anxiety levels of work outside their own department.

Material and Methods

Universe and Sample

The universe of the study consists of medical pathology expert working in different health institutions in Turkey. In the study, internet survey method was used in order to ensure the participation of employees by reaching all regions. 38 (21.5%) were male and 138 (78.4%) were female. 75 of them are 39 years old and under (42.6%), 68 were between the ages of 40 and 49 (38.6%), 31 were between the ages of 50 and 59 (17.6%), 3 were aged 60 and over (1.7%). 36 of them were 1-5 years (20.4%), 43 of them were 6-10 years (24.4%) experts, 38 of them were 11-15 years (21.5%), 23 of them were 16-20 years (13%), 36 of 21 were above (20.4%). 109 were ministry of health hospitals (61.9%), 59 (33.5%) were university hospitals, 5 were other (2%), 3 were private hospitals (1.7%). 6 (3.4%) were assistants (in the final period), 13 (7.3%) were associate professors, 26 (14.7%) were doctor lecturer 30 (17%) were professors, 101 (57.3%) were specialists. 138 (78.4%) were working in a pandemic hospital, 15 (8.5%) were in non-pandemic hospitals, 23 (13%) were not working in a pandemic hospital but in a hospital that had corona patients. 84 (47.7%) encountered COVID-19 cases, 92 (52.2%) did not encounter COVID-19 cases.

Data Collection Tool and Process

In the research, the COVID-19 Pandemic Medical Pathology Laboratory and Clinical Activities Scale were used as a data collection tool to reveal the contact status of the participants about COVID-19 and their work in pandemic hospitals, their working conditions, and their views on fighting Covid 19 in general.

During the development of the scale, first of all, in-depth interviews with health professionals (in whatsapp groups), their views on working conditions and the general epidemic were identified. In the second stage, expressions forming the scale were created by the researchers (Table 1).

Beck anxiety scale was used to determine the level of anxiety [9].

The basal characteristics (age, gender, etc.) of the physicians were recorded and their answers were recorded by asking the beck anxiety scale questions.

Since face-to-face meeting is not possible due to the pandemic, the internet environment was used to collect data, and a survey was shared on pathology platforms across the country, and the medical pathologists reached were requested to fill in the questionnaire by clicking the attached link. The answers on the scale were as follows; never / never disagree, rarely / disagree, occasional / partially agree, mostly / agree, always / fully agree, no idea. As a result of the study, data was obtained from 176 medical pathology expert.

Statistical Analysis

SPSS v26 (IBM Inc., Chicago, IL, USA) were used to test the aims of the study. The analyzes were carried out within the 95% ($p = 0.05$) confidence interval. Descriptive statistical methods, Chi-square analysis and frequency analysis were used in the study.

Results

The medical pathologist serving the COVID-19 patient was 47.16% (83 people).

Within the scope of the pandemic, the distribution of physicians assigned in the outpatient and clinical processes of coronavirus patients; 112 people ((63.6%, rarely; 10, occasional; 15, mostly; 19, always; 68)) 152 (86.3%) experts stated that frozen cases decreased and 24 (13.6%) did not. Frozen reduction in 150 centers (85.2%) was attributed to the postponement of elective cases, it did not decrease in 12 centers (6.8%), but did not frozen in 14 centers (7.9%).

As the three most successful countries, 115 people voted for South Korea, 114 people for Germany, 81 people for China. Turkey (73 people found success) fourth, Singapore (31 people found success) was fifth. The most unsuccessful countries were Italy, 137 people, USA 136 people, Spain 102 people. England 44 people, France 19 people were 4th and 5th respectively.

COVID-19 test status; 32 people (18.18%) had the test and (1 person (0.5%) positive (contact with covid case)), 31 (17.6%) negative. 144 (81.8%) people did not get tested.

As seen in table-1 and gfigure-1; number 1: 62.5% (110 people) was answered as " always ". Number 2: 39.2% (69 people) was answered as " always "(answered the question the most). Number 3 and 4: The answer was the same as the previous vote. Number 5: 63% (111 people) was answered as " never ". Number 6: 71% (125 people) was answered as " always ". Number 7: (56.2%) 99 people gave the highest answer to the question. Number 8: 51.7% (91 people) was answered as " always ". Number 9: The question was never 28.9%

(51 people) and the answer was always equal and highest. Number 10: 52.8% (93 people) was answered as " always " (the most). Number 11 and 12: 60.7% (107 people) and 59% (104 people) were the most responsive, respectively. Number 13: 42.6% (75 people) was answered as " always ". Number 14: 57.3% (101 people) was answered as " always " (highest answer). Number 15: 77.8% (137 people) was answered as " never ". Number 16: 73.2% (129 people) was answered as "never" (the highest response). Number 17: 59.6% (105 people) was answered as "never" (the highest response). Number 18: 27.2% (48 people) was answered as " always" (the highest response), 26.7% (47 people) was answered as "never" (the highest response). Number 19: 32.9% (58 people) of the answers were "always"(the highest). Number 20: 58.5% (103 people) of the answers were "never"(the highest). Number 21: 40.9% (72 people) of the answers were "always". Number 22: 59% (104 people) of the answers were "always" (the most response). Number 23: 38.6% (68 people) of the answers were "always"(the highest) and 35.7% (63 people) of the answers were "never"(the highest) and. Number 24: 39.2% (69 people) of the answers were "always"(the highest) and 35.7% (63 people)) of the answers were "mostly". Number 25: 36.3% (64 people) of the answers were "always"(the highest) and 36.3% (64 people) of the answers were "mostly".

The change in the anxiety level of the participants by age groups is given in Table 2. As a result of the chi-square test, it was determined that the anxiety levels of the participants did not change according to age groups ($p > 0.05$).

The change of the anxiety levels of the participants according to the answers to the question " When I look at the pandemic cases, I do not have the protective equipment shortage" is given in Table 3. The chi-square test was not found to be significant for the relationship between variables ($p > 0.05$).

The change in the anxiety levels of the participants according to hospital type, "Have you ever encountered COVID-19 patients?" “Did you examine a COVID-19 patient?” , gender variables is given in Table 4. As a result of the chi-square test, it was observed that the anxiety levels of the participants did not change significantly according to the hospital type, " Have you ever encountered COVID-19 patients?" “Did you examine a COVID-19 patient?”, gender variables ($p > 0.05$).

Table 1. COVID-19 Pandemic, Medical Pathology Laboratory and Clinical Activities Influence Scale

Number	
1	We continue to accept routine cases during the pandemic process
2	During the pandemic process, the number of cases has decreased drastically.
3	In the pandemic process, we ask whether the cases carry COVID-19 suspicion on the request sheet.
4	Our frozen practice continues in the pandemic process.
5	We postpone cases during the pandemic process
6	We accept cytological samples in the pandemic process.
7	I use a biosafety cabinet for cytological samples (add notes if there is no suitable option)
8	I use safety equipment in macroscopic sampling during my pandemic
9	I use a mask for microscopic evaluation during my pandemic.
10	During the pandemic, I disinfect the microscope and my work area in microscopic evaluation.
11	During the pandemic, I ventilate my workspace in microscopic evaluation.
12	During the pandemic, I ventilate my work area in macroscopic evaluation.
13	I don't have protective equipment shortage when looking at pandemic cases
14	I use the protective equipment correctly.
15	Have any injuries, such as incisions, happened in macroscopic sampling in your pandemic process?
16	Did you have problems with COVID-19 after the incision?
17	(Regarding 16) Was there any suspicion of COVID-19 in the sampled cases?
18	Do you attend academic meetings with telemedicine techniques and online systems in the pandemic process?
19	I am not making a specific assessment of COVID-19 when accepting cases during the pandemic process.
20	While accepting the cases in the pandemic process, if there is suspicion of COVID-19, I accept it according to whether the case is diagnostic or not.
21	I think that we have a positive solidarity with our colleagues during the pandemic process.
22	During the pandemic process, we cannot carry out our in-clinical scientific meeting/seminar programs.
23	In the pandemic process, I am assigned to the polyclinic and clinical processes of COVID-19 patients.
24	I think we are successful as a health system in the fight against pandemic.
25	I think we are successful as a country in fighting pandemic.

Table 2. Distribution of anxiety grade and age ranges

age	Degree of Anxiety 0-1		2		3.4		p
	n	%	n	%	n	%	
39 and below	39	47.0	22	44.0	13	30.2	0.228 (LRχ^2=8.146)
Between 40-49	28	33.7	22	44.0	18	41.9	
Between 50-59	15	18.1	6	12.0	10	23.3	
60 and above	1	1.2	0	0.0	2	4.7	
Total	**83**		**50**		**43**		

Table 3. Relationship between anxiety degree and protective equipment

When I look at the pandemic cases, I do not have the protective equipment shortage	Degree of Anxiety 0-1	2	3.4	p
Never / Never Disagree	7(8.4)	5(10.0)	3(7.0)	0.717 (LRχ2=6.918)
Rarely / Disagree	1(1.2)	2(4.0)	3(7.0)	
Occasional / PartiallyAgree	10(12.0)	3(6.0)	7(16.3)	
Mostly / Agree	16(19.3)	13(26.0)	9(20.9)	
Always / FullyAgree	48(57.8)	26(52.0)	20(46.5)	
No idea	1(1.2)	1(2.0)	1(2.3)	

Table 4. Relationship between the degree of anxiety and the hospital studied, gender and encounter with COVID-19

	Degree of Anxiety 0-1	Anxiety degree 0-1	2	3.4	p
Type of hospital	In a pandemic hospital	65(47.1%)	41(29.7%)	32(23.2%)	0.776 (LRχ2=1.872)
	Hospitals that accept corona patients,	10(43.5%)	5(21.7%)	8(34.8%)	
	no corona cases	8(53.3%)	4(26.7%)	3(20.0%)	
Have you ever encountered COVID-19 patients?	yes	44(52.4%)	25(29.8%)	15(17.9%)	0.144 (χ2=3.876)
	no	39(42.4%)	25(27.2%)	28(30.4%)	
Did you examine a COVID-19 patient?	yes	42(50.6%)	26(31.3%)	15(18.1%)	0.177 (χ2=3.465)
	no	41(44.1%)	24(25.8%)	28(30.1%)	
Gender	man	16(42.1%)	8(21.1%)	14(36.8%)	0.120 (χ2=4.241)
	woman	67(48.6)	42(30.4)	29(21.0)	

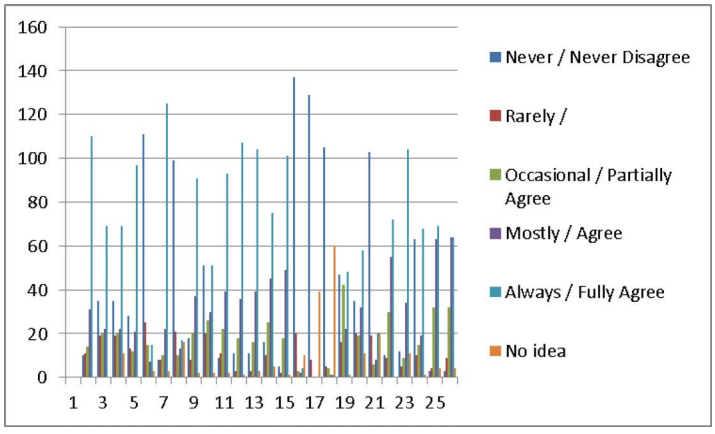


Figure 1. Distribution of the responses of the participants to the Clinical Activities Impact Scale

Discussion

The attitude of the authorities brings success in the pandemic process. The attitude of the countries in the pandemic process and the patient density are followed by the world through the media. Both the equipment adequacy and the capacity of the hospitals became one of the most important parameters here. Countries that took precautions previously in particular were more successful in this process. The satisfaction of the health worker is important for the health system. If the system is good enough, it will be so good in the tussle. In the survey results, it is seen that there is a general satisfaction. (always; 39.77%, mostly; 35.80%, occasional; 18.18%, rarely; 2.27%). The attitude of the units and local administrations studied here are also the parameters affecting the satisfaction.

In this process, the World Health Organization periodically updated the guides and tried to reach all health workers in terms of both

prevention methods and treatment (World health organization whatsapp). Communication networks were created. New developments were announced to the world quickly. As a result, each specialty in the COVID-19 pandemic has begun managing its division against the crisis.

During the COVID-19 pandemic period, biopsies and resections sent for pathology assessment were reduced. However, emergency cases, especially tumor cases, continued. According to the results of our survey, 62.5% routine case acceptance was continued. However, it was stated that the number of cases decreased significantly (39.2%). The reason for this is that many hospitals in our country have been converted to pandemic hospitals and postponed to reduce the risk of transmission of elective cases depending on the guidelines.

When taking fresh samples, pathologists should be particularly informed about the condition of COVID-19. In this regard, pathologists want COVID-19 status to be indicated on the request paper (always; 39.20%). Because especially in positive cases, it should be more cautious. Care should be taken in both sampling, preparation and microscopic evaluation. Since protective equipment is not easy to use, especially positive cases must be reported [6,7].

Difficulties with the use of protective equipment are expressed on many platforms. Even for a few hours, difficulties in basic needs such as eating, going to the toilet and other problems have been reported both in social media and in publications [10].

According to the results of the questionnaire, there was no general change in the acceptance of the incoming material (we accept cytological samples (always); 71.02%, we continue to accept routine cases (always; 62.50%, mostly; 17.61%). There was no significant delay in the conclusion of the cases. However, it is in close contact with our colleagues and it is necessary to request a case to be sent when only necessary [6,7].

The ratio of the formalin in the container in which the cases to be sent in the formalin are placed should be ensured and should be sent in the double container, if possible. The importance of this situation has been determined in the guidelines [6,7].

According to the answers to the questions about frozen in our survey, it was stated that the frozen practice continues, however the number of cases decreased (always; 74,43%). Cytological materials continued to be accepted. The usage rate could not be evaluated clearly since the question of whether there is a biosafety cabinet or not (not in the survey questions). Compliance with safety equipment was high, especially in macroscopic sampling, the use of protective equipment, and compliance with ventilation disinfection rules. There was no problem with protective equipment. Participation in online training programs increased during the pandemic period attending seminars (all and nothing) at the same rates may possibly be related to the unit and academic position he / she worked in.

In the diagnosis and treatment phase of COVID-19 positive cases, medical pathologists were found to be assigned to a large extent (63.6%) with varying frequency. The difference in frequency may be related to the center studied, patient density, number of staff and different business planning of the local authority. One of the important factors is whether the hospital studied is a university hospital, a hospital affiliated to the ministry of health, or a private hospital. As the majority of the ministry of health hospitals serve as a pandemic hospital, it is likely to be more deployed.

From the outset regarding the pandemic functioning, manuals and algorithms have been constantly updated by the authorities and periodic needs have been determined. The staff was asked to work in shifts against possible quarantine situations. In our survey, the health system was found to be largely successful (72.6%).

In the guide published by the World Health Organization, recommendations regarding the use of COVID-19 positive samples, the definition of transportation conditions and how to deliver the samples are specified in detail [6]. Since it is not known whether patients without COVID-19 assessment are asymptomatic, it will be more reliable to treat each case with caution and it will make the health worker feel safe.

As mentioned earlier, it has been suggested that cytological samples should be prepared and frozen assessment should be reduced unless mandatory. It has been reported that cytopathological changes in cytological samples contain nonspecific findings related to pulmonary damage for COVID-19 [11].

In our opinion, in terms of being very infectious, if there is no different diagnostic requirement, the evaluation requests should be minimized. If it is not urgent, it should be postponed. Again, a biosafety cabinet (level 2) is recommended in the manual (6,7). In the units without a biosafety cabinet may pose a risk for droplet and aerosol formation and contamination [6,7].

Examination of fresh tissue with frozen process which is performed by freezing, if absolutely necessary, it should be requested.[6,7]If frozen assessment is mandatory, technical and medical personnel should take action by wearing protective equipment [6,7]. Laboratory workers and pathologists should wear appropriate protective equipment such as goggles, medical mask, lab coat with sleeves and specific gowns, gloves [6,7].

In 2019-nCoV cases, it should be prudent because it can form aerosols in the cryostat.[12] Darnell et al. stated that formalin and glutaraldehyde inactivate SARS-CoV depending on temperature and time. They reported that formalin at 37 ° C or room temperature significantly reduced the infectivity of the virus on the first day, while glutaraldehyde inactivated SARS-CoV after 1-2 days of incubation [6,7].

It is the most used fixative formalin in the routine. Since the biopsies are small, they allow sampling on the same day, but it may be more appropriate to postpone them a day later in terms of their protective measures.

Duan et al. found that of several coronaviruses for 90 minutes at 56 ° C, 60 minutes at 67 ° C, and 30 minutes at 75 ° C. was not contagious after exposure to heat [14].

As with other coronaviruses such as SARS and MERS, Kampf et al. stated that COVID-19 can remain on inanimate surfaces such as metal, glass or plastic for up to 9 days. However, it can be effectively inactivated by standing for 1 minute with surface disinfection procedures containing 62-71% ethanol, 0.5% hydrogen peroxide or 0.1% sodium hypochlorite [15].

Duan et al stated that viral load is reduced with ultraviolet light in the culture medium [14].

In macroscopic evaluation, knife incisions are injuries experienced in routine. Such injuries may be important in terms of transmission in macroscopic sampling during your pandemic process. 29 people (16.4%) stated that they were injured at varying frequency. Afterwards, when asked whether they had problems with COVID-19, 13 people (7%) stated that they had problems at different frequencies. These two situations may be related to each other or they may be two independent situations. Nevertheless, utmost attention should be paid to measures during the pandemic process, which has many unknowns.

In all processes, healthcare personnel also have a fear of serious infection. They may develop behavioral responses due to fear of infection. It is known that psychological factors play a vital role in a person's success. Public health strategies used in the treatment of epidemics are important. Health anxiety is important in influencing the success or failure of each of the strategies implemented [16].

People with high health anxiety in viral outbreaks can develop incompatible safety behaviors. These can be included excessive handwashing, social withdrawal, and panic attacks. In order to avoid all these behaviors, public health recommendations and guidelines recommended by the authority should be followed in the management of epidemics. In pandemics, those with high health anxiety may have extreme points that may have negative consequences for the individual and society. For example, unnecessary stockings can be made (eg hand sanitizer, medicines, protective masks, foods). Low health anxiety can also have negative effects on health behavior or result with neglection. In this period, the attitude of decision makers is very important in directing the society [16].

While uncertainty was more intense in the first months of the pandemic, this situation has eased at the moment. Guidelines and algorithms, and an increase in the number of healing patients give hope to society.

When we look at anxiety levels in our survey, it was seen that the level of anxiety was significantly low. The reason for this may be the reduction of the pandemic table, as we mentioned above. When we examine the table again, it was seen that anxiety was lower in the people who examined a COVID-19 patient. This may be because they have seen the controllability of the disease. The higher rate in women may also be related to the emotional differences of the female male gender or due to the excess of women in the sample ($p=0.228$).

Conclusion

As a result, medical pathologists continue to do their part in the pandemic process by either continuing their routine services or working actively in the COVID-19 outpatient clinic. No contamination was detected in our routine, as there was no shortage of protective equipment supply and elective cases were delayed. According to our colleagues at the front line of medical pathologists, the risk of infection was low. The biosafety cabinet is especially necessary for the safe preparation of infectious materials. As always, positive solidarity with our colleagues continues in the pandemic process.

Acknowledgements
I would like to thank all participants who answered the questionnaire and Yeliz Kaşko Arıcı who helped with statistics.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
The financial support no have.

Ethical approval
This study was approved by Ordu University Clinical Research Ethics Committee with decision number 2020/73.

References

1. Figen Sezen. Influenza Pandemileri. Türk Hij Den Biyol Derg. 2009;66:21-4.
2. Huang C, Wang Y, Li X, , et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395:497-506.
3. T.C. Saglik Bakanligi. Turkiye'deki guncel durum. 2020. Available at: https://covid19.saglik.gov.tr/ accessed date 29 April 2020
4. Lai J, Ma S, Wang Y, et al. Factors associated with mental health outcomes among health care workers exposed to coronavirus disease 2019. JAMA Netw Open. 2020;3:203976.
5. Bai Y, Lin CC, Lin CY, et al. Survey of stress reactions among health care workers involved with the SARS outbreak. Psychiatr Serv. 2004;55:1055-7.
6. Republic of Turkey Ministry of Health. Public health general directorate. Laboratory biosafety guidance related to coronavirus disease 2019 (COVID-19). Ankara, Turkey: Republic of Turkey Ministry of Health; 2020.
7. World Health Organization. Infection prevention and control during health care when novel coronavirus (nCoV) infection is suspected: interim guidance, 25 January 2020. World Health Organization; 2020, pp 1-5.
8. Paules CI, Marston HD, Fauci AS. Coronavirus infections—more than just the common cold. JAMA. 2020;323:707–8.
9. Beck AT, Epstein N, Brown G, et al. An inventory for measuring clinical anxiety: psychometric properties. J Consult Clin Psychol. 1988;56:893-7.
10. Buckley C, Wee SL, Qin A. China's doctors, Fighting the Coronavirus, Beg for masks. https:// www.nytimes.com/2020/02/14/world/asia/chinacoronavirus-doctors.html. accessed date 29 April 2020
11. Stefan E. Pambuccian.The COVID-19 pandemic: implications for the cytology laboratory. J Am Soc Cytopathol. 2020;9:202-11.
12. Henwood AF. Coronavirus disinfection in histopathology. J Histotechnol. 2020;43:102-4.
13. Darnell ME, Subbarao K, Feinstone SM, et al. Inactivation of the coronavirus that induces severe acute respiratory syndrome, SARS-CoV. J Virol Methods. 2004;121:85–91.
14. Duan SM, Zhao XS, Wen RF, et al. Stability of SARS coronavirus in human specimens and environment and its sensitivity to heating and UV irradiation. Biomed Environ Sci. 2003;16:246–55.
15. Kampf G, Todt D, Pfaender S, et al. Persistence of coronaviruses on inanimate surfaces and its inactivation with biocidal agents. J Hosp Infect. 2020;104:246-51.
16. Asmundson GJ, Taylor S, Carleton RN, et al. Should health anxiety be carved at the joint? A look at the health anxiety construct using factor mixture modeling in a non-clinical sample. J Anxiety Disord. 2012;26:246-51.

Available online at www.medicinescience.org

ORIGINAL ARTICLE

Medicine Science International Medical Journal

Medicine Science 2021;10(1):46-50

Factors affecting glycemic control in patients with type 2 diabetes mellitus using oral antidiabetics: A single-center experience

Aysegul Sakin[1], Murat Alay[2]

[1]Department of Internal Medicine, University of Health Sciences, Van Research and Training Hospital, Van, Turkey
[2]Department of Endocrinology and Metabolism, Yuzuncu Yil University, Van, Turkey

Received 05 September 2020; Accepted 16 November 2020
Available online 01.01.2021 with doi: 10.5455/medscience.2020.09.179

Abstract

In this retrospective study, we aimed to investigate the factors affecting glycemic control in patients with type 2 diabetes mellitus (DM) treated with oral antidiabetic drugs (OADs). From 2019 to 2020, type 2 DM patients treated with OADs were included in this study. Patients less than 18 years old and those treated with insulin were excluded from the study. The patients were divided into two groups according to HbA1C levels as follows: good glycemic control (GGC) (<7%) or poor glycemic control (PGC) (≥7). Of the 505 type 2 DM patients, 270 (53.5%) were female. There were 194 (38.4%) patients in the GGC group and 311 (61.6%) in the PGC group. The rate of marriage and employment were higher in the GGC group than those in the PGC group. Likewise, education level and, and high-density lipoprotein were higher in the GGC group than those in the PGC group. In the multivariate analysis, being married (odds ratio [OR], 0.39), duration of DM (OR, 1.12), having a high-school graduate (OR, 0.43), triglyceride level (OR, 1.001), and high-density lipoprotein level (OR, 0.979) were the factors affecting glycemic control. In this study, we found that being married and having a higher education level and high-density lipoprotein level were associated with GGC in type 2 DM patients treated with OADs.

Keywords: Glycemic control, oral antidiabetic drugs, marital status, body mass index

Introduction

Diabetes is a major cause of death globally. The prevalence of type 2 diabetes mellitus (DM) is approximately 6.4% in adults, ranging from 3.8% to 10.2% by region. The incidence of undetected diabetes is estimated to be 50% in some areas. Type 2 DM is characterized by insulin resistance and relative impairment in insulin secretion, resulting in hyperglycemia. The prevalence of DM markedly increases by obesity and sedentary lifestyle [1-3].

DM is associated with a high prevalence of micro- and macro-vascular diseases. about %50 of patients experience one of the following vasculary complications which adversely impact employment, absenteeism, and business productivity; myocardial infarction, stroke, end-stage kidney disease, retinopathy, and foot ulcers, [4, 5].

In response to insulin resistance, Hyperinsulinemia may play an important role in formation of several abnormalities including hypertension, low serum high-density lipoprotein (HDL) level, and high serum low-density lipoprotein (LDL) level [6].

Good glycemic control (GGC) in DM is associated with a lower risk of microvascular complications. A lower glycated hemoglobin (HbA1C) level is associated with improved long-term outcomes. Several randomized trials have demonstrated a beneficial effect of intensive treatment on outcomes in DM. A reasonable treatment target for most DM patients is to lower the HbA1C level below 7.0% [7-9].

Aggressive multifactor risk reduction lowers the risk of micro- and macro-vascular complications. Cardiovascular risk reduction must be the most important priority for all patients. A decrease in serum lipids, smoking cessation, blood pressure control, exercise, diet, and weight-loss are important factors for a GGC [10, 11].

In addition to exercise, body mass index (BMI), antidiabetic drugs, sociocultural factors, education level, and economic conditions affect glycemic control. In this retrospective study, we aimed to investigate the factors affecting glycemic control in type 2 DM patients treated with oral antidiabetic drugs (OADs).

***Coresponding Author:** Aysegul Sakin , Department of Internal Medicine, University of Health Sciences, Van Research and Training Hospital, Van, Turkey
E-mail: mdaysegulsakin@gmail.com

Material and Methods

Study population

A total type 2 DM 505 patients treated and followed from 2019 through 2020 at Yüzüncü Yıl University Hospital were enrolled. Of these patients, 270 (53.5%) were female. The median age was 56 years (range, 30–85). Patients older than 18 years and were treated with OADs for type 2 DM were included.

Data collection

The patients' gender, age, marital status (married or unmarried), family history of DM, employment status (unemployed or employed), education level (illiterate, elementary, high school, or college), duration of DM, BMI, hypertension, and total cholesterol, triglyceride, LDL, HDL, HbA1C, and fasting plasma glucose (FPG) levels were obtained from the archive files. BMI was calculated by the weight divided by the height squared. The patients were divided into two groups according to HbA1C level as follows: GGC=HbA1C≤7% and poor glycemic control (PGC) =HbA1C>7%.

Ethics committee approval

This study was conducted in accordance with the Declaration of Helsinki, and it was approved by the Ethics Committee of Yüzüncü Yıl University (ID:2020/06-05).

Statistical analysis

The Statistical Package for Social Sciences 22.0 for Windows software (IBM Corp., Armonk NY, 2013) was used for all statistical analyses. Descriptive statistics are presented as the mean, standard deviation, minimum, and maximum for numerical variables and as the frequency and percentage for categorical variables. The Student t test was used to compare numerical variables with a normal distribution between two independent groups, whereas the Mann–Whitney U test was used to compare variables without a normal distribution. Chi-square analysis was used to compare the ratios between the groups. Monte Carlo simulation was applied when the conditions were not met. The determinant factors were examined by logistic regression analysis. The Enter model was used with parameters having a $p<0.05$. The statistical significance level was $p<0.05$.

Results

Of the 505 DM patients, 270 (53.5%) patients were female, and 235 (46.5%) were male, with a median age of 56 years (range, 30–82). About 91.5% of the patients were married and 394 (78%) patients had a family history of DM. The median duration of DM was 6.6 years. About 362 (71.7%) patients had hypertension. The mean HbA1C and FPG levels were 8.0% and 153 mg/dl respectively. The lipid levels are shown in Table 1.

Table 1. Patients data.

Characteristics		n	&
Gender	Female	270	53.5
	Male	235	46.5
Age(years)	Median (min-max)	56 (30-85)	
Marital status	Unmarried	43	8.5
	Married	462	91.5
Family history of DM	Absence	111	22.0
	Presence	394	78.0
Employment status	Unemployed	349	69.1
	Employed	156	30.9
Education level	Illiterate	65	12.9
	Elementary education	289	57.2
	High school	104	20.6
	College	47	9.3
Duration of DM	Mean + SD (median)	6.6+6.3 (5.0)	
BMI	Overweight	59	11.7
	Normal weight	219	43.4
	Obese	227	45.0
Hypertension	Absence	143	28.3
	Presence	362	71.7
Total cholesterol	mg/dL	208.2+46.6 (202.0)	
Triglycerides	mg/dL	180.5+121.0 (157.0)	
Low-density lipoprotein	mg/dL	125.7+39.1 (120.0)	
High-density lipoprotein	mg/dL	47.4+13.4 (46.0)	
HBA1C		8.0+2.1 (7.4)	
Fasting plasma glucose	mg/dL	153.0+64.8 (131.0)	

Abbreviations: BMI, Body mass index; DM, Diabetes mellitus

Among 505 patients, 194 (38.4%) were in the GGC group, and 311 (61.6%) were in the PGC group. There were no statistically significant differences between the groups in terms of gender, age, BMI, total cholesterol levels, and LDL levels. The family history of DM, employment status, education level, duration of DM, hypertension status, triglyceride levels, HDL levels, HbA1c levels, and fasting plasma glucose levels significantly differed between the groups (Table 2).

In the multivariate analysis, the duration of DM (p<0.001), marital status (p=0.027), education level (p<0.001), triglyceride level (p=0.029), and HDL level (p=0.010) were the factors affecting glycemic control (Table 3).

Table 1. Patients data according to glycemic control status.

Characteristics		Good glycemic control		Poor glycemic control		p
		n	%	n	%	
Gender	Women	108	55.7	162	52.1	0.433
	Male	86	44.3	149	47.9	
Age(years)	Median (min-max)	56.0 (30-85)		57.0 (30-85)		0.763
Marital status	Unmarried	9	4.6	34	10.9	0.014
	Married	185	95.4	277	89.1	
Family history of DM	Absence	57	29.4	54	17.4	0.002
	Presence	137	70.6	257	82.6	
Employment status	Unemployed	120	61.9	229	73.6	0.005
	Employed	74	38.1	82	26.4	
Education level	Illiterate	19	9.8	46	14.8	<0.001
	Elementary education	87	44.8	202	65.0	
	High school	61	31.4	43	13.8	
	College	27	13.9	20	6.4	
Duration of DM	Mean + SD (median)	4.5+5.0		7.9+6.7		<0.001
BMI	Overweight	26	13.4	33	10.6	0.433
	Normal weight	87	44.8	132	42.4	
	Obese	81	41.8	146	46.9	
Hypertension	Absence	74	38.1	69	22.2	<0.001
	Presence	120	61.9	242	77.8	
Total cholesterol	mg/dL	205.5+43.2(198)		209.8+48.7(48.7)		0.463
Triglycerides	mg/dL	152.2+83.1(136.5)		195+137.7(170.0)		<0.001
Low-density lipoprotein	mg/dL	122.2+39.3(119.5)		127.5+38.8(123.0)		0.209
High-density lipoprotein	mg/dL	49.7+12.5(48)		45.9+13.7(45.0)		<0.001
HBA1C		6.3+0.3(6.4)		9.0+2.0(8.4)		<0.001
Fasting plasma glucose	mg/dL	109.2+17.6(108.0)		180.3+68.4(165.0)		<0.001

Abbreviations: BMI, Body mass index; DM, Diabetes mellitus

Table 3. Multivariate analysis for glycemic control.

Characteristics		OR	%95 CI	p
DM time	**Year**	1.120	1.071-1.172	<0.001
Marital status	**Married vs. Unmarried**	0.393	0.172-0.899	0.027
Family history of DM	**Presence vs. Absence**	1.523	0.940-2.456	0.087
Employment status	**Employed vs. Unemployed**	0.975	0.615-1.544	0.913
Education level	**Illiterate(Ref.)**			<0.001
	Elementary education	1.410	0.728-2.728	0.308
	High school	0.431	0.202-0.919	0.029
	College	0.571	0.236-1.382	0.214
Triglycerides	**mg/dL**	1.003	1.000-1.005	0.029
High-density lipoprotein	**mg/dL**	0.979	0.962-0.995	0.010

Abbreviations: DM, Diabetes mellitus

Discussion

In the present study which represents real-life data, we aimed to evaluate the factors affecting glycemic control in type 2 DM patients treated with OADs, using. We observed that glycemic control was better in patients who were married and had a shorter duration of DM, a higher education level, a low triglyceride level, and a high HDL level .

Diabetes is a chronic disease with a rapidly increasing prevalence worldwide due to genetic factors and negative changes in lifestyle, such as obesity and physical inactivity. As of 2010, the prevalence of diabetes was 6.4% in the adult population and it is expected to reach 7.7% in 2030. DM is a main cause of morbidity and mortality in the world and in our country, with an increasing frequency despite new advances in its treatment [12, 13].

Since sedentary lifestyle and obesity are the two most important determinants of diabetes, lifestyle changes are the main approach to prevent and treat the disease. Lifestyle changes also have a positive effect on all risk factors, including hyperglycemia. It is indispensable in all stages of the disease [14-16]. Previous studies have shown that healthy lifestyle changes can prevent or delay DM and reduce the risk by 44-58%, emphasizing that regular exercise is critical in preventing complications and achieving GGC [16-19].

In a study conducted by Yanik et al., 57.0% of the patients were treated with OADs. The average time to diagnosis in individuals with diabetes was 9.5 years, and 60.4% of the patients had a family history of DM. In this study, it was determined that self-sufficiency increased when the education level of individuals increased. However, no statistically significant differences were found in the self-sufficiency level according to gender, marital status, or employment status of individuals with diabetes [20].

In the study of Çıtıl et al., there was no statistically significant difference between the genders in terms of metabolic control level; as the duration of the disease progressed, the rate of patients with good metabolic control decreased; and as the education level increased, the rate of patients with good metabolic control increased significantly. In the study, 71.8% of the DM patients had another chronic disease, with hypertension, hyperlipidemia and coronary artery diseases being the most prevalent [21]. In our study, patients with low glycemic control were found to have HT more frequently.

Previous studies have shown that the frequency of diabetes decreases when the education level increase [22, 23]. In other studies, the DM prevalence was higher among those with a family history of diabetes [24-26]. Additionally, some studies have shown that hypertension increases the incidence of DM [27, 28]. In our study, the relationship between these factors and glycemic control was examined and we found that glycemic control was better in patients who had a shorter duration of DM, were married, and had a high school education.

Mahato et al. found that in patients with HbA1c greater than 7%, the total cholesterol, LDL, and triglyceride levels were higher than in those with HbA1c less than 7%; however, the HDL cholesterol level did not significantly differ between the two groups[29]. Khan et al. found a positive correlation between HbA1c and triglycerides and a negative correlation between HDL cholesterol and HbA1C. However, there were no significant correlations among LDL, total cholesterol, and HbA1C [27]. In our study, glycemic control was better in patients with a low triglyceride level and high HDL level and there was no relationship between total cholesterol and LDL. Our study has some limitations. It was a single-centered retrospective study. In addition, we did not know which OADs were used for DM.

Conclusion

In conclusion, we found that glycemic control was better in patients who were married and had a shorter duration of DM, high school education, low triglyceride level, and high HDL level. In these patients, we recommend that more efforts should be paid to lower the triglyceride level. Increasing the HDL level may help improve glycemic control.

Acknowledgements
I would like to thank all participants who answered the questionnaire and Yeliz Kaşko Arıcı who helped with statistics.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
The financial support no have.

Ethical approval
This study and all relevant procedures were performed in accordance with the Helsinki Declaration after obtaining the ethical board approval from the Yüzüncü Yıl University Ethics Committee (ID:2020/06-05).

References

1. Sullivan PW, Morrato EH, Ghushchyan V, et al. Obesity, inactivity, and the prevalence of diabetes and diabetes-related cardiovascular comorbidities in the U.S., 2000-2002. Diabetes Care. 2005;28:1599-603.
2. American Diabetes A. 2. Classification and diagnosis of diabetes. Diabetes Care. 2017;40(Suppl 1):11-24.
3. Mokdad AH, Ford ES, Bowman BA, et al. Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. JAMA. 2003;289:76-9.
4. Katon WJ, Rutter C, Simon G, et al. The association of comorbid depression with mortality in patients with type 2 diabetes. Diabetes Care. 2005;28:2668-72.
5. Tunceli K, Bradley CJ, Nerenz D, et al. The impact of diabetes on employment and work productivity. Diabetes Care. 2005;28:2662-7.
6. DeFronzo RA, Ferrannini E. Insulin resistance. A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. Diabetes Care. 1991;14:173-94.
7. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998;352:837-53.
8. Holman RR, Paul SK, Bethel MA, et al. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med. 2008;359:1577-89.
9. Hayward RA, Reaven PD, Wiitala WL, et al. Follow-up of glycemic control and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2015;372:2197-206.
10. Gaede P, Vedel P, Larsen N, et al. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. N Engl J Med. 2003;348:383-93.
11. Pal K, Eastwood SV, Michie S, et al. Computer-based diabetes selfmanagement interventions for adults with type 2 diabetes mellitus. Cochrane Database Syst Rev. 2013:CD008776.
12. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med. 1998;15:539-53.

13. Onat A, Ozhan H, Esen AM, et al. Prospective epidemiologic evidence of a "protective" effect of smoking on metabolic syndrome and diabetes among doi: 10.5455/medscience.2020.09.179 Med Science 2021;10(1):46-50 50 Turkish women--without associated overall health benefit. Atherosclerosis. 2007;193:380-8.

14. Pan XR, Li GW, Hu YH, et al. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. Diabetes Care. 1997;20:537-44.

15. Gong Q, Zhang P, Wang J, et al. Morbidity and mortality after lifestyle intervention for people with impaired glucose tolerance: 30-year results of the da qing diabetes prevention outcome study. Lancet Diabetes Endocrinol. 2019;7:452-61.

16. Association AD. 1. Improving care and promoting health in populations: standards of medical care in diabetes-2020. Diabetes Care. 2020;43(Suppl 1):7-13.

17. Clark CM, Jr., Kinney ED. Standards for the care of diabetes. Origins, uses and implications for third-party payment. Diabetes Care. 1992;15 Suppl 1:10-4.

18. Kirk A, Mutrie N, MacIntyre P, Fisher M. Increasing physical activity in people with type 2 diabetes. Diabetes Care. 2003;26:1186-92.

19. Amanat S, Ghahri S, Dianatinasab A, et al. Exercise and type 2 diabetes. Adv Exp Med Biol. 2020;1228:91-105.

20. Tekin Yanık Y, Erol Ö. Tip 2 diyabetli bireylerin öz-yeterlilik düzeylerinin değerlendirilmesi. J Anatolia Nursing Health Sci. 2016;19:166-74.

21. Rıza çitil YÖ, Osman Günay. Kayseri il merkezinde bir sağlık ocağında başvuran diyabetik hastalarda metabolik kontrol durumu ve eşlik eden faktörler. Erciyes Tıp Dergisi. 32:111-22.

22. Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Committee. World Health Organ Tech Rep Ser. 1995;854:1-452.

23. Navaneethan SD, Kirwan JP, Remer EM, et al. Adiposity, Physical Function, and Their Associations With Insulin Resistance, Inflammation, and Adipokines in CKD. Am J Kidney Dis. 2021;77:44-55.

24. Mahley RW, Palaoglu KE, Atak Z, et al. Turkish Heart Study: lipids, lipoproteins, and apolipoproteins. J Lipid Res. 1995;36:839-59.

25. Bo S, Gentile L, Cavallo-Perin P, et al. Sex- and BMI-related differences in risk factors for coronary artery disease in patients with type 2 diabetes mellitus. Acta Diabetol. 1999;36:147-53.

26. Haffner SM, Mykkanen L, Festa A, et al. Insulin-resistant prediabetic subjects have more atherogenic risk factors than insulin-sensitive prediabetic subjects: implications for preventing coronary heart disease during the prediabetic state. Circulation. 2000;101:975-80.

27. Khan HA, Sobki SH, Khan SA. Association between glycaemic control and serum lipids profile in type 2 diabetic patients: HbA1c predicts dyslipidaemia. Clin Exp Med. 2007;7:24-9.

28. Urrea C, Mignogna A. Development of an expert system for pre-diagnosis of hypertension, diabetes mellitus type 2 and metabolic syndrome. Health Informatics J. 2020:1460458220937095.

29. Mahato PG RV, Raut P Psd, Regmi P, et al Association between glycaemic control and serum lipid profile in type 2 diabetic patients: Glycated haemoglobin as a dual biomarker. Biomedical Research. 2011;22:375-80.

Available online at www.medicinescience.org

ORIGINAL ARTICLE

Medicine Science International Medical Journal

Medicine Science 2021;10(1):51-5

Determination of metabolic syndrome and insulin resistance rate among adults with ultrasound diagnosed non-alcoholic fatty liver disease

Filiz Araz[1], Murat Sert[2]

[1]*Baskent University, Adana Dr. Turgut Noyan Training and Research Hospital, Gastroenterology, Adana, Turkey*
[2]*Cukurova University, Faculty of Medicine, Department of Endocrinology, Adana, Turkey*

Received 10 July 2020; Accepted 01 September 2020
Available online 20.12.2020 with doi: 10.5455/medscience.2020.07.134

Abstract

Metabolic syndrome (MS) has close association with nonalcoholic fatty liver disease (NAFLD) and is characterized by insulin insensitivity, central obesity, dyslipidemia, hypertension and high glucose levels. This study aimed to define the prevalence of MS, insulin resistance and diabetes among subjects with NAFLD. Patients and method: In a tertiary center, patients diagnosed to have fatty liver disease by ultrasound were included. Cases with drug and/or alcohol use and liver diseases were excluded. Anthropometric measures were applied. Fasting glucose, insulin, c-peptide and transaminase levels were measured. Oral glucose tolerance test was applied to all cases. Homeostasis Model Assessment-Insulin Resistance (HOMA-IR) index was calculated. Insulin resistance was defined as HOMA-IR ≥2.7. ATP III criteria were applied for diagnosis of MS. 230 patients were enrolled. 141 patients (61.3%) were female. Mean age was 50.3±10 (18-95) years. Mean body-mass index (BMI) was 30.5±10.6 (18-50). Mean HOMA index was 3.3±2.6 (0.5-26.5). Impaired fasting glycemia was diagnosed in 78 (33.9%) patients, while impaired glucose tolerance and type 2 diabetes were diagnosed in 65 (28.3%) and 51 (22.1%) patients, respectively. MS prevalence among patients with NAFLD was 56.5%. MS was present in 73.2% of patients with HOMA index ≥ 2.7. Independently from BMI, insulin resistance is high in patients with NAFLD. Transaminase levels did not change with MS among NAFLD patients. NAFLD is associated with increased prevalence rate for metabolic syndrome, insulin resistance and type 2 diabetes.

Keywords: Nonalcoholic fatty liver disease, metabolic syndrome, insulin resistance, HOMA

Introduction

Nonalcoholic fatty liver disease (NAFLD) is defined as hepatic steatosis in patients without other causes, drug use and heavy alcohol consumption (females >20 gr/day, males>30 gr/ day) for secondary hepatic fat accumulation [1-3]. NAFLD may potentially advance to cirrhosis and is accepted as a considerable cause for cryptogenic liver disease [4,5]. NAFLD has worldwide distribution with different prevalence rates. Prevalence of NAFLD is 10-30% in whole population in different countries [6,7]. Estimated prevalence of NAFLD in the US is 19% to 46% [7,8]. Imaging-based global NAFLD prevalence was estimated as 25.24 % by a recent meta-analysis. According to this estimation, Middle East (31.79%) and South America (30.45%) have the highest prevalence rates [9]. Age > 45, obesity (BMI ≥ 30), central obesity (defined as waist/hip ratio over 0.9 in men or over 0.85 in women, and waist ≥102 cm in men or ≥88 cm in women), presence of type 2 diabetes mellitus, family history of type 2 diabetes and dyslipidemia are major risk factors for NAFLD [10].

Components of metabolic syndrome are presence of hyperglycemia, abdominal obesity, dyslipidemia, and hypertension [11,12]. MS is related with insulin resistance, high risk of type 2 diabetes and development of atherosclerotic cardiovascular disease [13]. In order to prevent associated macrovascular complications of type 2 diabetes, it is critical to diagnose prediabetes which is defined as impaired fasting glycemia and/or impaired glucose tolerance [14,15].

NAFLD and MS have close associations. Some evidence supports common pathogenetic mechanisms for these two entities. Due to its close relationship with insulin resistance, obesity and dyslipidemia, NAFLD was referred as liver manifestation of MS [16]. Higher MS prevalence has been reported among patients with NAFLD. MS is also related with higher risk of steatohepatitis and fibrosis among NAFLD patients [17].

This study aimed to define the prevalence of MS and its components, including insulin resistance, type 2 diabetes and prediabetes,

***Coresponding Author:** Filiz Araz, Baskent University, Adana Dr. Turgut Noyan Training and Research Hospital, Gastroenterology, Adana, Turkey,
E-mail: filizaraz2@hotmail.com

among adult patients with NAFLD who were diagnosed during routine examinations and have no known systemic disease.

Material and Methods

Patient characteristics

This prospective study was conducted at outpatient clinic of Internal Medicine department in Çukurova University. Adult subjects who were diagnosed as NAFLD by ultrasonography and had no known diabetes and/or liver disease were included into the study.

Patients were excluded if they had any one of following criteria;

1. Diagnosis of type 2 diabetes, chronic hepatitis B, chronic hepatitis C, cirrhosis, congestive cardiac failure or renal failure.
2. Heavy alcohol consumption (females >20 gr/day, males>30 gr/ day)
3. Drug use (including amiodarone, corticosteroid, methotrexate, tamoxifen and oral contraceptives)
4. Jejunoileal by-pass or wide small intestinal resection, 5. Malignancy
5. Total parenteral nutrition
6. Hypo or hyperthyroidism
7. Pregnancy

Laboratory analysis and measurements

Height, weight and waist circumference of all patients were recorded. Basal laboratory examination including fasting blood glucose, insulin, c-peptide, transaminases, albumin, lipid profile, thyroid stimulating hormone, HbA1C, C-reactive protein and Apo-B were performed. Oral glucose tolerance test (OGTT) with 75 gr glucose load was applied to all subjects. Formula was used to calculate Homeostasis Model Assessment-Insulin Resistance (HOMA-IR) index for each subject.

Definitions

ADA criteria was used to diagnose type 2 diabetes [18]. Subjects with fasting glucose level ≥ 126 mg/ dL or 2-hour plasma glucose level ≥ 200 mg/ dL during OGTT using glucose load of 75 gr or random plasma glucose level ≥ 200 mg/ dL were diagnosed as type 2 diabetes. Impaired fasting glycemia was defined as plasma glucose level of 100-125 mg/dL. Plasma glucose level of 140-199 mg/ dL 120 minutes after glucose load was defined as impaired glucose tolerance. Systolic blood pressure of 120-139 mm Hg and diastolic blood pressure of 80-89 mm Hg were accepted as prehypertension [19].

The formula using fasting glucose and fasting insulin levels was used to calculate HOMA-IR. HOMA-IR ≥2.7 was accepted as cut off to define insulin resistance [20,21].

HOMA-IR=[Fasting glucose (mmol/L)x Fasting insulin (mU/ml)]/22.5 ATP III criteria defines the metabolic syndrome as having three of the following five criteria [11].

- Central obesity (waist circumference ≥102 cm in male and ≥88 cm in female)
- Serum triglycerides ≥150 mg/dL or drug treatment for hypertriglyceridemia.
- Serum high-density lipoprotein (HDL) cholesterol <40 mg/dL in male and <50 mg/dL in female
- Blood pressure equal or higher 130/85 mmHg or taking antihypertensive medication
- Fasting plasma glucose (FPG) ≥110 mg/dL or taking anti-diabetic medication.

Çukurova University Institutional Review Board approved this study.

Statistical analysis

SPSS 15.0 software was used to perform statistical analyses. Parameters were expressed as Mean ± SD or n (%). Continuous variables were compared by Student's t-test. For comparison of categorical variables, Pearson Chi-squared test was used. For comparing variables of more than two groups, ANOVA test was applied. For Spearman's coefficient, $p < 0.05$ was accepted as significant.

Results

Two hundred and thirty adult subjects who were diagnosed as AFLD by ultrasonography and had no history of diabetes and/or liver disease were enrolled into the study. Mean age of whole cohort was 50.3±10.6 (18-95) years. One-hundred and forty-one (61.3%) of all patients were female. Mean level for fasting glucose was 101.39±27.9 (69-364). Mean HOMA-IR index was 3.3±2.6 (0.5-26.5). Demographic and laboratory parameters of patients are shown in Table 1.

Fasting blood glucose level was normal in 138 (60%) subjects, while 78 (33.9%) and 14 (6.1%) of patients were diagnosed as impaired fasting glycemia (IFG) and type 2 diabetes, respectively. After OGTT, impaired glucose tolerance (IGT) was present in 65 (28.3%) subjects, while type 2 diabetes was diagnosed in 51 (22.1%) of all subjects.

Among 75 (32.6%) subjects with family history of type 2 DM, IFG was present in 22 (29.3%) and type 2 DM was present in 20 (26.2%) subjects. Among 155 (67.4%) patients with no family history of type 2 DM, IFG and type 2 DM were present in 43 (27.7%) and 31(20%) subjects, respectively. For NAFLD, having family history of type 2 DM did not significantly affect the diagnosis rate of type 2 DM or IFG.

BMI was normal (18.5-25) in 26 (11.3%) subjects. For 91 (39.6%) and 70 (30.4%) subjects BMI was between 25-29.9 and 30-35, respectively. For 43 (18.7%) patients BMI was over 35. Table 2 shows characteristics of patients by BMI. Diagnosis of IGT and type 2 DM did not significantly differ by BMI (p: 0.10).

Fifty-nine (27.5%) of 230 subjects had normal blood pressure. Prehypertension was present in 41 (17.8%) of all subjects. 130 (56.5%) subjects had hypertension or were treated for hypertension.

Metabolic syndrome by ATP-III criteria was present in 56.5% of

patients with ultrasound diagnosed NAFLD. MS was present in 57.9% of females, while it was present in 54.4% of males (p: 0.610). Among subjects with MS, mean HOMA-IR was 2.5±16 (0.5-14.2), while for subjects without MS, mean HOMAIR was 3.9 ±2.4 (1.2-16.5) (p: 0.0001). Table 1 shows patient characteristics according to the presence of metabolic syndrome. Metabolic syndrome was detected in 93 (73.2%) out of 127 subjects whom HOMA-IR was ≥2.7 (Table 3). HOMA-IR was positively correlated with increasing component of ATP III criteria (r=0.409, p=0.0001).

Insulin resistance was not affected significantly by BMI in this study. Mean HOMA-IR was 2.79 ±2.33 for subjects with BMI < 25. For subjects with BMI of 25-29.9 and 30-35, mean HOMA-IR were 2.94 ±1.81 and 3.92± 3.51, respectively. Mean HOMA-IR was 3.6 ±2.0 for subjects with BMI > 35 (p: 0.059). HOMA-IR did not show any correlation with BMI (p: 0.061, r: 0.124).

Mean ALT level was 33.2 ± 22.1 (6-143) U/L. In 53.5% of all subjects, ALT level was ≥ 25 U/L. In 48.7% of all subjects ALT level was ≥30 U/L. Among our patients with NAFLD, presence of metabolic syndrome was not related with significant elevation in transaminase levels (p>0.05).

Table 1. Demographic and biochemical parameters of patients

	All patients (n:230)	MS (n: 130)	No-MS (n: 100)	p
Female n (%)	141(61.3)	81 (57.9)	60 (42.1)	.610
Age (years)*	50.3±10.6	51.4 ± 10.5	49 ± 10.6	.096
Body-mass index (kg/m²)*	30.5± 4.9	31.4±4.9	29.4±4.8	.002
Waist circumference*	104.8±10.0	107.8±9.2	100.8± 9.8	.0001
Fasting blood glucose (mg/dl)*	101.39±27.9	108.7±34.8	91.9±8.5	.0001
OGTT 2h blood glucose (mg/dl)*	142.8±52.7	157.7± 58.7	124.3±36.8	.0001
Fasting insulin (mU/ml)*	13.2± 8.1	15.1±9.1	10.7±5.7	.0001
C-peptide (ng/ml)*	3.1±1.1	3.5±1.2	2.6±0.8	.0001
HOMA-IR*	3.3 ±2.3	3.9±2.4	2.5±1.6	.0001
HbA1C (%)*	5.8±0.8	6.0±0.8	5.5±0.5	.0001
AST (U/L)*	28.0 ±15.4	28.8±16.1	27± 14.6	.388
ALT (U/L)*	33.2±22.1	33.2±21.4	33.2± 23.2	.988
Total cholesterol (mg/dl)*	200.5±53.8	204.9±54.3	196.3±49.8	.218
HDL (mg/dl)*	48.3±13.9	43±10.6	55.1±13.8	.0001
LDL (mg/dl)*	120.7±42.2	122.8±44.8	118.1±38.6	.406
Triglyceride (mg/dl)*	163.8±92.8	194.0±101.8	124.7±60.8	.0001
APO-B (mg/dl)*	95.8±28.5	101.2±27.3	88.8±28.6	.001
CRP (mg/L)*	7.1± 9.2	7.7±9.2	6.4±9.2	.268

Assessment-Insulin Resistance, CRP: C-reactive protein, AST: Aspartate aminotransferase, ALT: Alanine Aspartate aminotransferase, Apo-A: Apolipoprotein-A, Apo-B: Apolipoprotein -B, HDL: High density lipoprotein, LDL: Low density lipoprotein, TG: Triglyceride * Mean ± Standard Deviation

Table 2. Characteristics of patients by Body-Mass Index.

	BMI<25 n=26	BMI: 25-29,9 n=91	BMI: 30-35 n=70	BMI>35 n=43	p
Age (years)	51.47 ± 10.9	49.8 ± 11.8	51.3 ± 9.3	49 ± 9.7	.619
Systolic blood pressure (mm-Hg)*	121.5 ± 18	129 ± 20.2	136 ± 18.7	139.7 ± 19,4	.0001
Diastolic blood pressure (mm-Hg)*	70.7 ± 12.3	77.6 ± 13.4	83.5 ± 12.8	85.6 ± 13.9	.0001
Fasting glucose (mg/dl)*	110 ± 57.5	100.9 ± 24.5	101 ± 21.4	97.9 ± 14.4	.366
OGTT 2h glucose (mg/dl)*	136.9 ± 36.1	133.5± 57.0	152.7 ± 49.6	149.4 ± 53.8	.103
Insulin (mU/L)*	11.1 ± 9.6	11.8 ± 6.3	14.9 ± 9.96	14.4 ± 6.6	.030
C-peptide (ng/ml)*	2.84 ± 1.43	2.93 ± 0.97	3.37 ± 1.25	3.2 ± 1.0	.068
HOMA-IR*	2.79 ± 2.33	2.94 ± 1.81	3,92 ± 3.51	3.6 ± 2.0	.059
HDL (mg/dl)*	48.1 ± 20.8	48.71 ± 12.9	49.4 ± 13.9	46.0 ± 10.2	.646
LDL (mg/dl)*	124.2 ± 60.6	127.7 ± 4.5	111.8 ± 35.3	118.3 ± 31.2	.112
TG (mg/dl)*	158.4 ± 71.3	157.0 ± 103.4	182.4 ± 94.7	151.6 ± 74.3	.247
APO-B (mg/dl)*	92.2 ± 29.3	100.1 ± 33.2	94.4 ± 24.3	91.1 ± 22.5	.286
CRP (mg/L)*	7.9 ± 11.6	7.3 ± 11.4	5.5 ± 3.7	9.03 ± 8.5	.240

OGTT: Oral glucose tolerance test, HOMA-IR: Homeostasis Model Assessment-Insulin Resistance, CRP: C-reactive protein, HDL: High density lipoprotein, LDL: Low density lipoprotein, TG: Triglyceride. * Mean ± Standard Deviation.

Table 3. Prevalence of metabolic syndrome by HOMA-IR groups

	MS n (%)	Non-MS n (%)	All patients n (%)
HOMA-IR< 2.7 n (%)	37 (35.9)	66 (64.1)	103 (44.8)
HOMA-IR≥ 2.7 n (%)	93 (73.2)	44 (26.8)	127 (55.2)
Total n (%)	130 (56.5)	100 (43.5)	230 (100)

p: 0.0001. MS: Metabolic syndrome, HOMA-IR: Homeostasis Model Assessment-Insulin Resistance

Discussion

NAFLD has worldwide and increasing prevalence. It has been reported in 10-30% of general population in different countries [6,7]. It has wide disease range from simple steatosis to steatohepatitis and severe fibrosis. NAFLD has the potential for progressing to liver cirrhosis [4,6,22]. Although the pathogenesis of NAFLD has not been fully clarified, insulin resistance has been accepted to play key role in disease pathogenesis [23,24]. A robust relationship between metabolic syndrome and the risk for future diagnosis of type 2 diabetes has been demonstrated [25,26]. Metabolic syndrome also designates high cardiovascular disease risk. Patients with NAFLD frequently have one or more components of metabolic syndrome [17].

As reported in NHANES III, MS is present in 22% of general population in USA [27]. But prevalence is higher among patients with NAFLD. Hamaguchi et al. reported the MS to be present among 194 (41%) of 478 males and 33 (29%) of 113 females with ultrasound diagnosed NAFLD [28]. In a study by Marchesini et al., MS was reported in 88% of patients with biopsy-proven steatohepatitis, while 53% of patients with simple steatosis had MS. In that study, presence of MS in NAFLD was found to be associated with steatohepatitis and severe fibrosis [17]. In our study, MS by ATP III criteria was detected in 56.5% of all patients with NAFLD. Study populations, histological or radiological diagnosis of NAFLD or the criteria used to define MS may cause differences in reported prevalence rates. We used ultrasonography for diagnosis of NAFLD in our study. Ultrasonography was found to be 89% sensitive and 93% specific for diagnosis of steatosis, especially moderate to severe steatosis [29].

Insulin resistance is closely associated with NAFLD. Marchesini et al reported mean HOMA-IR as 1.8 ±0.6 in controls, while it was 3.3 ±1.0 in patients with NAFLD [24]. Another study with histologically proven 64 NAFLD patients with mean BMI of 28 ±3.5 reported mean HOMA-IR as 2.7± 1.7. But mean HOMA-IR among those with MS was 3.6 ±2.1 [20]. In our study, for 127 (55.2%) of all patients, HOMA-IR was ≥2.7. Among patients with MS, 73.3% had HOMA-IR ≥2.7.

The association between NAFLD and MS is bidirectional. Features of MS are common in NAFLD and on the other hand presence of MS components increase the risk of developing NAFLD [2]. NASH was reported to be more progressive as the components of metabolic syndrome increase in number. In that study by Ampuero et al, NASH was found to be more frequent in both obese and non-obese metabolically unhealthy patients than metabolically healthy patients (both obese and non-obese). Thus, they pointed to greater impact of metabolic status than obesity on NAFLD-related liver histology [30]. Independent of obesity, insulin resistance was reported to be associated with NASH [23]. Similarly, HOMA-IR did not show any correlation with BMI in our study.

As compatible with our study, Saely et al. reported increase in HOMA-IR score with increasing components of MS, namely number of ATP III criteria. They concluded that HOMA-IR and MS were predictive for increased incidence of vascular outcomes [31]. Increased diabetes risk, higher MS prevalence and insulin resistance in NAFLD associate this entity with increased cardiovascular risk.

According to TURDEP study in Turkey, 15% of subjects between age 40 and 60 years were newly diagnosed with IGT and/or type 2 diabetes [32]. This ratio has been reported as 44% among NAFLD patients in Turkey [33]. In an extensive cohort including 3091 patients with NAFLD, IFG was reported in 44.1% of patients [34]. Another prevalence study reported IGT in 42.3% of 661 patients with NAFLD [35]. Presence of NAFLD has been reported to be associated with 2-fold increased risk for type 2 diabetes even though age, gender, BMI and ethnicity were similar [36]. In our study, 50.4% of NAFLD patients had IGT and/or type II diabetes.

Apo-B was shown to be a better predictive than LDL for coronary events [37]. In our study, patients with MS had significantly higher mean Apo-B levels. Similar association was also reported by Sattar et al. In that study, patients having normal HDL and high Apo-B levels had higher BMI, waist circumference, fasting insulin and lower insulin resistance compared to patients having normal Apo-B and high non-HDL cholesterol level in whole cohort. Among patients with MS according to NCEP criteria, waist circumference and fasting insulin were higher in normal HDL/ hyper Apo-B group. They associated the increased Apo-B levels with higher cardiovascular disease risk for patients with hypertriglyceridemia [38].

Conclusion

In conclusion, prevalence rates of insulin resistance, type 2 diabetes and metabolic syndrome were increased among patients with NAFLD. Due to the increased cardiovascular risk, diagnosis and early treatment of these comorbidities has critical importance.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
All authors declare no financial support.

Ethical approval
This study was approved by Çukurova University Institutional Review Board.

References

1. Younossi ZM, Diehl AM, Ong JP. Nonalcoholic fatty liver disease: An Agenda for clinical research. Hepatology. 2002; 35:746-52.
2. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American association for the study of liver diseases. Hepatology, 2018;1:328-57.
3. Naga Chalasani N, Younossi ZM, Lavine JE, et al. The diagnosis and management of non alcoholic fatty liver disease: Practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. Hepatology. 2012;55:2005-23.

4. Wong RJ, Aguilar M, Cheung R, et al. Nonalcoholic steatohepatitis is the second leading etiology of liver disease among adults awaiting liver transplantation in the United States. Gastroenterology. 2015;148:547–55.

5. Vernon G, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. Aliment Pharmacol Ther. 2011;34:274-85.

6. Angulo P. Nonalcoholic fatty liver disease. N Engl J Med. 2002;16:1221-31.

7. Williams CD, Stengel J, Asike MI et al. Prevalence of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis among a largely middleaged population utilizing ultrasound and liver biopsy: a prospective study. Gastroenterology. 2011;140:124–31.

8. Lazo M, Hernaez R, Eberhardt MS, et al. Prevalence of non- alcoholic fatty liver disease in the United States: The Third National Health and Nutrition Examination Survey, 1998-1994. Am J Epidemiyol. 2013;178:38-45.

9. Younossi ZM, Koenig AB, Abdelatif D, et al. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology. 2016;64:73-84.

10. Farrell GC. Nonalcoholic steatohepatitis: What is it, and why is it important in the Asia- Pasific region? J Gastroenterol Hepatol. 2003;18:124-38.

11. Third report of the national cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) Final Report [no authors listed]. Circulation 2003;106:3143–420.

12. Kim D, Touros A, Kim WR. Nonalcoholic fatty liver disease and metabolic syndrome. Clin Liver Dis. 2018;22:133-40.

13. Fulop T, Tessier D, Carpentier A. The metabolic syndrome. Pathologie Biologie. 2006;54:375-86.

14. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: an American heart association /national heart, lung and blood insitute scientific statement. Circulation. 2005;112:2735-52.

15. Grundy SM, Cleeman JI, Daniels SR. et al. Diagnosis and management of the metabolic syndrome: an American heart association/national heart, lung, and blood institute scientific statement: executive summary. Crit Pathw Cardiol, 2005;4:198-203.

16. Wainwright P, Byrne CD. Bidirectional relationships and disconnects between NAFLD and features of the metabolic syndrome. Int J Mol Sci. 2016;17:367.

17. Marchesini G, Forlani G, Bugianesi E, et al. Nonalcoholic fatty liver, steatohepatitis and metabolic syndrome. Hepatology. 2003;37:917-23.

18. AMERICAN DIABETES ASSOCIATION. Standards of Medical Care in Diabetes—2011. Diabetes Care 2011; 34 (supplement): 11-61.

19. Chobanian AV, Bakris GL, Black HR,et al. The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: The JNC 7 report. JAMA. 2003;289:2560-72.

20. Siqueira ACG, Cotrim HP, Rocha R, et al. Nonalcoholic fatty liver disease and insulin resistance: importance of risk factors and histological spectrum. Eur J Gastroenterol Hepatol. 2005;17:837-841.

21. Bonora E, Kiehl S, Willeit J, et al. Prevalance of insulin resistance in metabolic disorders. Diabetes. 1998;47:1643-9.Med Science 2021;10(1):25-30.

22. Matteoni CA,Younossi ZM, Gramlich T, et al. Nonalcoholic fatty liver disease: a spectrum of clinical and pathological severity. Gastroenterology. 1999;116:1413-9.

23. Chitturi S, Abeygunasekera S, Farrell GC, et al. NASH and insulin resistance: Insulin hypersecretion and specific association with the insulin resistance syndrome. Hepatology. 2002;35:373-9.

24. Marchesini G, Brizi M, Morselli-Labate AM, et al. Association of nonalcoholic fatty liver disease with insulin resistance. Am J Med. 1999;107:450-5.

25. Hanson RL, Imperatore G, Bennett PH, et al. Components of the "Metabolic Syndrome" and incidence of type 2 diabetes. Diabetes. 2002;51:3120-7.

26. Klein BE, Klein R, Lee KE. Components of the metabolic syndrome and risk of cardiovascular disease and diabetes in Beaver Dam. Diabetes Care. 2002;25:1790-4.

27. Ford ES, Giles WH, Dietz WH. Prevalence of metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. JAMA. 2002;287:356-59.

28. Hamaguchi M, Kojima T, Takeda N, et al. The metabolic syndrome as predictor of nonalcoholic fatty liver disease. Ann of Int Med. 2005;143:722-8.

29. Joseph AE, Saverymuttu SH, al-Sam S, et al. Comparison of liver histology with ultrasonography in assessing diffuse parenchymal liver disease. Clin Radiol. 1991;43:26-31.

30. Ampuero J, Aller R, Gallego-Durán R, et al. The effects of metabolic status on non-alcoholic fatty liver disease-related outcomes, beyond the presence of obesity. Aliment Pharmacol Ther. 2018;48:1260-70.

31. Saely CH, Aczel S, Marte T, The metabolic syndrome, insulin resistance and cardiovascular risk in diabetic and nondiabetic patients. J Clin Endocrinol Metabolism. 2005;90:5698-703.

32. Satman I, Yılmaz T, Sengül A, et al. Population-based study of diabetes and risk characteristics in Turkey; the results of Turkish Diabetes Epidemiology Study (TURDEP). Diabetes Care. 2002:4:1551-6.

33. Sargin M, Bayramiçli UO, Sargin H, et al. Association of nonalcoholic fatty liver disease with insulin resistance. Is OGGT indicated in nonalcoholic fatty liver disease? J Clin Gastroenterol. 2003;37:399-402.

34. Oh SY, Cho YK, Kang MS, et al. The association between increased alanine aminotransferase activity and metabolic factors in in nonalcoholic fatty liver disease. Metabolism Clin Experimental. 2006;5:1604-9.

35. Fan JG, Zhu J, Li XJ, et al. Fatty liver and the metabolic syndrome among Shanghai adults. J Gastroenterol Hepatol. 2005;20:1825-32.

36. Seppala Lindroos A, Vehkavaara S, Hakinken AM, et al. Fat accumulation in the liver is associated with defects in insulin suppression of glucose production and serum free fatty acids independent of obesity in normal men. J Clin Endocrinol Metabolism. 2002;87:3023-8.

37. Sniderman AD, Furberg CD, Keech A. Apolipoproteins versus lipids as indices of coronary risk and as targets for statin therapy. Lancet, 2003;361:777-80.

38. Sattar N, Williams K, Sniderman AD, et al. Comparison of the associations of apolipoprotein B and non-high-density lipoprotein cholesterol with factors in patients with the metabolic syndrome in the insulin resistance atherosclerosis study. Circulation. 2004;110:2687-93.

Available online at www.medicinescience.org

ORIGINAL ARTICLE

Medicine Science International Medical Journal

Medicine Science 2021;10(1):56-9

Comparison of single-use flexible URS and re-usable flexible URS: Effectiveness, reliability, cost-efficiency analysis

Mustafa Erkoc[1], Huseyin Besiroglu[2]

[1]Beylikduzu State Hospital, Department of Urology, Istanbul,Turkey
[2]Catalca Ilyas Cokay State Hospital, Department of Urology, Istanbul,Turkey

Received 21 July 2020; Accepted 06 September 2020
Available online 31.12.2020 with doi: 10.5455/medscience.2020.07.139

Abstract

Comparison of Single-use Flexible Ureterorenoscopy (SF-URS) with Reusable Fiberoptic Flexible Ureterorenoscopy (RF-URS) is one of the most popular subject in Endourology. Flexible Ureterorenoscopy (F-URS) is the gold standard method used in the treatment of kidney and ureteral stones smaller than 2 cm and together with ESWL.SF-URS has been widely used along with RF-URS. Our study aims to analyze retrospectively RF-URS and SF-URS in terms of effectiveness, reliability and cost. 200 patients who underwent F-URS due to renal stones were included in our study. Patients were divided into 2 groups: 100 patients who underwent SF-URS and 100 patients who underwent RF-URS. Mean age of the two groups was 49.58, 50.24 in the RF-URS and SF-URS groups, respectively. The presence of hypertension and diabetes, Body Mass-Index (BMI), and stone characteristics were recorded, and postoperative stone-free rates, duration of hospital stay, duration of operation, post-operative hemoglobin loss, postoperative urosepsis, and auxiliary procedures were evaluated. A cost effective analysis was carried out. The demographic data and stone characteristics of both groups were similar and there was no statistically significant difference ($p> 0.05$). The SF-URS group was found to be more advantageous in terms of the duration of operation ($p<0.05$). Other operational data were similar to each other and no statistically significant difference was found ($p>0.05$). The RF-URS group was found to be more advantageous after a cost-effective analysis ($p<0.05$). SF-URS has an advantage over RF-URS in terms of image quality, ease of use and duration of operation. RF-URS was found to be more advantageous in a cost-effective analysis. In terms of other operational data, both procedures were similar. Well-designed prospective randomized controlled trials are needed.

Keywords: Flexible URS, kidney stone, RIRS, stone

Introduction

Renal stone disease is one of the most common diseases in daily urology practice [1]. With the advanced technologies, minimally invasive procedures for kidney stones and ureteral calculi have become prominent. Although the treatment method for the stone depends on the size and location of the stone, percutaneous nephrolithotomy is recommended for the treatment of kidney stones greater than 2 cm, whereas ESWL (Extracorporeal Shockwave Lithotripsy) and Flexible Ureterorenoscopy (F-URS) are recommended as the gold standard for stones smaller than 2 cm. Especially in ESWL-resistant stones, the most important treatment method is F-URS [2-5]. Furthermore, F-URS can be used for all age groups, from pediatric patients to geriatric patients, thanks to its low complication rates and its less invasive intervention [4,5].

With the technological developments in laser systems, and considerable improvements in imaging methods, F-URS is also used for much larger stones [6].

Although the stone size of 1-2 cm has been specified as the optimal usage range in studies, Flexible URS can also be used for stones up to 3 cm [7]. Recently, Single-use Flexible Ureteroscopes (SF-URS) have been developed as an alternative to Re-usable Fiberoptic F-URS (RF-URS). While RF-URSs in our clinic use fiber-optic imaging systems, SF-URSs uses digital video imaging systems. This difference enables SF-URS to be more advantageous in terms of weight of the device and vision quality [8]. These two types of URS used in the treatment have been discussed in terms of effectiveness, reliability and cost, and have recently been a popular topic to popular publications [9]. Although there have been some studies on this subject in the literature, there is a need for more studies comparing these two groups. Reusable digital F-URS devices are also used in the treatment of renal and ureteric stones. There are studies about this device; however, it is not available in our clinic [10]. Accordingly, our study aims to analyze RF-URS and SF-URS in terms of effectiveness, reliability and cost.

***Coresponding Author:** Mustafa Erkoc, Beylikduzu State Hospital, Department of Urology, Istanbul,Turkey. E-mail: mustafa.erkoc@yahoo.com

Material and Methods

This study was carried out with the Okmeydani Training and Research Hospital Ethics Committee's approval dated 16.04.2019 and numbered 1234.Informed consent form was obtained from all patients.The type of the study was retrospective. Two hundred patients who underwent operations due to kidney and ureteral stones were included in the study. RF-URS was applied to 100 of the patients, and SF-URS was applied to the other 100. Patients between 20-70 years of age with renal pelvis or proximal ureteral stone size of 10-24 mm, and who did not receive prior surgical treatment, were included in the study. Patients who had previous surgical treatments, used anticoagulants, had serious additional comorbidities and had congenital kidney anomalies were excluded. All operations were performed by a single surgeon. Patients underwent a routine hemogram, biochemistry tests, INR and urine culture before the operation. Unenhanced abdominal computerized tomography was applied to all patients before the operation. In addition, contrast imaging methods were applied to the patients if necessary. Firstly, the urethra, bladder and ureter were observed by semi-rigid URS in all patients. Then, a guide-wire was left in the kidney. A ureteral access sheath (Navigator HD Boston Scientific 11-13 F) was introduced through guide wire. In patients in which ureteral access sheaths could not be placed, direct access was made through the guide. Double J(DJ) stents were placed in 40 patients, where it was not possible to enter the ureter and they were re-operated on 4 weeks later. The stone was found by F-URS. With a Holmium Yag laser (QUANTA Holmium; Yag laser litho DK30 watt) device, stones were pulverized. Laser settings were standard for all patients (1.2 Joule,8 Heartz,9.6 Watt).DJ stents were applied to all patients after the operation. The kidney and urinary system were monitored by using X-rays 24 hours after the operation. DJ stents were removed from patients two weeks later. The Storz Flex-X2 Flexible Ureteroscope was used as the RF-URS device. A total of 3 RF-URS devices were used in 100 patients. Since the first RF-URS device broke down after the 35th patient, and the second RF-URS device broke down after the 72nd patient, they were replaced with a new one. The AnQing Eu Single-Use Digital Flexible Ureteroscope(Shanghai AnQing Medical Instrument Co.,Shangai,China) was used for each patient as the SF-URS device.

The patients were classified into two groups, being RF-URS and SF-URS. The presence of hypertension and diabetes, Body Mass-Index (BMI), stone location, stone size, stone density and hounsfield unit (HU) score of all patients was recorded. Postoperative stone-free rates, length of hospital stay, operating time, loss of postoperative Hb loss, postoperative urosepsis, ESWL and the data on whether a second operation is needed or not were recorded. The stone-free rate was determined according to unenhanced abdominal computerized tomography applied 3 months after the operation. A cost-effective analysis of the operation was examined. The data were analyzed by using Statistical Package for the Social Sciences, V. 22.0 (SPSS; SPSS Inc, Chicago, IL, USA). Continuous variables were compared by independent samples t-tests in case the variables had normal distribution according to Kolmogorov-Smirnov test. Otherwise the Mann Whitney-U test was used. Categorical variables were compared by chi-square or Fisher exact tests, as appropriate. The value of ($p<0.05$) was considered as statistically significant.

Results

Demographic data and stone characteristics of the patients were analyzed. The age, gender, BMI, stone density at tomography, stone size, operation-side and stone locations were examined, and no statistically significant difference was found ($p>0.05$). The demographic and stone characteristics of the patients are shown in detail in Table 1.

Table 1. Demographic data and stone characteristics

Parameters	RF-URS(100)	SF-URS(100)	P value
Age(y) mean±SD	49.58±12.58	50.24±12.12	0.630
Sex n%			
Male	72(72%)	70(70%)	0.952
Female	28(28%)	30(30%)	0.782
BMI (kg/m²), mean ±SD	26.07±4.55	25.84±3.56	0.756
Stone CT density (Hu), mean ±SD	978.42±288.28	1012.52±290.48	0.236
Stone size (mm), mean±SD	15.84 ±5.15	16.18±5.32	0.872
Operation Side n%			
Right	60(60%)	58(58%)	0.932
Left	40(40%)	42(42%)	0.898
Stone Location			
Upper Calix	2	3	0.728
Mid Calix	3	3	1.000
Lower Calix	25	25	1.000
Pelvis	32	30	0.882
Proximal Ureter	38	39	0.920

The mean operation time was found as 72.48 ± 24.32 and 58.14 ± 18.68 minutes in the RF-URS and SF-URS groups, respectively, and statistically significant difference was found (p <0.05). Stone-free rates of the patients were 83 (83%), 85 (85%) in the RF-URS and SF-URS groups, respectively, and no statistically significant difference was found (p>0.05). Durations of hospital stay were found to be 1.92 ± 0.32 and 1.74 ± 0.28 days in the RF-URS and SF-URS groups, respectively, and no statistically significant difference was found (p> 0.05). Also, after analyzing the rates of hospitalization due to secondary intervention rates, postoperative hemoglobin loss, and postoperative urosepsis, no statistically significant difference was found (p >0.05). Operational data of the patients is summarized in Table 2.

Table 2. Operational data of patients and cost-effective analysis

Parameters	RF-URS(100)	SF-URS(100)	P value
Operating time (mn)	72.48±24.32	58.14±18.68	0.0098
Duration of hospital stay (day)	1.92±0.32	1.74±0.28	0.236
Stone free rate n%	83(83%)	85(85%)	0.732
Secondary intervention (ESWL,Operation) n%	17(17%)	15(15)	0.584
Postoperative hemoglobin loss (g/dl) mean ±	0.842±0.392	0.834±0.348	0.968
Postoperative urosepsis n %	2(2%)	2(2%)	1.000
Cost Effective Analysis Per Patient(USD)	465	1100	0,012

A cost-effective analysis on the patients was carried out for the F-URS costs only, since the patients' operation procedures were the same except for F-URS. Cumulatively, in the SF-URS group, the single-use URS cost in our country was USD 110.000, and the cost per patient was USD 1.100. A total of three F-URS devices were used for 100 patients in the RF-URS group. 35 patients used the first RF-URS device and 37 patients used the second RF-URS device. The study was completed without any failure in the 3rd device. The price of the RF-URS device we use in our country is around USD 15.000. There is no difference between the maintenance and exchange costs for the devices in our country. Therefore, the devices are exchanged. Sterilization of RF-URS is performed via the hydrogen peroxide device. In our hospital, each application costs 15 US Dollars. A total of 100 applications would create a sterilization cost of 1500 US Dollars. Cumulatively, the cost in the RF-URS group was USD 46.500. The cost per patient was approximately USD 465. A statistically significant difference was found (p<0.05).

Discussion

AF-URS plays an important role in the treatment of kidney stones smaller than 2 cm. After the use of F-URS devices as a treatment modality, they have become the gold standard method due to low stone-free rates and complication rates [11]. In a study consisted of 279 patients conducted by Elbir et al, stone-free rate was found to be 78.4%, therefore, it was found that F-URS was an effective and reliable method in proximal ureters and kidney stones [12]. In addition, there are studies that suggest that it may be an alternative to PCNL for kidney stones greater than 2 cm [13]. Furthermore, it has been demonstrated that F-URS can be used effectively in all age groups [4,5,14].

SF-URS devices have been recently preferred due to their easy portability and better image quality compared with RF-URS devices. Salvado et al. examined the effectiveness of SF-URS in 71 patients. Their stone-free rates were as follows: 97.9% in stones smaller than 10 mm, 95.4% in stones between 10-20 mm, and 78.9% in stones greater than 20 mm. They reported that SF-URS technique is a reliable and effective method in kidney stone surgeries [15]. Many studies are available comparing the effectiveness of SF-URS and RF-URS devices. Davis et al. found similar stone-free rates for both procedures in a systematic review of 11 studies including 466 patients. This study demonstrated that SF-URS devices are easier to use and have better image quality compared with RF-URS devices, but it was stated that a cost-effective analysis should also be done [16]. Qi et al. divided 126 patients into two equal groups and compared SF-URS and digital reusable F-URS differently other studies. They demonstrated that SF-URS can be used as a reliable and effective method like digital reusable F-URS [9].

With the emergence of the comparable outcomes of SF-URS in terms of the stone free and complication rates, and with more favorable ergonomic advantages compared with RF-URS, the two methods are starting to be compared in terms of cost-effectiveness. Hennessey DB et al. examined both procedures in terms of cost-effectiveness and demonstrated that RF-URS is more advantageous, especially in hospitals with a high number of patients [17]. In the systematic review in which Talso et al. and PETRA URO Group analyzed 19 studies to compare both procedures in terms of cost-effectiveness, they found that RF-URS was more advantageous, although both methods had similar effectiveness rates [18].

Unlike other studies, our study found that SF-URS is more advantageous than RF-URS in terms of operating time. It also revealed that both procedures have similar results and are consistent with the literature in terms of stone-free rates, duration of hospital stay, and postoperative hemoglobin loss. Additionally, in accordance with the literature, RF-URS is more advantageous in terms of cost-effectiveness. Despite the fact that the costs of SF-URS are high, it should be considered that it provides ease of learning without the fear of breaking down particularly in hospitals, which offer assistant training; and that the breakdown of RF-URS device would result in higher costs. In addition, it should be noted that a substitute device is required in hospitals where RF-URS device is used as a measure in the case of breakdown. The experience of the surgeon is of utmost importance in F-URS.

The studies have shown that RF-URS has an economic life of 24-44. Our study is in line with the literature [9,18]. We could also say that our surgeon, who implements the operation procedure, is experienced in the field [5].

There are various limitations in our study. Our study is retrospective, and the duration of fluoroscopy was not recorded. Furthermore, the high costs of the devices in our country should also be taken into consideration. In addition, it should be considered that the economic life of the RF-URS could vary based on the experience of the surgeon and localization of the stone. The operation period is approximately 20% shorter in the SF-URS group when compared to the other group. This does not affect the operation costs in the RF-URS group statistically; however, it may increase them to a certain extent. Considering that the consumables to be used in both procedures are similar, the cost of staff, cleaning and nursing services is 25 USD per operation in our country, which is negligible when compared to other costs [19]. It was not included in the data of the study as it was not recorded.

Conclusion

SF-URS devices were found to be more advantageous than RF-URS devices in terms of the ease of use, image quality [8] and operating time. RF-URS was found to be more advantageous in terms of cost-effectiveness. There is a need for better designed wide-range studies to support our results on this subject.

Acknowledgements
No research support or funding was received in connection with this study. The authors have no significant affiliation or involvement, either direct or indirect, with any organization or entity with a direct financial interest in the subject matter or materials discussed.

Conflict of interests
*There is no conflict of interests between authors***.**

Financial Disclosure
All authors declare no financial support.

Ethical approval
This study was carried out with the Okmeydani Training and Research Hospital Ethics Committee's approval dated 16.04.2019 and numbered 1234.

References

1. Johnson CM, Wilson DM, O'Fallon WM, et al. Renal Stone epidemiology: a 25-year study in Rochester, Minnesota. Kidney Int. 1979;16:624-31.
2. Kijvikai K, Haleblian GE, Preminger GM et al. Shock wave lithotripsy or ureteroscopy fort he management of proximal ureteral calculi: an old discussion revisited. J Urol. 2007;178:1157-63.
3. Maltaga BR. Contemporary surgical management of upper urinary tract calculi. J Urol. 2009;181:2418-34.
4. Ekici M, Ozgur BC, Senturk AB et al. Efficacy and reliability of retrograde intrarenal surgery in treatment of pediatric kidney stones. Cureus. 2018;10:3719.
5. Erkoc M,Agalarov S. RIRS (Retrograde Intrarenal Surgery) is safe and effective in aging male patients: A single surgeon experience Annals Med Res. 2019;26:2545-8
6. Galvin DJ, Pearle MS. The contemporary management of renal and ureteric calculi. BJU Int. 2006;98:1283-8.
7. Goldberg H, Golomb D, Shtabholtz Y et al.The "old" 15 mm renal stone size limit for RIRS remains a clinically significant threshold size. World J Urol. 2017;35:1947-54.
8. Moore B, Proietti S, Giusti G et al. Single-Use ureteroscopes. Urol Clin North Am. 2019;46:165-74.
9. Scotland KB, Chan JYH, Chew BH. Single-use flexible ureteroscopes: how dothey compare with reusable ureteroscopes? J Endourol. 2019;33:71-8.
10. Qi S, Yang E, Bao J et al. Single-Use Versus reusable digital flexible ureteroscopes for the treatment of renal calculi: a prospective multicenter randomized controlled trial. J Endourol. 2020;34:18-24.
11. Schmidt S, Miernik A.Extracorporeal shock wave lithotripsy (ESWL) versus percutaneous nephrolithotomy (PCNL) or retrograde intrarenal surgery (RIRS) for kidney stones. Urologe A. 2015;54:1283-6.
12. Elbir F, Başıbüyük I, Topaktaş R et al .Flexible ureterorenoscopy results: Analysis of 279 cases. Turk J Urol. 2015;41:113-8.
13. Bai Y, Wang X, Yang Y et al.Percutaneous nephrolithotomy versus retrograde intrarenal surgery for the treatment of kidney stones up to 2 cm in patients with solitary kidney: a single centre experience. BMC Urol. 2017;17:9.
14. Berardinelli F, De Francesco P, Marchioni M et al. RIRS in the elderly: Is it feasible and safe? Int J Surg. 2017;42:147-51.
15. Salvadó JA, Olivares R, Cabello JM et al. Retrograde intrarenal surgery using the single - use flexible ureteroscope Uscope 3022 (Pusen™): evaluation of clinical results. Cent European J Urol. 2018;71:202-7.
16. Davis NF, Quinlan MR, Browne C et al. Single-use flexible ureteropyeloscopy: a systematic review. World J Urol. 2018;36:529-36.
17. Hennessey DB, Fojecki GL, Papa NP et al. Single-use disposable digital flexible ureteroscopes: an ex vivo assessment and cost analysis.BJU Int. 2018;3:55-61.
18. Talso M, Goumas IK, Kamphuis GM et al. Reusable flexible ureterorenoscopes are more cost-effective than single-use scopes: results of a systematic review from PETRA Uro-group. Transl Androl Urol. 2019;8:418-25.
19. Erkol U, Agirbas I. Cost analysis in hospitals and an application of activity based costing method. Ankara Üniversitesi Tıp Fakültesi Mecmuası. 2011,64.

Available online at www.medicinescience.org

ORIGINAL ARTICLE

Medicine Science International Medical Journal

Medicine Science 2021;10(1):60-3

Evaluation of type 1 diabetic patients: A single center experience

Gulsah Elbuken[1], Resul Yildiz[2], Ismail Yildiz[1], Sayid Shafi Zuhur[1]

[1]Tekirdag Namik Kemal University Faculty of Medicine, Department of Endocrinology Metabolism, Tekirdag, Turkey
[2]Tekirdag Namik Kemal University Faculty of Medical, Department of Internal Medicine, Tekirdag, Turkey

Received 29 April 2020; Accepted 08 August 2020
Available online 31.12.2020 with doi: 10.5455/medscience.2020.04.067

Abstract

We evaluated patients diagnosed with type 1 DM who were followed at our clinic by conducting a retrospective chart review. Medical records of a total of 147 patients with type 1 DM (70 females, 77 males) with a mean (±SD) age of 31.2±9.7 years were reviewed retrospectively. The study patients had a mean duration of follow-up of 13.9±9.5 years, mean duration of follow-up of 4±2.6 years at our clinic and a mean HbA1c value of 8.3±2.1%. Microvascular complications were recorded in medical files for 128 patients. There were 48 (37.5%) patients with at least one microvascular complication. Medical records showed that out of 128 patients, 23 (18%) had diabetic neuropathy alone, 4(3%) had diabetic retinopathy alone and 5 (4%) had diabetic nephropathy alone. Ten patients (8%) had both diabetic nephropathy and diabetic retinopathy and 6 (4.7%) patients had all three microvascular complications. No significant difference was observed between patients with or without microvascular complications in terms of HbA1c (HbA1c 8.3% versus 8.1%; p=0.85). A history of diabetic foot ulcer was present in 4 patients in the study sample (4/147=2.7% of all patients).Twenty-two (15%) patients were on insulin pump therapy during follow-up. Insulin pump users had a significantly lower HbA1c value (7.9%) compared to those not using insulin pump (8.5%) (p=0.02). At our clinic, special efforts are being made to ensure type 1 diabetic individuals have regular outpatient examinations. Despite all these measures, our patients are still far from reaching their target HbA1c values, suggesting that we have to do much more help patients achieve their glycemic goals.

Keywords: Type 1 Diabetes Mellitus (Type 1 DM), insulin pump, glycemic control, HbA1c, microvascular complications

Introduction

Type 1 Diabetes Mellitus (DM) is a chronic disease characterized by absolute insulin deficiency. Individuals are often diagnosed with this condition during childhood or young adulthood. Since these individuals spend a significant portion of their lives as diabetic patients, they face risk of developing micro- and macrovascular complications of diabetes. Maintenance of appropriate blood glucose regulation through replacement of deficient insulin and protecting the individual from diabetes complications are the major goals in the follow-up of type 1 DM [1-3]. Microvascular complications of diabetes can be avoided and even premature death due to macrovascular complications can be prevented with the best possible glucose regulation [4-5]. Many international bodies recommend targeting a HbA1c level below 7% [6,7] but unfortunately this is not a very target to achieve [8].

Two common methods are used for the treatment that relies of the principle of replacement of deficient insulin. One of these methods, the "intensive insulin therapy" generally consists of administration of 1 basal insulin and three injections of short-acting subcutaneous insulin before meals. The second method is "insulin pump therapy" that provides continuous subcutaneous insulin delivered from a reservoir in the pump and infused into the body through a needle set inserted under the patient's skin. The insulin pump allows administration of short-acting insulin before meals according to the carbohydrate content of the meal [9,10]. The dose of insulin to be infused by the insulin pump can be adjusted, offering the advantage of dosage flexibility. However, compared to conventional intensive insulin therapy, insulin pump requires multiple measurements of blood glucose and also is more costly due to its expensive equipment such as infusion set. Moreover, insulin pump therapy requires active involvement of the patient in his or her own therapy including the need to calculate the carbohydrate content of the meal, perform more frequent self-monitoring of blood glucose and adjust the insulin infusion rate to meet their needs. In theory, patients using insulin pump should have improved glucose regulation. However, failures in administration and monitoring may preclude achievement of target glucose values [11,12]. Therefore, we aimed to retrospectively review the data of type 1 DM patients using or not

*Coresponding Author: Gulsah Elbuken Tekirdag Namik Kemal University Faculty of Medicine, Department of Endocrinology Metabolism, Tekirdag, Turkey
E-mail: gelbuken@yahoo.com.tr

using insulin pump who are being followed at our clinic.

Material and Methods

Medical records of a total of 147 patients with type 1 DM were reviewed retrospectively.

The study was approved by the local Ethics Committee of the Medical Faculty of the Tekirdag Namik Kemal University and performed in accordance with Good Clinical Practice procedures and the current revision of the Declaration of Helsinki (No: 2020.246.11.06).

Results

Mean (±SD) age of 70 females and 77 males was 31.2±9.7 years. No difference was observed between females and males in terms of mean age and the duration of diabetes.

The mean age of patients at the time of type 1 DM diagnosis was 17.6±9.1years. The study patients had a mean duration of follow-up of 13.9±9.5 years, mean duration of follow-up of 4±2.6 years at our clinic and a mean HbA1c value of 8.3±2.1% (Table 1).

Table 1. Demographic, clinic and diabetes-related characteristics of patients with type 1 diabetes

Parameter/(unit)	Mean±Standard Deviation (SD)	Min	Max
Age (years)	31.2±9.7	17	67
Age at DM diagnosis	17.6±9.1	1	40
Duration of DM (years)	13.9±9.5	1	44
Duration of follow-up at our clinic (years)	4±2.6	1	10
HbA1c (%)	8.3±2.1	5.6	13.2

*HbA1c value is expressed as %.

Twenty-two (15%)patients were on insulin pump therapy during follow-up. Insulin pump users had a significantly lower HbA1c value (7.9%) compared to those not using insulin pump (8.5%) (p=0.02) (Table 2).

Table 2. HbA1c values in insulin pump users versus non-users

Parameter	Insulin pump use	Mean± Standard Deviation (SD)	P
HbA1c* (n=147)	Yes (n=22)	7.9±1.7	0.02
	No (n= 125)	8.5±2.3	

*HbA1c value is expressed as%.

A total of 128 patients were evaluated for microvascular complications of diabetes. While diabetic nephropathy can occur even at the onset of "microalbuminuria", patients with a glomerular filtration rate (GFR) less than 60 ml/min/1.73 m² were defined as having diabetic nephropathy in the present study. Patients with findings of proliferative or non-proliferative retinopathy included in the ocular examination records were considered as having diabetic retinopathy. Diabetic neuropathy was recorded as present or absent based on whether the patient had complained of bilateral distal symmetric sensory neuropathy. There were 48 (37.5%) patients with at least one microvascular complication. Medical records showed that out of 128 patients, 23 (18%) had diabetic neuropathy alone,4 (3%) had diabetic retinopathy alone and 5 (4%) had diabetic nephropathy alone. Ten patients (8%) had both diabetic nephropathy and diabetic retinopathy and 6 (4.7%) patients had all three microvascular complications. A history of diabetic foot ulcer was present in 4 patients in the study sample (4/147=2.7% of all patients).Patients with diabetic foot ulcer had all microvascular complications in addition to diabetic neuropathy. Although patients without microvascular complications had a lower mean HbA1c than in patients with such complications, the difference was not statistically significant (Table 3).

Table 3. HbA1c levels based on the presence or absence of microvascular complications

Parameter	Microvascular complications	Mean± Standard Deviation (SD)	P
HbA1c* (n=128)	Yes (n=48)	8.3±1.5	0.85
	No (n= 80)	8.1±1.7	

*HbA1c value is expressed as %.

Of 22 insulin pump users, 7 (31.8%) had at least one microvascular complication. Diabetic neuropathy alone was present in 6 patients and 1 patient had all three microvascular complications. The latter patient had DM for 25 years. Among 22 insulin pump users, those with microvascular complications were older, had a longer duration of diabetes and higher HbA1c levels compared to those without microvascular complications. While age and DM duration were statistically significantly different between patients with or without microvascular complications, HbA1c levels were not significantly different (Table 4).

Table 4. Clinical features of 22 insulin pump users with or without microvascular complications

Parameters	Age (years)	DM duration (years)	HbA1c (%)
Microvascular complications present (n=7)	45.3±12.7	27.1±10.1	8.3±1.5
Microvascular complications absent (n=15)	29.9±7.3	12.8±4.8	7.4±1.4
p	0.02	<0.01	0.17

*HbA1c value is expressed as %.

Among 48 patients with microvascular complications, mean HbA1c level was 8.9±2 % in 41 patients not on insulin pump treatment and 8.3±1.5 % in 7 patients on insulin pump treatment, (p=0.13).

"Regular follow-up patients" were defined as those with HbA1c follow-up visits at least every 3 months and "irregular follow-up patients" were those who had follow-up visits at an interval of more than 3 months or less than 4 HbA1c visits per year. Patients with "regular follow-up" appeared to have a lower mean HbA1c value versus "irregular follow-up" patients but the difference did not reach statistical significance (Table5).

Table 5. HbA1c levels according to the follow-up status

Parameters	Follow-up Status	Mean± Standard Deviation (SD)	p
HbA1c (n=147)	Regular (n=76)	8.2±2.4	0.14
	Irregular (n=71)	8.5±1.9	

*HbA1c value is expressed as%

Discussion

Patients with type 1 DM are at risk for diabetes complications because the underlying pathophysiology is absolute insulin deficiency and the diagnosis occurs at an early age. Poorly controlled diabetes has been recognized to be a risk factor for microvascular complications in type 1 diabetic patients since the Diabetes Control and Complications Trial (DCCT) [1,2]. Although all physicians engaged in diabetes follow-up strive to achieve good glycemic control, unfortunately the outcomes fall short of expectations. The major finding of the present study was that patients with type 1 DM failed to achieve the desired HbA1c values. However, our results are consistent with those reported by international cohort studies [13-16]. Interestingly, median HbA1c values which were retrospectively reviewed in a New Zealand study published in 2020 closely match our results [17]. Failure to attain target HbA1c values as observed in the current study may be associated with many physician- or patient related factors. Patient-related factors include poor adherence to insulin therapy leading to irregular insulin injections and even missing some doses, inadequate administration of insulin doses due to fear of hypoglycemia and non-compliance to exercise and diet. Physician-related factors include lack of proper education of diabetic patient by the healthcare provider on the physiopathology of diabetes, management of hypo- and hyperglycemia and diabetes complications as well as low frequency of patient follow-up visits and limited time dedicated for an individual. Being far away from target HbA1c values in our patients indicates that we need to take more stringent measures to improve educational and follow-up activities for type 1 DM patients at our clinic. Our findings underscore the need for tighter glycemic control in both patients receiving intensive therapy and patients using insulin pump to attain glycemic targets and type 1 diabetic population should be followed more closely and more frequently than type 2 diabetic population [18]. Unfortunately, little information on hypoglycemic episodes was included in the medical records of our patients. This is one of the most important shortcomings that we face during follow-up of our patients. Hypoglycemic episodes should be investigated and recorded at each visit for all patients. We occasionally observe elevated glucose values in type 1 diabetic population due to fear of "hypoglycemia". It would be possible for us to reduce the development of chronic complications by providing more comprehensive patient education on the management of hypoglycemic episodes and setting more stringent glycemic targets in type 1 diabetic patients [19-22].

Due to the retrospective nature of our study, the patients could not be assessed for macrovascular complications of diabetes. While a total of 147 patients were evaluated, only 128 of them were questioned with regard to microvascular complications as noted in their records. Thus, a microvascular complication rate of 37.5% (48/128) may not reflect the true prevalence of microvascular complications in our sample. Based on our findings, diabetic neuropathy alone was present in 18%, diabetic retinopathy alone in 3%, diabetic nephropathy alone in 4% of the patients; 8% of patients had both diabetic nephropathy and diabetic retinopathy and4.7% of patients had all 3 microvascular complications. Thus, 22.5% of the patients had symptoms of neuropathy, 15.7% had symptoms of retinopathy and 17.7% had symptoms of nephropathy. These figures are consistent with the rates of microvascular complications reported for patients with poorly controlled diabetes [12,15,19,23]. However, such high rates might have been detected in our study due to inclusion of patients evaluated for microvascular complications, particularly neuropathy. Furthermore, since our outpatient clinic is part of a tertiary health-care facility, more complicated patients may have presented for medical help.

Although the study patients with microvascular complications had relatively low HbA1c levels, statistical significance was not observed. However, the fact that HbA1c levels are far away from target glycemic goals in both groups suggests that the subset of patients without microvascular complications are at risk for developing such complications. The DCCT trial was the first and most important study to show the significance of good glycemic control to both prevent the appearance (primary prevention) and the progression of microvascular complications (secondary intervention) in type 1 diabetic individuals and later studies corroborated these findings [1,2,3,19]. The prevalence of microvascular complications may vary according to the time lived with diabetes and whether the glycemic control is good or poor for an individual patient. Also, the criteria used for defining neuropathy, retinopathy and nephropathy may result in variable rates.

In the current study, microvascular complications were present in 7 of 22 patients on insulin pump therapy. Among those patients with microvascular complications, 6 had only diabetic neuropathy with no nephropathy or retinopathy. One patient with all three microvascular complications was both older and had a much longer diabetes duration compared to other patients. Patients who had microvascular complications were older and had a longer duration of diabetes than those who did not. While slightly elevated HbA1c values were found in individuals with microvascular complications, the elevation was not statistically significant. This suggests that HbA1c is not the sole factor involved in the development of complications in type 1 diabetes but the duration of diabetes may also have an impact .

Moreover, since our study was of retrospective nature, it is not known how long these patients have been using an insulin pump and whether the insulin pump was present before or after complications occurred. In addition, slightly greater HbA1c levels may have been found in individuals with chronic complications, since slightlyhigh average blood glucose levels are desired in such patients in order to protect them from hypoglycemia. Further prospective studies are needed to demonstrate the impact of the insulin pump on the occurrence of chronic complications of diabetes.

In our study, "regular follow-up patients" were defined as those with HbA1c follow-up visits every 3 months and no significant

difference was found between these patients and “irregular follow-up patients” with respect to HbA1c values. This suggests that HbA1c follow-up visits every 3 months are not sufficient alone particularly in type 1 diabetic patients. It also suggests that all patients with type 1 diabetes should be more closely followed than type 2 diabetic patients and possibly more frequently (at an interval of less than 3 months) until they develop adequate diabetes self-management skills.

Another important finding of this study was that patients using insulin pump had relatively better HbA1c values when compared with other patients. This may be explained by the fact that insulin pump users perform more frequent glucose measurements and are able to increase or reduce their bolus insulin doses in a flexible manner based on carbohydrate counting. It is known that insulin pump has positive effects on "hypoglycemia, glycemic fluctuation and quality of life" in individuals with type 1 DM. One of the limitations of this study includes its retrospective nature and lack of detailed information in patient files, which precluded assessment of these important parameters.

However, this patient group is also far from being at their target goals, suggesting that a more satisfactory and closer follow-up is needed for insulin pump users [10,11,24].

Conclusion

At our clinic, special efforts are being made to ensure type 1 diabetic individuals have regular outpatient examinations. In addition, patients are educated on carbohydrate counting and insulin pump use is promoted at follow-up visits. Also, individuals who wish to switch to insulin pump treatment are supported by a physician, a dietitian and a diabetes education nurse. Despite all these measures, our patients are still far from reaching their target HbA1c values, suggesting that we have to do much more help patients achieve their glycemic goals.

Conflict of interests
The authors declare that they have no competing interest

Financial Disclosure
All authors declare no financial support.

Ethical approval
The study protocol was approved by the Tekirdag Namik Kemal University Ethics Committee (No: 2020.246.11.06)

Note
The results of this study were reported as oral presentation at the Post-Graduate Training Course, Endo Course 4 held between October 4-6, 2019.

References

1. Molitch ME, Steffes MW, Cleary PA, et al. Baseline analysis of renal function in the Diabetes Control and Complications Trial. The Diabetes Control and Complications Trial Research Group. Kidney Int. 1993;43:668.

2. Diabetes Control and Complications Trial Research Group, Nathan DM, Genuth S, et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993;329:977.

3. The relationship of glycemic exposure (HbA1c) to the risk of development and progression of retinopathy in the diabetes control and complications trial. Diabetes. 1995;44:968.

4. Reichard P, Nilsson BY, Rosenqvist U. The effect of long-term intensified insulin treatment on the development of microvascular complications of diabetes mellitus. N Engl J Med. 1993;329:304.

5. Shankar A, Klein R, Klein BE, et al. Association between glycosylated hemoglobin level and cardiovascular and all-cause mortality in type 1 diabetes. Am J Epidemiol. 2007;166:393.

6. National Institute for Health and Care Excellence. Type 1 diabetes in adults: diagnosis and management. www.nice.org.uk/guidance/ng17/Standards of Medical Care in Diabetes-2019 accessed 09.17.2018

7. Miller KM, Foster NC, Beck RW, et al. Current state of type 1 diabetes treatment in the US: updated data from the T1D Exchange clinic registry. Diabetes Care. 2015;38:971-8.

8. Nathan DM, Cleary PA, Backlund JY, et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med. 2005;353:2643.

9. Benkhadra K, Alahdab F, Tamhane SU, et al. Continuous subcutaneous insulin infusion versus multiple daily injections in individuals with type 1 diabetes: a systematic review and meta-analysis. Endocrine. 2017;55:77.

10. Misso ML, Egberts KJ, Page M, et al. Continuous subcutaneous insulin infusion (CSII) versus multiple insulin injections for type 1 diabetes mellitus. Cochrane Database Syst Rev. 2010;CD005103.

11. REPOSE Study Group. Relative effectiveness of insulin pump treatment over multiple daily injections and structured education during flexible intensive insulin treatment for type 1 diabetes: cluster randomised trial (REPOSE). Br Med J. 2017;356:1285.

12. Patterson CC, Dahlquist GG, Gyürüs E, et al. Incidence trends for childhood type 1 diabetes in Europe during 1989-2003 and predicted new cases 2005-20: a multicentre prospective registration study. Lancet. 2009;373:2027.

13. Tuomilehto J. Theemerging global epidemic of type 1 diabetes. Curr Diab Rep. 2013;13:795.

14. Vehik K, Hamman RF, Lezotte D, et al. Increasing incidence of type 1 diabetes in 0- to 17-year-old Colorado youth. Diabetes Care. 2007;30:503.

15. Lipman TH, LevittKatz LE, Ratcliffe SJ, et al. Increasing incidence of type 1 diabetes in youth: twenty years of the Philadelphia Pediatric Diabetes Registry. Diabetes Care. 2013;36:1597.

16. Tamatea JAU, Chepulis LM, Wang C, et al. Glycaemic control across the lifespan in a cohort of New Zealand patients with type 1 diabetes mellitus. Intern Med J. 2020 Mar 16.

17. Mayer-Davis EJ, Lawrence JM, Dabelea D, et al. Incidence Trends of Type 1 and Type 2 Diabetes among Youths, 2002-2012. N Engl J Med. 2017;376:1419.

18. Nathan DM, Bayless M, Cleary P, et al. Diabetes control and complications trial/epidemiology of diabetes interventions and complications study at 30 years: advances and contributions. Diabetes 2013;62:3976.

19. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis. 2002;39:1.

20. Levey AS, Coresh J, Balk E, et al. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Ann Intern Med. 2003;139:137.

21. Levey AS, Eckardt KU, Tsukamoto Y, et al. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int. 2005;67:2089.

22. Pettus JH, Zhou FL, Shepherd L, et al. Differences between patients with type 1 diabetes with optimal and suboptimal glycaemic control: A real-world study of more than 30 000 patients in a US electronic health record database. Diabetes Obes Metab. 2020;22:622-30.

23. Fullerton B, Jeitler K, Seitz M, et al. Intensive glucose control versus conventional glucose control for type 1 diabetes mellitus. Cochrane Database Syst Rev. 2014;009122.

Available online at www.medicinescience.org

ORIGINAL ARTICLE

Medicine Science International Medical Journal

Medicine Science 2021;10(1):64-76

Nutritional status and frequency of overweight and physical activity behaviors of medical school students and factors affecting these variables

Allahverdi Aghayev[1], Kursat Gurel[2], Ozen Tugba Simsek[1], Hande Ipek[3], Erhan Eser[4]

[1]*Manisa Celal Bayar University, Faculty of Medicine, Manisa, Turkey*
[2]*Columbia University, College of Physicians and Surgeon, Department of Neurology, New York, USA*
[3]*Doç. Dr. Mustafa Kalemli Tavşanlı State Hospital, Department of Emergency Medicine, Kütahya, Turkey*
[4]*Manisa Celal Bayar University, Faculty of Medicine, Department of Public Health, Manisa, Turkey*

Received 27 July 2020; Accepted 29 September 2020
Available online 17.01.2021 with doi: 10.5455/medscience.2020.07.146

Abstract

Adequate nutrition and physical activity are of great importance for the general health and school success of individual, and for preventing obesity, cardiovascular diseases, diabetes mellitus, and cancer. The aim of study is to reveal the dimensions of the nutrition and physical activity behaviors of students in the 1-6 years of our medical faculty. In this study, 670 people (58.6%) were reached. The dependent variables are physical activity, nutrition, and body mass index (BMI). 16.3% of the students were overweight or obese; only 37.7% had a physical exercise at least one day a week. 29.4% of the students skip meals very often, 30.7% made a diet in the last 12 months. Students BMI> 25 had less diet; use more addictive substances, less participate in organized activities; are members of the community to a lesser extent and personal beliefs were found to be weaker. The most important variables affecting BMI are body perception and participation in organized activities. Living in a family home or dormitory and having room are the factors that affect the nutrition behavior positively and at least one cigarette per day affects negatively. The most important factors affecting adequate physical activity are to pay attention to weight, to make a holiday, to meet with friends in the evening and to study less than 2 hours per day. Being upper grades, not participating in organized activities, and depressive mood are other factors cause physical inactivity. In conclusion, systemic exercise and eating habits are insufficient. Students' positive habits are gradually decreasing as the period progresses. Faculty administrations should take measures for health promotion activities and should concentrate on students who are in grades 4 and above.

Keywords: Nutrition research, obesity, exercise epidemiology, young adult

Introduction

Nutrition during adolescence and youth is of great importance in terms of the continuation of the healthy life of the individual, school success, obesity that may occur at later ages, also for the prevention of chronic diseases [1,2]. A balanced nutrition should be evaluated together with adequate physical activity. Both nutrition and exercise have complementary effects especially in the anthropometric development of the body in young people. The importance of adequate and regular exercise for the development of healthy lifestyle behavior patterns has been shown in many sources in the literature. Physical inactivity is a changeable risk factor for cardiovascular diseases and also it affects the medical management of many physiological disorders such as hypertension, obesity, cancer, diabetes mellitus, rheumatic diseases, and depression [3].

***Coresponding Author:** Allahverdi Aghayev, Manisa Celal Bayar University, Faculty of Medicine, Department of Bölüm Belirtiniz Manisa, Turkey,
E-mail: aghayevallahverdi@gmail.com

The statistical data published by the WHO Regional Office for Europe show that the prevalence of overweight in the European Region is between 30-80% among adults, approximately 20% among children and adolescents, and one-third of those are obese [4]. In a study on 3rd-grade students in medical school in Greece, it was found that one-third of students were overweight or obese and BMI was a strong predictor for hypertension, also it had been revealed that obese students had high cardiovascular disease risk factors such as serum lipids and lipoproteins [5].

In several studies done on university students in Turkey, students and young people were found to have poor and imbalanced nutrition [6-9]. Obesity prevalence in youth has an increasing trend in Turkey. Turkey Statistical Institute (TUIK) reported obesity prevalence in young people as 3.3% in 2014 and 3.8% in 2016 [10]. Individual small studies reported a range between 5.3% (Istanbul) and 23.7% (Bartın) [6, 7]

Nutritional behavior in adolescents and youth is influenced by many individual characteristics such as health status, nutrition information, personal belief, body image, nutritional preference,

growth process, genetic effects, individual control; environmental characteristics such as socio-cultural values, popular food, family structure, friend effect, socioeconomic status, country food production, food availability, and accessibility; and lifestyle factors such as money or shortage of time [11, 12].

Although obesity is primarily a result of physical inactivity and overfeeding, many additional individuals or social predisposing factors of obesity may be listed as age, marital status, smoking and alcohol habits, number of births, education level, occupation, working conditions, and income level [11, 12].

When international data are examined in terms of physical activity, we encounter different rates in university students in different countries. For example, in a study conducted on 216 medical students in Sudan, 44.9% of students had low, 32% had medium, 23.1% had a high level of physical activity [13]; in a study conducted at the University of Belgrade Medical School in Serbia, 15.3% of the students were physically inactive, 62.2% were minimally active [14]; 43% of the medical students in Poland exercised high, 45% had moderate exercise and 12% of the students exercised inadequately [15]; whereas the medical students of Kasturba (India) have a good physical activity at a rate of 61.9% [16].

The studies conducted in Turkey showed a very low-level physical activity in university students: The rate of moderate to high physical activity prevalence was only 17% among Hacettepe University students [17] and around 19% in Istanbul Universities [18].

Literature findings showed that physical activity rate has been affected by various physical factors (accessibility, possibilities), cultural factors (habit, perspective) and social environment (number of participants, education level, urbanization, transportation). However, when different demographic (population, economic status, occupation) and biological factors (age, gender, heredity) are examined, it was determined that physical inactivity increased with age and males are more active than females. The rate of exercise varies according to many psychological (mental state, motivational) and emotional factors (enjoyment, relaxation, stress) [19-20].

The aim of this study is to find the frequency of overweight and obesity and physical activity behaviors of class 1-6 students of Manisa Celal Bayar University School of Medicine in Manisa and the predictive factors of overweight/obesity and physical activity.

Material and Methods

Study Population

TThe data of this cross-sectional study was extracted from a comprehensive study titled “Health promotion behaviors and their causality in medical faculty students [Tıp fakültesi Öğrencilerinin Sağlığı geliştirme davranışları ve nedenselliği] “. This research is based on the analysis of nutritional and physical activity data of a cross-sectional health promotion study that aims to reach all students without any sample selection, including the students of the class 1-6 students of Manisa Celal Bayar University Medical Faculty, who were educated in the 2016-2017 academic year. The study data were collected in the lecture halls at the end of the lecture and after the verbal information was given to the students and the questionnaires were applied to the students who accepted to participate. In the medical faculty of the MCBU, 1154 medical students were studying in the period 2016-2017. The participation rate of the study was 58.06%. When the participation rate was evaluated according to the classes, the

participation rate was 87.4% for period 1, 57.1% for period 2, 61.7% for period 3, 58.3% for period 4, 32.6% for period 5 and 40.6% for term 6. The present study was approved by the Ethical Committee of Celal Bayar University Faculty of Health Sciences (ref no:47114). The more details about the study population were published elsewhere [21].

Dependent variables

Physical activity, nutrition habits, and Overweight/obesity are the dependent variables of our study.

Physical activity

Three questions were asked using the WHO exercise definition pattern to assess the physical activity variable: 1- "How often do you do physical training for at least 30 minutes, enough to sweat your underwear?; 2- “What physical activity do you do if you exercise? (housework, running, hiking, sports activities or other)”; and 3- “What is your status as a licensed athlete?". WHO recommends that 18-64-year-old people should perform moderate physical activity for a total of approximately 150 minutes per week, often for at least two or three days a week and at least half an hour a day [22].

Nutrition habits

We assessed nutritional habits by three questions: 1- skipping meals; 2-weekly fruit consumption and 3- being on diet in the past year.

Overweight/obesity

Overweight/obesity was assessed by Body Mass Index (BMI). BMI was calculated by dividing the weight in kilograms by the square of the weight in meters. The subcategories of BMI are as follows: less than18 kg/m^2 were underweighted, the values between 18.00-24.99 kg / m^2 were normal and 25 kg/m^2 were overweighted or obese.

Independent variables

Age, school class, family type, marital status, place of residence (dormitory/family home/student house), own room, number of siblings, education level of parents, family income, diagnosed a disease requiring continuous use of medication in the individual or his/her family, smoking-alcohol-addictive use situation, thought about the body, attention to weight, giving importance to general health and oral health, daily studying hours, participation in organized activities, membership in the official or social community, have a holiday in the last 12 months, sleep problems, assessment of health status compared to last year, the hopes about the future, the existence of affinities in which troubles and happiness are shared, personal belief and mood variables were questioned and evaluated as independent variables.

The World Health Organization Well-Being Index (WHO 5) was used to assess the depressive mood. WHO5 is a 5-item scale that evaluates emotional well-being within the last two weeks [23].

Univariate and multivariate analyses were conducted in this study. Chi-square tests were used in the comparison of categorical variables and Fisher's exact test in non-parametric conditions; Student T-tests were used in the comparison of two means for parametric conditions. Multivariate Logistic Regression models were established by using the variables which were found to be significant in the univariate analyses. SPSS 23.0 statistical package was used in statistical analysis. Type 1 error was accepted as 0.05 or less in all hypothesis testing.

Results

A total of 670 students participated in this study. The mean age of the participants was 21.25 ± 2.18 and the median age was 21.00 (min: 17, max: 33). Only 5 students (0.7%) were married. The other sociodemographic characteristics of the students were presented in table 1. 33.7% of the students were living with their families, 30.1% of them were living independently at their own house single of with their friends. Only 24.2% of the students stay in dormitories. 88.8% of the students have their individual own rooms in the place where they stay; 9.7% had no siblings, 10.9% had three or more siblings.

The distribution of the dependent variables is shown in Table 2. The mean BMI was 22.38 ± 3.66 and the median BMI was 21.95. 16.3% of the students were overweight or obese according to the BMI values.

When asked about the frequency of doing physical exercise weekly for at least 30 minutes and enough to sweat the underwear, About one-third (37.7%) of the students were doing exercise at least one day in a week, at least 30 minutes a day. The type of exercise is 35.2% walking, 25.5% sports activities, 19.1% household chores, 10.7% running, and 4.2% other activities such as yoga, pilates, cycling, weight training, bodybuilding.

It was found that 12.2% of the students were involved in more than one physical activity.

The frequency of skipping food (frequently or very frequently) was 29.4% and the mean number of fruit consuming days was 3.55 ± 2.06 (median:3.00 days) and 30.7% of the students had a diet in the last 12 months.

The distribution of the socio-economic and health risk variables are given in Table 3. The 10.1% of the students have at least one medically confirmed illness; 18.2% of the students are regular smokers; 13.1% consume alcohol drinks at least once or twice a week; 44.6% of the students have watched their weight; 18.2% had no or very little concerns about their general health; 9.5% had no or little emphasis on oral and dental health; 50.7% of them visited a dentist at least once in the past year.

316 (47.2%) of the students reach daily news via social media, 92 (13.7%) via television, 80 (11.9%) via internet newspapers, 68 (10.1%) via e-mail, 43 (6.4%) via friends or neighbors and 38 (5.7%) via newspaper or magazine.

Table 1. Socio-demographic characteristics of the study population

Gender	Categories	Frequency (%)
Class (Degree)	1	181 (27.0)
	2	126 (18.8)
	3	129 (19.3)
	4	109 (16.3)
	5	56 (8.4)
	6	69 (10.2)
Marital status	Single	658 (98.3)
	Married	5 (0.7)
	Missing	7(1.0)
Living situation	With family	226 (33.7)
	Dormitory	162 (24.3)
	With peers	202 (30.1)
	Alone	80 (11.9)
Having own room	Yes	595 (88.8)
	No	73 (10.9)
	Missing	2(0.3)
Family Type	Extended family	49 (7.3)
	Nuclear family	582 (86.9)
	Fragmented family	39 (5.8)
Number of siblings	None	65 (9.7)
	One or two	523 (78.1)
	Three or more	73 (10.9)
	Missing	9(1.3)
Educational status of mother	Illiterate	17 (2.5)
	Primary school graduate	111 (16.6)
	Middle school graduate	43 (6.4)
	High school graduate	165 (24.6)
	College degree or more	333 (49.8)
	Missing	1(0.1)
Educational status of mother	Illiterate	9 (1.3)
	Primary school graduate	71 (10.6)
	Middle school graduate	30 (4.5)
	High school graduate	116 (17.3)
	College degree or more	441 (65.9)
	Missing	3(0.4)
Family income staus	Higher than family expenditure	304 (45.4)
	Lower than family expenditure	50 (7.5)
	Equal to family expenditure	313 (46.7)
	Missing	3(0.4)

Table 2. Distribution of variables questioning physical activity and nutrition

Variables	Categories	Frequency (%)
Physical Activity		
Physical activity frequency	Never	85 (12.7)
	Occasionally	332 (49.6)
	1-2 days in a week	137 (20.4)
	3-4 days in a week	80 (11.9)
	5-6 days in a week	14 (2.1)
	Everyday	22 (3.3)
The most common type of physical activity	Chores	128 (19.1)
	Running	72 (10.7)
	Walking	236 (35.2)
Living situation	Sports activities	171 (25.5)
	Other	28 (4.2)
Being a licensed athlete	I'm still a licensed athlete	9 (1.3)
	I was a licensed athlete in the past	134 (20.0)
	I don't have a license	521 (77.8)
Nutrition		
BMI	Less than 18.0	36 (5.4)
	18-24.99	455 (67.9)
	25-29.99	86 (12.9)
	30 and over	23(3.4)
	Missing	67(10.0)
Frequency of skipping meal	Never	164 (24.5)
	Seldom	307 (45.8)
	Sometimes	156 (23.3)
	Often	41 (6.1)
	Missing	2(0.3)
How many days do you consume fruit in a week?	Never or 1 day	90 (13.4)
	2 or 3 days	285 (42.5)
	4 or 5 days	154 (23)
	6 or 7 days	130 (19.4)
	Missing	11(1.6)
Diet in the last year	Yes	206 (30.7)
	No	452 (67.5)
	Missing	12(1.8)
Body image perception	Too thin	9 (1.3)
	Thin	68 (10.7)
	Just right	352 (52.5)
	Fat	206 (30.7)
	Too fat	31 (4.6)
	Missing	4(0.6)

Table 2 continued.		
Do you watch your weight?	Never	72 (10.7)
	Seldom	227 (33.9)
	Sometimes	264 (39.4)
	Often	106 (15.8)
	Missing	1(0.1)
The factor that determines the behavior to pay attention to weight	Friend recommendation	17 (2.5)
	Measuring body weight	94 (14)
	Tight clothes	45 (6.7)
	Discontent with physical appearance	264 (39.4)
	Health	68 (10.1)
	Sport	6 (0.9)
	Missing	176(26.3)

Table 3. Distribution of social and health risk variables that affect nutrition and physical activity behavior

Variables	Categories	Frequency (%)
Existence of a person have a chronic disease in the family	Yes	222(33.1)
	No	448(66.9)
Having chronic disease	Yes	68(10.1)
	No	597(89.1)
	Missing	5(0.7)
Smoking at least one cigarette a day for six months or more	Evet	172 (25.7)
	Hayır	498 (74.3)
Keeping smoking	Everyday	122 (18.2)
	Occasionally	46 (6.9)
	Quit	90 (13.4)
	Don't smoke	412(61.5)
Frequency of consuming alcoholic beverages	Never	307 (45.8)
	Occasionally	138 (20.6)
	One time or more in a month	133 (19.9)
	One time or more in a week	77 (11.5)
	Everyday	11 (1.6)
	Missing	4(0.6)
Addictive substances use (except smoking/alcohol intake)	Yes	43 (6.4)
	No	622 (92.8)
	Missing	5(0.7)
Taking care of general health	None	16 (2.4)
	Very little	106 (15.8)
	Not bad	402 (60.0)
	Quite well	146 (21.8)
Taking care of oral health	None	7 (1.0)
	Very little	57 (8.5)
	Not bad	315 (47)
	Quite well	288 (43)
	Missing	3(0.4)

Table 3 continued.		
The last dental visit	In the past year	340(50.7)
	In the past 2 years	93 (13.9)
	In the past 3 years	37(5.5)
	4 years or more	94(14.0)
	I've never been	101(15)
	Missing	5(0.7)
Frequency of any sleep problems	Never	138(20.6)
	A little	228(34.0)
	Somewhat	153(22.8)
	Much	89(13.4)
	A great deal	55 (8.2)
	Missing	7(1.0)
Spirituality/Personal beliefs	Very strong(excellent)	171(25.5)
	Fairly strong(good)	31(47.3)
	Slightly strong(Not good)	113(16.9)
	Not strong(poor)	62(9.3)
	Missing	7(1.0)
Presence of intimate friendship	I have	570(85.0)
	I haven't(absent)	36 (5.4)
	Uncertain	60 (9.0)
	Missing	4(0.6)
Daily average study duration	0-4 hours	549(81.9)
	More than 4 hours	94 (14.1)
	Missing	27(4.0)
Spending time with friends after school	Never	59 (8.8)
	One or two days a week	294 (43.9)
	Three days or more a week	317 (47.3)
Time spent on social media in a day	0-2 hours	234 (34.9)
	2-4 hours	216(32.3)
	4 hours or more	159 (23.7)
	Uncertain	61(9.1)
Vacation length in last year	0-10 days	308 (46.0)
	More than 10 days	362 (54.0)
Membership of non-governmental organization or of social group	Yes	184 (27.5)
	No	475 (70.9)
	Missing	11(1.6)
Participation of organization as music band theater group. dance group, except sport organizations	Never	233(34.8)
	Seldom	317(47.3)
	Sometimes	84(12.5)
	Often	24(3.6)
	Missing	12(1.8)

When considering the academic burden and social activities of the students, we saw that students were studying 2.59 ± 1.79 days a week and %14 of them were studying daily four hours and over, and 2.69 ± 1.97 days in a week were spending time outside with friends in the evenings. The mean and median annual vacation days of the students were 18.2 and 10 days respectively, excluding their family visit days, whereas %16.7 had never gone on vacation in the past year. The average screen time (via the internet or cellular phones) was 3.64 ± 2.58 hours a day.

570 (85.1%) students had a friend who could share their worries or happiness. When asked what depth was shared with friends who were known to share their troubles, in which 73.6 of these friends are intimate with close friends. 11.1% of the students were hopeless or very hopeless but the future and 48.6% of them were hopeful or very hopeful and 27.5% of them were members of any official social community (association, sports club, community, etc.). Only 34.8% did not participate in non-sports organized activities such as music groups, theater groups, chess club, dance, foreign language education. 21.5 of the students reported severe sleep problems; 44.1% had depressive mood in the last two weeks according to WHO criteria (WHO5).

Univariate statistical analysis results are given in Table 4.

Table 4. Relationship between nutrition and physical activity and independent variables (Univariate analysis)

Variables		BMI ≥25 kg/m² n (%)	Regular and adequate nutrition n(%)	Adequate physical activity n(%)
Class(degree)	First-grade	20 (13.1)	***74 (40.9)	***92 (50.8)
	2nd, 3rd, 4th and 5th grades	77 (20.2)	144 (34.3)	147 (35.0)
	Final-grade	12 (17.4)	9 (13.0)	14 (20.3)
Living Situation	With family or dormitory	274 (80.8)	***171 (44.1)	**165 (42.5)
	With peers or alone	220 (83.3)	56 (19.9)	88 (31.2)
Having own room	Yes	99 (18.4)	***214 (36)	223 (37.5)
	No	10 (15.6)	12 (16.4)	29 (39.7)
Number of siblings	None	14 (23.0)	*33 (50.8)	29 (44.6)
	One or two	83 (17.8)	169 (32.3)	196 (37.5)
	Three or more	10 (15.2)	23 (31.5)	26 (35.6)
Smoking history	Yes	35 (22.0)	***39 (22.7)	65 (37.8)
	No	74 (16.7)	188 (37.8)	188 (37.8)
Current smoking status	Everyday	23 (20.5)	***19 (15.6)	42 (34.4)
	Ocaasionally	5 (11.6)	16 (34.8)	22 (47.8)
	Quit	17 (20.7)	36 (40.0)	35 (38.9)
Frequency of consuming alcoholic beverages	Never or occasionally	92 (17.8)	199 (34.4)	***205 (35.5)
	Once a month or a week or more	17 (20.0)	27 (30.7)	47 (53.4)
Addictive substances	Yes	**14 (34.1)	*8 (18.6)	**24 (55.8)
	Hayır	95 (17.0)	217 (34.9)	227 (36.5)
Body image perception	Too thin or thin	***0 (0.0)	30 (39.0)	23 (29.9)
	Just Right	30 (9.2)	115 (32.7)	139 (39.5)
	Fat or too fat	79 (37.8)	79 (33.3)	89 (37.6)
Watching own weight	Never or seldom	50 (18.5)	92 (30.8)	***56 (18.7)
	Sometimes or often	59 (17.8)	134 (36.2)	197 (53.2)
Diet in the last 12 month	Yes	***49 (25.8)	***89 (43.2)	**94 (45.6)
	No	60 (14.9)	136 (30.1)	153 (33.8)

Chi Square: *= p<0.05; **= p<0.01; ***= p<0.001 ;

Table 4 continued.

Variables		BMI ≥25 kg/m² n (%)	Regular and adequate nutrition n(%)	Adequate physical activity n(%)
Taking care of general health	None or very little	23 (20.4)	**28 (23.0)	43(35.2)
	Not bad or quite well	86 (17.6)	199 (36.3)	210 (38.3)
Last dental visit	In the past year	47 (15.3)	*128 (37.6)	**145 (42.6)
	Never or more than a year	61 (20.8)	94 (28.9)	106 (32.6)
Participation in organized activities	Never or seldom	*97 (19.7)	180 (32.7)	***193 (35.1)
	Sometimes or often	9 (9.0)	42 (38.9)	56 (51.9)
Membership to the social community	Yes	*22 (12.9)	70 (38.0)	*80 (43.5)
	No	84 (19.9)	152 (32.0)	165 (34.7)
Vacation length in last year	Never	25 (25.5)	***53 (47.3)	***43 (38.4)
	1-9 days	30 (16.7)	37 (18.9)	37 (18.9)
	10 days or more	54 (16.6)	137 (37.8)	173 (47.8)
Daily average study duration	0-2 hour	61 (18.8)	***135 (37.5)	***168 (46.7)
	2-4 hour	20 (11.8)	68 (36.0)	53 (28.0)
	4 hour and more	18 (20.5)	16 (17.0)	22 (23.4)
Going out with friends in the evening	Zero days a week	12 (24.5)	***32 (54.2)	**13 (22.0)
	One or two days a week	47 (18.1)	110 (37.4)	102 (34.7)
	Three days a week or more	50 (17.0)	85 (26.8)	138 (43.5)
Personal belief	Very or fairly strong	**67 (15.4)	160 (32.8)	174 (35.7)
	Slightly or not strong	41 (25.5)	62 (35.4)	75 (42.9)
Mood	Depressive	52 (19.8)	***75 (25.7)	***75 (25.7)
	Non-depressive	56 (16.8)	150 (40.5)	174 (47,0)
BMI	24.99kg/m² and below	-	160 (32.4)	188 (38.1)
	25 kg/m² and above		38 (34.9)	45 (41.3)
Nutrition character	Positive/regular	38 (19.2)	-	**102 (44.9)
	Negative/irregular	71 (17.5)		151 (34.1)
Physical activity	Adequate level	45 (19.3)	**102 (40.3)	-
	Inadequate level	64 (17.3)	125 (30.0)	

Chi Square: *= p<0.05; **= p<0.01; ***= p<0.001 ;

The independent variables that had not shown a significant relationship with any of the dependent variables are family type; marital status; mother and father education level; a disease that requires constant use of medicines; chronic illness in the family; the level of importance given to oral and dental health; the presence of hepatitis B vaccine; daily social media or console game playing duration; frequency of sleep problems and the presence of a friend who is shared trouble or happiness.

Overweight/obesity

The age of the students was not found as a predictive factor for any of the dependent variables (p> 0.05). In the univariate analyses, it was found that 27.5% of the students having BMI > 25.00 perceived themselves inconsistently in normal body weight(p <0.001). The students having BMI > 25.00 was significantly more likely on diet during past 12 months (p <0.001); used more addictive except for smoking and alcohol (p <0.01); had less participation in organized social activities (p <0.05); had fewer membership rates to the societies or community groups (p <0.05) and had weaker personal beliefs or spirituality (p <0.001).

Nutrition

The relationship between positive and balanced nutrition and independent variables are presented in Table 4. The students who are in the advanced classes (p <0.001); who are living at home alone or with friends (p <0.001); who are living in a shared room

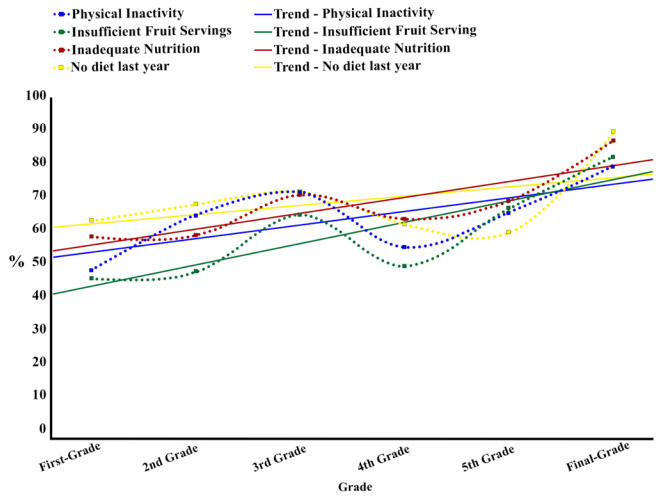
(p <0.001); who has higher the number of siblings (p <0.05); who are smokers (p <0.001) has insufficient and unbalanced nutritional behaviors. Additionally, non-alcohol addictive substance users (p <0.05); those who was on diet in the last 12 months (p <0.001); who are physical activity (p <0.01); who pay more attention to their general health (p <0.01) and who had more dentist examinations in the last year (p <0.05) had balanced and adequate nutrition. It was also observed that the students who had enough and balanced nutrition had less vacation (p <0.001); studied less lessons per day (p <0.001); had less time with their friends in the evenings after the lesson (p <0.001) and had more positive moods in the last two weeks (p <0.001) with significant relationships.

Physical activity

Physical activity levels are lower in students of advanced school classes (p <0.001); in students who live with their family members or in dormitory compared to living friends or alone (p <0.01). The students who consumed alcohol (p <0.001) and those who had addictive substance experience had more positive physical activity levels than others.

Students who paid less attention to their weight (p <0.001); who have negative and unbalanced nutrition (p <0.01); who have less diet in the last twelve months (p <0.01); who have never gone to the last dental examination for more than a year (p <0.01); who participated less in organized activities (p <0.001) and who were not members of a formal or social community (p <0.05) had higher levels of physical inactivity as well. It was also found that those who did inadequate physical activity had less holiday (p <0.001); studied more daily lessons (p <0.001); had less time with their friends after the lesson in the evenings (p <0.01) and had more depressive mood in the last two weeks (p <0.001).

As presented in Figure 1, negative behaviors such as physical inactivity, unbalanced nutrition, inadequate fruit serving, and skipping meals have increasing trends towards upper classes (p <0.001 for each).



	First-Grade	2nd Grade	3rd Grade	4th Grade	5th Grade	Final-Grade
Physical Inactivity	49.2	65.1	72.1	56	66.1	79.7
Insufficient Fruit Servings	59.1	59.5	71.3	64.2	69.6	87
Inadequate Nutrition	46.9	48.8	65.6	50.5	67.3	82.6
No diet last year	63.7	68.8	72.4	62.9	60.4	89.9

Figure 1. Distribution of dependent variables by class

In logistic regression analysis, the most important variable affecting BMI is "body perception". Participation in organized activities was found to be another variable affecting the BMI (Table 5a).

As a result of univariate analysis, a significant positive relationship was found between nutrition characteristics and variables examined in the logistic regression model, it was understood that staying in a family or dormitory and having an individual's own room were the variables affecting the nutrition behavior of the individual. In addition, it was determined that smoking and dieting are other factors that affect dietary behavior (Table 5b).

When logistic regression analysis was performed to determine the predictors of physical activity, the most important factors affecting students' positive physical activity behavior were attention to weight, spending holiday for 10 days or more, meeting with friends outside the home in the evening, and less than 2 hours of daily study variables. However, being in an advanced school class, less participation in organized activities, and having depressive mood are other predictors of physical inactivity (Table 5c).

Table 5. Independent variables affecting BMI, nutrition and physical activity (Stepped Logistic regression reduced end models)

Model 1: Dependent variable BMI*

	P	OR**	%95 Confidence Interval	
			Lower Limit	Upper Limit
Body image perception	p<0.001	7.685	4.684	12.608
Participation in organized activities	p<0.05	2.398	1.074	5.352
Constant	p<0.001	0.035		

Negelkerke R2: 0.256 ; * The variables that give results in Table 4 are included in the model.**OR: Ods Ratio

Model 2: Dependent variable Nutrition*

	P	OR**	%95 Confidence Interval	
			Lower Limit	Upper Limit
Living situation	p<0.01	2.691	1.313	5.516
Having own room	p<0.01	8.112	1.933	34.031
Current smoking status	p<0.05			
Smoking at least one daily	p<0.001	3.199	1.490	6.869
Diet last 12 month	p<0.05	2.037	1.031	4.024
Going out with friends in the evening	p>0.05			
Going out for less days in the evening	p<0.05	0.244	0.068	0.871
Constant	p>0.05	0.262		

Negelkerke R2: 0.292 ; * The variables that give results in Table 4 are included in the model.**OR: Ods Ratio

Model 3: Dependent variable Physical Activity*				
	P	OR**	%95 Confidence Interval	
			Lower Limit	Upper Limit
Class(degree)	p<0.05			
Watching own weight	p<0.001	4.431	2.925	6.713
Participation in organized activities	p<0.01	1.961	1.190	3.231
Vacation length in last year	p<0.001	3.045	1.840	5.041
Daily study time	p<0.001			
Less study time per day	p<0.05	0.504	0.259	0.981
Going out in the evening	p<0.01			
Going out for more days in the evening	p<0.001	4.132	1.892	9.022
Mood	p<0.05	1.525	1.021	2.279
Constant	p<0.01	0.186		

Negelkerke R2: 0.327 ; * The variables that give results in Table 4 are included in the model.**OR: Ods Ratio

Discussion

The foundations of health behaviors that affect the quality of life in older ages are laid during childhood and youth. So, it is important to question these behaviors at younger ages and to investigate the factors that affect them. This study differs from others in that, it is not only conducted on the young population but also on medical faculty students who will guide the population in terms of health promotion after graduation.

The mean BMI of the university students who participated in our study was 22.38 (± 3.66) kg/m^2. In a study involving female students studying at three different universities in Istanbul, the mean BMI was 20.8 ± 3.0 kg / m^2 [6]; In another study involving the university students of Bartın, the mean BMI was 22.92 ± 3.71 kg / m^2 [7]; In the study conducted among the medical students in Ankara, BMI values were found as 21.30 ± 2.72 kg / m^2 [17]. When the international literature were analyzed, the mean BMI distributions of university students were 22.8 ± 4.3 kg / m^2 in Sudan [13]; 22.24 ± 2.95 [14] in Belgrade, Serbia; 21.2 ± 0.3 for female students and 24.2 ± 0.4 for male medical students in Poland [15]; 22.2 ± 3.3 [24]; on average 22.2 kg / m^2 for men and 20.8 for women in eight South-East Asian countries [25]; 25.5 ± 0.5 kg / m^2 for boys and 22.7 ± 0.4 kg / m^2 for girls among medical students in US [26]; and the mean BMI 24.1 kg/m2 in males, 29.4 kg/m^2 in females in Saudi Arabia medical school [27]; and 21.717 ± 4.33 kg/m^2 in Pakistan [28]. Our mean BMI figures are closer to developed countries than in developing countries' medical students.

The overweight and obesity prevalences in our study sample were 14.3% and 3.8% respectively. The overweight and obesity prevalences were 18.8% and 4.9% in Bartın University, whereas the overall overweight plus obesity rate is around 11% in Zonguldak university. Our figures are somewhat higher than Zonguldak but lower than Bartın University's findings. When we consider the weakness (BMI<18.00) prevalence of our medical faculty (6.5%) it's rather lower than Istanbul University which is around 15%. This difference is very difficult to interpret. This great gap between two universities may be attributed to the gender composition of the samples: Istanbul sample is a pure female sample while ours is a mixed sample. It was thought that the fact that the rate of weakness (15.7%) in the study in Istanbul was higher than the obesity rate (5.3%) was probably due to the increased interest in the body image of female students in the research universe and the trend of having a "slim body" appearance, which is widespread especially among women [6]. Again, according to the study data in Bartın, it was assumed that the prevalence of obesity prevalence among female students was statistically less than that of male students because female students paid more attention to their feeding habits and body appearance [7].

When the prevalence distributions of overweight and obesity among university students were examined, the prevalence of overweight and obesity was determined to be 22.2% and 6.5% in Sudan, [13]; 16.6% and 1.2% in Serbia [14]; 21.3% and 2.9% [16] in India; 17% and 2% in Malaysia [29]; 16.6% and 1% [30] in Iran; 10.2% and 20.9% in Pakistan [31] respectively. In a study of medical students in the USA, the prevalence of overweight and obesity was 25.8% and 6.2% for first-year students and 27.8% and 5.1% for fourth-year students, respectively [26]. In another study of Pakistan Karachi, the combined frequency of pre-obese and obese medical students was 33.2%, also 14.8% of students were pre-obesity, 11.9% were obesity class I, and 6.5% were obesity class II [28]. Turkish medical students have closer BMI figures to developing countries but lower than in the US, whereas the BMI prevalences are rather higher in the medical students of poor countries such as Pakistan, India, and Sudan. The recent BMI increase in the urban populations of the poor countries may explain this difference.

We found that in this study, 62.3% of the students had insufficient physical activity and 12.7% had no physical activity. Similarly, in a previous study on first-year medical students in our university, it was found that 13.8% of the first-year students did not exercise at all and about 90% did not perform physical activity at the recommended level [32]. Several studies that were conducted on the physical activity levels of university students revealed that 15% of the students were not physically active in a study conducted in Ankara [17]; and 30.7% in Istanbul [18]. Compared to other studies conducted in Turkey, our students are more inactive than the ones studying in Istanbul [18] and Ankara [17] universities. This difference may be attributed to the "adequate exercise" criterion. Our exercise criteria are "lasting at least half an hour and enough to sweat the underwear" at least one day in a week.

When we consider physical activity levels in the interantional studies: in Sudan, 44.9% of students have low, 32,0% have moderate and 23.1% have high physical activity levels [13]; 15.3% of the students were physically inactive and 62.2% were minimally active in Serbia [14]; 43% of students had high, 45% moderate and 12% had low level of exercise in Poland [15]; 61.9% of students had good physical activity in India [16]; half of the students (49.9%) had low physical activity, 33.6% moderate and 16.6% high physical activity in South East Asian countries [25];

10.5% of the students were involved in mild activity, 20.7% were in moderate activity, and 68.9% were in severe activity another study on medical students in South India [33]; 30% of university students had been exercising regular exercises for more than six months in Iran [30]; 65% of the male and 80% of the female medical students were not exercise in Saudi Arabia [27]; 36% of females and 52% of males medical students exercised ≥150 minutes/week in California [34]; %47.8 of medical students of Pakistan had regular physical activity [28]. We think that the prevalence of high levels of physical activity in India stems from the opportunities provided by the university because in this study it was found that more than half of the students (55%) used the sports facilities provided on the university campus [16]. In another study conducted in Malaysia, 84% of students exercising on campus, and 75% of all students stated that the sports facilities on campus were adequate [29]. The frequency of sufficient exercising is somewhat close to that of in Sudan [13], Serbia [14], and Iran [30] but lower than India [16] and Poland [15].

In a study conducted on preclinical students in the Medical School in Malaysia, it was determined that 76% of the students were physically active; 59% of the students exercising regularly; 78% of female students continued to exercise during the menstrual cycle; 10% represent the university, state or country in athletic competitions; 25% won medals in the competitions [29]. In our study, it was found that 20% of the students were athletes in their past and 1.2% were still licensed, athletes. This shows that government-wide measures should be taken for sports and young people should be encouraged for sports activities.

Students who had adequate physical activity had more positive feeding habits ($p < 0.01$). Similar to our findings in a study conducted in Samsun, it was found that physical exercise positively influenced eating habits [8]. In Malaysia, the majority of physically inactive students (67%), students with low (63%) and moderate (61%) activity had three meals a day, while 50% of students with high physical activity had more than three meals a day and half of those took nutritional supplements [29]. However, we found that having a balanced and adequate nutrition perception did not have a significant effect on physical activity [29]. In the study conducted at the University of Belgrade, it was determined by the statistical significance relationship that those who do high levels of physical activity consume more vegetables, fruits, and whole-grain bread; however, minimal active students consumed more margarine, mayonnaise, white flour products and commercial drinks [14]. In Poland, it was revealed that university students with high levels of physical activity consumed fewer carbohydrates such as galactose and sucrose [15].

In our study, there was no significant relationship between BMI and adequate physical activity. Similarly, some studies in the literature also did not determine the meaning relationship in terms of BMI and physical activity indicators [13, 14, 17, 25, 29-31]. This is thought to be due to individual differences in the selected research universe. In a study evaluating physical activity in medical students in South India, no significant relationship was found between BMI and physical activity, but students with BMI ≥25 kg / m^2 were found to be physically more active, and this situation was assumed to be overweight as a strong motivation for students to initiate physical activity [33].

In the Turkish studies mentioned above, students have consumed unhealthy and unbalanced food [6-9] and this negative behavior pattern in youth poses a risk for future health problems [3, 8). In several international studies, poor nutrition including snacks, low red meat consumption, abstinence from fatty foods and abundant cholesterol, being a man, and coming from a wealthy family were associated with BMI obesity [15, 25, 31].

In our study, it was determined that 29.4% of the students skipped meals frequently or very frequently. This finding is consistent with other studies conducted in Turkey [7, 8, 32, 35] and some other international studies [25, 29, 31, 28]. These studies showed that one of the main problems related to the nutritional behaviors of university students is skipping main meals, especially breakfast. Accordingly, informing young people that the skipping behavior causes unhealthy ready-to-eat food consumption as well as that there is no suitable process to lose weight should be one of the main goals in gaining proper and healthy eating habits.

It was found that 13.4% of the students who participated in our study ate fruit only one day or never ate it. Different percentages were obtained in different international studies: In South-East Asia, the average number of daily fruit servings of university students was found to be 1.4 [25]. In Saudi Arabia,

it was appointed that 35% of medical students did not consume regular basis fruits and vegetables [27] and in California, it was detected that merely 10% of students consumed the recommended servings of fruit and vegetables [34).

Only 33.9% of the students were fed adequately in terms of positive and balanced nutritional value that we created by dichotomizing the variables of skipping meals and eating fruits. In a study on 438 undergraduate medical students in South India, less than 50% consumed a balanced diet [33]. In a study on 638 adolescents in Istanbul, it was found that 99.8% of the students were in the risk group in terms of feeding habits at different degrees [9]. In another study, it was determined that 40% of university students were not fed enough and balanced [7]. In the study conducted on university students in Samsun province, the frequency of obesity was significantly higher in those who were fed with sugary and fatty foods in intermediate meals [8]. As a result, it is of great importance that university students gain healthy and balanced eating habits for health protection and health promotion.

The trends of overweight, malnutrition, and inadequate physical activity:

The trends of obesity and overweight among classes showed similar reverse U shaped patterns. At the beginning of medical education (1st class) the rates were quite low (13.1% for BMI >25.00 and 1.7% for BMI>30.0); the trend of body weight peak was observed at the mid classes (especially at class 3; 21.8% for BMI >25.00 and 4.6% for BMI>30.0) and then BMI starts to decrease in the final classes (17.4% for BMI >25.00 and 4.3% for BMI>30.0).

Inadequate physical activity and nutrition trends, on the other hand, showed a different trend (S-shaped) pattern than BMI (see figure 1). Both physical activity and nutrition showed similar trends in classes. Linear increases of inadequate physical activity and poor nutrition prevalences are observed from the 1st class

to 3rd class and the worse situation is observed in the 3rd class (midclass). The mid classes have a very high theoretical academic load which might lead to unbalanced nutrition. The lower physical activity levels that were seen in the mid classes are consistent with this fact. In contrary to the obesity trend -which starts to decrease from the 3rd class to the final class- a slight recovery is observed in the 4th class in physical activity and nutrition, but a linear worsening trend is observed from the 4th class to the final class. This increasing trend may be due to the pressure of the upcoming final board exam (Medical specialty Board Exam – TUS) which restricts the time of the medical students to allocate exercise and other social activities.

In our study, it was seen that the students who were educated in the advanced classes performed less physical activity than the early classes of medical school. Its already known that students of advanced classes have subjected to more intensive theoretical and practical training in clinical rotations, and the final grade students were also prepared for the specialty (board) exams. In a study on medical students in the USA, cardiovascular fitness scores of the students from the first grade to the fourth grade were found to tend to decrease, but these rates were 'very good' for both sexes [26]. However, in a study conducted among preclinical students in Malaysia, it was found that age was not a significant statistical variable for physical activity, but most of the physically active students were first-year students [29].

In our study, a statistically significant relationship was found between the class of the students and the positive and balanced nutrition behavior. It was determined that 40.9% of the students in the first year of education have balanced nutrition features, but only 13% of the students in the sixth grade received a balanced diet. We assume that this may be caused by factors such as fatigue, lack of time, stress, and anorexia based on stress, due to the intensive working conditions of sixth-grade medical students. In a study on medical students in Pakistan, a statistically significant increase was found between upper-class education and central obesity [31]. In a study on first, third, and sixth-grade medical school students in Saudi Arabia, no significant difference was found between classes in terms of obesity, regular eating habits, regular weekly fruit-eating, and physical activity [27].

To see the relationship between overweight and inadequate physical activity we performed a series of univariate and multivariate analyses. Overweight, inadequate nutrition and inadequate physical activity are the dependent variables of this study.

There was a consistency between BMI and body perception in univariate and multivariate analyses. This consistency between body perception and body image on BMI has been shown in a study on female students at the Medical School in Brazil as well [24].

In our study, both univariate analyzes and multivariate regression analyzes showed that the students who paid attention to their weight had more physical activity. In the study conducted in Istanbul, it was found that 72.6% of the students exercised for healthy living, 71.2% for feeling good, 60.6% for relieving tension, and 31.4% for entertainment [18]. In the study conducted in Malaysia, it was found that 53% of the students exercised to be healthy, 29% for staying physically fit, and 12% for recreational purposes [29].

The predictors of

The predictors of dieting in this study are being overweight, having adequate physical activity. This shows that health promotion is a multi-factorial pattern of behavior and that an individual with a positive trait is likely to exhibit another positive behavior as expected. Similar findings were observed in the literature as well [8].

In our study, it was found that those who live in families or dormitories were fed more balanced and had more physical activities than those living with friends or alone at home ($p < 0.01$). Similar findings were observed in a study cınducted in university students in Bartın [7] and Malaysia [29].

We found that smoker students have negative and unbalanced feeding habits, consistent with Serbian study results [14]. Our results also revealed that negative and unbalanced nutrition characteristics were predictors of depressive mood in line with the finding of another Turkish study conducted in Ankara [35] and Pakistan Karachi [28] and physically active students had more positive moods [8, 18]. Our results also showed that students who went to the dentist examination in the last year were more physically active and had more regular and balanced nutrition. We observed that overweight and obese students were less involved in organized social activities and had fewer contacts with their intimate friends.

These results may indicate that the coexistence of negative health-promoting attributes such as obesity, unbalanced nutrition, and smoking habit in students can provide evidence for a holistic health promotion pattern (all or nothing) in students.

Limitations of the study: One of the important limitations of this study is the low participation rate (58.1%). The low participation rates differ by classes and higher rates were reached in pre-clinic classes whereas lower rates were obtained in clinic classes. We could only conduct one round for questionnaire application and could not follow to a second-round since the questionnaires were filled out anonymously by the students, and therefore, those who did not fill out the questionnaire later could not be reached. Another and very important imitation is the self-reported height and weight values. This may not bias the results since we assume that all university students are aware of this height and weight but we are not sure if they were honest when reporting their values.

Conclusion

The results of this study revealed that overweight and obesity prevalences in medical students are similar to that of developed countries except for the US, but systematic exercise (physical activity) habits were inadequate among medical students globally. The most important variable affecting body weight is body perception. Positive nutrition and exercise habits of medical students gradually decrease as the class (term) progresses.

There is a need to promote physical activity and adequate nutrition habits in medical schools and to emphasize the importance of promoting physical activity. The school authorities should take effective measures to support the students in terms of health promotion activities, and these measures should be focused

especially on students who are in terms of 4 and above.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
All authors declare no financial support.

Ethical approval
This study was approved by the Ethical Committee of Celal Bayar University Faculty of Health Sciences (ref no: 47114)

References

1. Mukudi E. Nutrition status, education participation, and school achievement among Kenyan middle-school children. J Nutr. 2003;19:612-6.
2. Şanlıer N, Yabancı N. Okul çağında beslenme. 7-14 yaş Çocuk Gelişimi ve Eğitimi Dizisi. 1. Baskı. Morpa Kültür Yayınları, İstanbul, 2005;139-58.
3. Warburton DE, Nicol CW, Bredin SS. Health benefits of physical activity: the evidence. CMAJ. 2006;174:801-9.
4. The challenge of obesity in the WHO European region and the strategies for response, Ed. Francesco Branca, Haik Nikogosian ve Tim Lobstein, WHO, Denmark, 2007. https://www.euro.who.int/__data/assets/pdf_file/0010/74746/E90711.pdf access date 6.11.2019
5. Bertsias G, Mammas I, Linardakis M, et al. Overweight and obesity in relation to cardiovascular disease risk factors among medical students in Crete, Greece. BMC Public Health. 2003;3:3.
6. Garibağaoğlu M, Budak N, Öner N, et al. Üç farklı üniversitede eğitim gören kız öğrencilerin beslenme durumları ve vücut ağırlıklarının değerlendirmesi. Saglik Bilim Derg. 2006;15:173-80.
7. Dülger H, Mayda AS. Bartın Üniversitesi Sağlık Hizmetleri Meslek Yüksekokulu Öğrencilerinde Beslenme Alışkanlıkları ve Obezite Prevalansı. DÜ Sağlık Bil Enst Derg. 2016;6:173-7.
8. Acar ZÖ. Üniversite öğrencilerinde obezite ve yaşam davranışları. Uzmanlık Tezi. Ondokuz Mayıs Üniversitesi, Samsun, 2015.
9. Demirezen E, Coşansu G. Adölesan Çağı Öğrencilerde Beslenme Alışkanlıklarının Değerlendirilmesi. STED. 2005;14:174-8.
10. Türkiye Sağlık Araştırması, TUİK, 2016. http://tuikweb.tuik.gov.tr/PreHaberBultenleri.do?id=24573# access date 31.05.2017
11. Neumark-Sztainer D, Story M, Perry C, et al. Factors influencing food choices of adolescents: Findings from focus-group discussions with adolescents. J Am Diet Assoc. 1999;99:929-37.
12. Gorin AA, Crane MM, Jelalian E, et al. The obesogenic environment, Handbook of Childhood and Adolescent Obesity. Springer Science, Business Media LLC, New York, USA. 2008:145-61.
13. Yousif MM, Kaddam LA, Humeda HS. Correlation between physical activity, eating behavior and obesity among Sudanese medical students Sudan. BMC Nutr. 2019;5:6.
14. Janković G, Stanojević Z, Mazić S, et al. Physical activity and dietary habits among second year students of the school of Medicine, University of Belgrad. J Phys Educ Sport. 2017;15:239-48.
15. Grygiel-Górniak B, Tomczak A, Krulikowska N, et al. Physical activity, nutritional status, and dietary habits of students of a medical university. J Sport Health Sci. 2016;12:261-7.
16. Rao CR, Darshan B, Das N, et al. Practice of physical activity among future doctors: a cross sectional analysis. Int J Prev Med. 2012;3:365-9.
17. Savcı S, Öztürk M, Arıkan H, et al. Üniversite öğrencilerinin fiziksel aktivite düzeyleri. Turk Kardiyol Dern Ars. 2006;34:166-172.
18. Oğuz S, Çamcı G, Yılmaz RK. Üniversite öğrencilerinin fiziksel aktivite yapma durumu ve fiziksel aktivitenin kalp sağlığına etkisini bilme durumu. GUSBD. 2018;7:54-61.
19. Eyler AA. Personal, social, and environmental correlates of physical activity in rural Midwestern white women, Am J Prev Med. 2003;25:86-92.
20. Vanhees L, Lefevre J, Philippaerts R, et al. How to assess physical activity? How to assess physical fitness? Eur J Cardiov Prev R. 2005;12:102-14.
21. Gurel K, Aghayev A, Ipek H, et al. Trends and determinants of quality of life and self-rated health in the course of medical education among medical students. Int J Med Sci. 2020;9:118-27.
22. World Health Organization. Global recommendations on physical activity for health. World Health Organization. https://apps.who.int/iris/handle/10665/44399 access date 17.01.2020
23. Saipanish R, Lotrakul M, Sumrithe S. Reliability and validity of the Thai version of the WHO-Five Well-Being Index in primary care patients. Psychiatry Clin Neurosci. 2009;63:141-6.
24. Bosi ML, Nogueira JA. Body image and eating behavior among medical students: eating disorders among medical students. Epidemiology (Sunnyvale). 2016;6(4).
25. Peltzer, K, Pengpid, S. The association of dietary behaviors and physical activity levels with general and central obesity among ASEAN University Students. AIMS Public Health. 2017;4:301-3.
26. Brehm B, Summer S, Khoury J, et al. Health status and lifestyle habits of us medical students: A longitudinal study. Ann Med Health Sci Res. 2016;6:341.
27. Al-Qahtani MH. Dietary Habits of Saudi Medical Students at University of Dammam. Int J Health Sci (Qassim). 2016;10:353–62.
28. Asghar A, Masood Shah A, Ali Hussain A, et al. Frequency of pre-obesity and obesity in medical students of karachi and the predisposing lifestyle habits. Cureus. 2019;11:e3948.
29. Asousi MA. Physical activity among preclinical medical students at the University of Malaya, Malaysia. JNHFS. 2016;4:1-8.
30. Najarkolaei FR, Talatappeh HD, Naghavi S. Physical activity and nutrition status in the university students: a mix method study. JHPSH. 2015;2:201-6.
31. Assir MK, Khan Z, Shafiq M, et al. High prevalence of preobesity and obesity among medical students of Lahore and its relation with dietary habits and physical activity. Indian J Endocr Metab. 2016;20:206.
32. Selçuk KT, Karataş S, Çetinkaya İE, et al. Celal Bayar Üniversitesi Tıp Fakültesi Dönem 1 öğrencilerinin bazı sağlık davranışları ve okul ortamından beklentilerinin değerlendirmesi. CBU-SBED. 2016;3:413-8.
33. Saranya SV, Rao CR, Kumar SC, et al. Dietary habits and physical activity among medical students of a teaching hospital in South India: A descriptive analysis. Trop J Med Res. 2016;19:172-7.
34. Bergeron N, Al-Saiegh S, Ip EJ. An analysis of california pharmacy and medical students' dietary and lifestyle practices. Am J Pharm Educ. 2017;81:5956.
35. Çetin G, Sarper F. Tıp fakültesi birinci ve son sınıfa devam eden öğrencilerin beslenme bilgi ve alışkanlıkları üzerine bir araştırma. 21. yüzyılda eğitim ve toplum. 2013;2:84-104.

Available online at www.medicinescience.org

ORIGINAL ARTICLE

Medicine Science International Medical Journal

Medicine Science 2021;10(1):77-81

New hematological biomarkers in patients with atrial septal aneurysm

Saadet Demirtas Inci[1], Sabiye Yilmaz[2]

[1]Health Sciences University, Diskapi Education and Research Hospital, Department of Cardiology, Ankara, Turkey
[2]University Education and Research Hospital, Department of Cardiology, Sakarya, Turkey

Received 25 November 2020; Accepted 18 December 2020
Available online 17.01.2021 with doi: 10.5455/medscience.2020.11.243

Abstract

Mean platelet volume/platelet count (MPV/PC) and monocyte/lymphocyte (MLR), neutrophil/lymphocyte (NLR) and platelet/lymphocyte (PLR) ratios are new hematological markers showing systemic platelet activation and inflammation. The aim of this study was to compare new hematological markers in patients with atrial septal aneurysm (ASA) and to determine their relationship in patients with ASA. 70 ASA and 47 healthy subjects (as control group) were included in the study. Demographic, clinical, echocardiographic and hematological values of the groups were recorded. MPV/PC ratio and MLR were significantly higher in ASA group compared to control group (0.03 ± 0.013 vs 0.02 ± 0.009, P=0.02 and 0.27 ± 0.15 vs 0.22 ± 0.08, P=0.03). NLR and PLR were not different between the groups. The presence of ASA was positively correlated with MLR and MPV/PC, left atrium, left ventricular (LV) septum thickness and LV posterior wall thickness, while red blood cell (RBC) was negatively correlated. However, in multivariate linear regression analysis, there was an independent relation between the presence of ASA and MPV/PC, MLR, LV septum thickness and RBC. We found that MPV/PC ratio and MLR from new hematological biomarkers are independent predictors for the presence of ASA.

Keywords: Atrial septal aneurysm, inflammation, platelet

Introduction

Atrial septal aneurysm (ASA) is generally seen at the level of fossa ovalis and defined as the possible cambering of atrial septum towards the right & left atrium or both of them. It can be seen alone but also often can be seen together with other heart diseases such as patent foramen ovale, atrial septal defect and mitral valve prolapse. ASA prevalence in adult population was found to be 2.4% in studies performed with transthoracic echocardiography [1]. Previous studies have reported that ASA can cause atrial-induced arrhythmia and cryptogenic stroke [2-5].

Neutrophil/lymphocyte (NLR), platelet/lymphocyte (PLR), mean platelet volume/platelet count (MPV/PC) and monocyte/lymphocyte (MLR), ratios are new hematological markers showing systemic plaletlet activation and inflammation. Neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) were also reported to be associated with inflammation and increased cardiovascular risk [6,7]. It was reported that the MLR is related to adverse clinical results in various cardiovascular diseases (i.e. heart failure, ST-segment elevation myocardial infarction) [8,9]. Increased MPV/PC ratio has been reported to be a better predictor for cardiovascular events [10]. Moreover, MPV and MPV/PC ratio are considered to be significant laboratory markers for the risk of acute ischemic stroke [11].

The aim of this study is to compare these NLR, PLR, MLR, MPV/PC ratio new hematological biomarkers in ASA and control cases and to determine their relationship with ASA.

Material and Methods

Selection of patients

70 study patients with ASA diagnosis (57 female, 13 male; mean age 44.5±16.4) and 47 individuals [control group] having normal echocardiographic parameters and with no any known disease (37 female, 10 male; mean age 40.0±10.1) were included in the study. Demographic and basic clinical properties and physical examination and blood-biochemistry parameters of both two groups were registered. Patients in sinus rhythm were taken to the study. Biochemical parameters (fasting blood sugar, lipid levels, complete blood count and kidney function tests) were examined in all patients.

Hypertension was defined as ≥140 mm Hg systolic and ≥90 mm Hg diastolic blood pressure or antihypertensive use. Diabetes mellitus

*Coresponding Author: Saadet Demirtas Inci, Health Sciences University, Diskapi Education and Research Hospital, Department of Cardiology, Ankara, Turkey, E-mail: saadet_demirtas@yahoo.com

diagnosis was determined as fasting blood glucose level ≥126 mg/dl or glucose level above 200 mg/dl in any measurement or active use and the available oral antidiabetic medicine or insulin use. If ejection fraction (EF) was <50%, it was accepted as left ventricular (LV) systolic dysfunction.

Exclusion criteria from the study were determined as coronary artery disease history, LV systolic dysfunction, hypertension, diabetes mellitus, hypertrophic cardiomyopathy, right or LV hypertrophy, serious valvular heart disease, chronic obstructive pulmonary disease, renal and hepatic failure, cancer, cerebrovascular disease, septicemia, thyroid dysfunction, hematologic diseases, acute or chronic infection or inflammatory state and antibiotic use.

Adhering to the working principles of the Helsinki Declaration, the study protocol was approved by the Sakarya University Ethics Committee.

Collection of laboratory parameters and blood samples

After 12 hours fasting, the forearm was squeezed to form a tiny venous stasis and peripheric venous bloods were taken from antecubital vessel. The blood samples were studied within 1 hour in the laboratory. The blood samples were taken into standard tubes including dipotassium ethylen dinitro tetraacetic acid (EDTA) complete blood count (CBC). By means of Abbott Cell-Dyn 3700 device, the complete blood cell numbers (hemoglobin, hematocrits, thrombocytes, neutrophils, lymphocytes, eosinophils and monocytes, basophils) were analysed. MPV/PC ratio, neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR) and monocyte/ lymphocyte ratio (MLR) were calculated using data.

Echocardiographic Measurements

Transthoracic echocardiographic examination was made after at least 15-minute rest, at lateral position (2-dimensional, M-mode, coloured parasternal Doppler echocardiography), by using Philips (Philips Medical Systems, Amsterdam, Holland) and X5 probe, from parasternal and apical windows. Each participant was made transthoracic echocardiography by conforming to standard displays and techniques taking place in the guideline of American Society of Echocardiography [12]. The ejection fraction (EF) was calculated according to modified Simpson's rule. ASA was defined as the replacement of interatrial septum >10 mm from atrial septal plane towards left or right atrium and its base width being ≥15 mm [2].

Statistical Analysis

The analysis was evaluated using SPSS program (SPSS version 23; Armonk, NY, USA: IBM Corp). With the Kolmogorov Smirnov test, the normality analysis was made. By the aim of comparing the two groups showing normal distribution for numeric variables, Student's t test was used. The variables, in which it was determined that pre-conditions of parametric tests didn't come true, were assessed by nonparametric statistical analysis methods. Mann-Whitney U test was used in order to compare the two groups in terms of these variables. The results were expressed as ± mean standard deviation and mean value. Fisher Exact test was used in the analysis of categorical variables. Categorical variables were expressed as absolute value and %. $P<0.05$ level was accepted statistically meaningful. The relation between the two continuous variables was measured by Pearson or Spearman correlation. Independent factors related to the presence of ASA were investigated in multivariate linear regression analysis.

Results

Demographic and basic clinical properties were detected as similar among the two groups. Clinical baseline characteristics of the two groups were shown in the Table 1. When groups were compared according to echocardiographic parameters, left ventricular ejection fraction (LVEF), left ventricular LV diastolic diameter, right atrium diameter and systolic pulmonary artery pressure were similar in two groups. However, left atrium, left ventricular LV septum thickness and left ventricular LV posterior wall thickness were detected higher in the group with ASA (Table 1).

Table 1. Clinical and echocardiographic findings of two groups

	ASA group (n = 70)	Control group (n = 47)	P value
Age (years)	44.5 ± 16.4	40.0 ± 10.1	0.09
Female, n (%)	57 (81.4%)	37 (78.7%)	0.81
Cigarette (+), n (%)	15 (21.4%)	7 (14.8%)	0.47
Systolic BP, (mmHg)	111.2 ± 14.6	110.2 ± 13.5	0.70
Diastolic BP, (mmHg)	68.5 ± 9.8	67.7 ± 12.9	0.70
Heart rate, (pulse/min)	71.8 ± 14.1	71.5 ± 14.2	0.92
LVEF, (%)	61.7 ± 2.7	61.9 ± 2.8	0.61
LVEDD, (cm)	4.3 ± 0.4	4.2 ± 0.3	0.13
LA, (cm)	3.3 ± 0.4	3.1 ± 0.4	0.02
IVS, (cm)	1.0 ± 0.2	0.9 ± 0.1	<0.001
LVPW, (cm)	1.0 ± 0.2	0.9 ± 0.1	0.001
RA, (cm)	3.2 ± 0.5	3.1 ± 0.4	0.58
SPAP, (mmHg)	26.6 ± 2.3	25.3 ± 2.6	0.20

BP: blood pressure, LVEF: left ventricular ejection fraction, LVEDD: left ventricular end-diastolic diameter, LA: left atrial diameter, IVS: interventricular septum thickness, LVPW: left ventricular posterior wall thickness, RA: right atrium, SPAP: systolic pulmonary arterial pressure

In the Table 2 the comparison of hematological parameters of both two groups were shown. Hemoglobin, white blood cell, neutrophil count, monocyte count and MPV and platelet distribution width (PDW) were similar in both two groups. Red blood cell (RBC), lymphocyte and thrombocyte count were lower meaningfully in the group with ASA. NLR and PLR were not different between the groups. However, MPV/PC ratio and MLR were significantly higher in patients with ASA compared to control group (Table 2).

In the Pearson correlation analysis, the presence of ASA was positively correlated with MLR and MPV/PC, left atrium, left ventricular LV septum thickness and LV posterior wall thickness, while RBC was negatively correlated ($r = 0.226$, $p=0.01$; $r = 0.214$, $p=0.02$; $r = 0.199$, $p=0.03$; $r = 0.385$, $p<0.001$; $r = 0.341$, $p<0.001$ and r:-0.224, $p=0.01$) respectively). However, in multivariable linear regression analysis, there was an independent relation between the presence of ASA and MPV/PC ratio, MLR, LV septum thickness and RBC (Table 3).

Table 2. Laboratory values of two groups

	ASA group (n = 70)	Control group (n = 47)	P value
Glucose, (mg/dL)	90.4 ± 13.6	98.7 ± 14.3	0.40
Creatinine, (mg/dL)	0.7 ± 0.1	0.6±0.1	0.44
Total cholesterol, (mg/dL)	230.8 ± 51.9	199.4 ± 20.8	0.24
LDL, (mg/dL)	133.7 ± 34.5	112.6 ± 10.4	0.23
TG, (mg/dL)	101.8 ± 21.2	101.6 ± 54.7	0.99
Hb, (g/dL)	13.2 ± 1.1	13.6 ± 1.2	0.08
RBC, (106/L)	4.4 ± 0.5	4.6 ± 0.4	0.02
Leukocyte, (10^3/L)	7.3 ± 2.2	7.7 ± 2.2	0.20
PC, (10^3/L)	249.4 ± 52.5	279.3 ± 61.2	0.006
MPV, (f/L)	8.2 ± 1.5	7.8 ± 1.3	0.15
RDW, (%)	15.2 ± 1.5	15.3 ± 2.0	0.81
Lymphocyte, (10^3/L)	2.1 ± 0.5	2.5 ± 0.8	0.001
Monocyte, (10^3/L)	0.6 ± 0.3	0.5 ± 0.1	0.30
Neutrophil, (10^3/L)	4.3 ± 1.8	4.4 ± 1.6	0.54
MLR	0.27 ± 0.15	0.22 ± 0.08	0.03
NLR	2.29 ± 1.93	1.85±0.88	0.14
PLR	126.6 ± 64.2	114.9 ± 41.5	0.27
MPV/PC	0.03 ± 0.01	0.02 ± 0.001	0.02

LDL: Low density lipoprotein cholesterol, HDL: High density lipoprotein cholesterol, TG: triglyceride, Hb: hemoglobin, RBC: red blood cell, PC: platelet count, MPV: mean platelet volume, RDW: red cell distribution width, MLR: monocyte/lymphocyte ratio, NLR: neutrophil lymphocyte ratio, PLR: platelet count/lymphocyte ratio, MPV/PC: mean platelet volume/platelet count

Table 3. Results of the multivariate linear regression analysis for factors affecting the presence of ASA

	ßeta±SE	Confidence interval (%)	P value
MPV/PC ratio	0.19 ± 3.3	1.17-14.64	0.02
MLR	0.16 ± 0.3	0.006-1.23	0.04
IVS	0.37 ± 0.24	0.61-1.59	<0.001
RBC	-0.22 ± 0.08	-0.83-1.09	0.009

IVS: interventricular septum thickness, RBC: red blood cell, MPV: mean platelet volume, PC: platelet count, MLR: monocyte/lymphocyte ratio

Discussion

In our study, it was found that there was a significant relation between ASA, MPV / PC ratio and MLR compared to the controls. Besides, in multivariate linear regression analysis, only the thickness of the interventricular septum was found to be associated with the presence of ASA among echocardiographic parameters. As far as we know, our study is the first to discuss the relationship between ASA and MPV/PC ratio and MLR.

It has been reported in previous studies that ASA causes arrhythmia. Hanley et al. In their study, they reported that atrial arrhythmia was present in 20 (25%) of 80 ASA cases [3]. Although its exact mechanism is not known, it is argued that the excessive movement

in the atrial septum and the fluctuating motion of the aneurysmal structure induce arrhythmias [13]. In studies on ASA patients, atrial fibrillation (AF) was frequently detected [14]. The role of systemic inflammation has been demonstrated in the pathophysiology of AF, and systemic inflammation plays an important role in the development and recurrence of AF [15-16] and high NLR has been shown to be associated with the risk of formation and relapse [16]. MLR was shown to be associated with various heart diseases such as heart failure and coronary artery disease [8,9]. However, no data on MLR and AF were detected in the literature. In our study, no difference was found between the groups in terms of NLR, whereas the group with ASA had higher MLR, and an independent relationship was found between the presence of ASA and MLR. In ASA patients, atrial and ventricular fibrosis was detected, and in the studies it was determined that the inflammatory state caused fibrosis in myocard [17]. It was detected that in animal studies the monocytes played an important role in this fibrosis process [18,19]. In these patients, increased inflammatory state may be facilitating the development of arrhythmia like AF. In other studies, it was stated that NLR can be used as an AF determiner [20]. However, in our study, NLR was similar among the groups, so MLR may be more valuable in determining the risk of arrhythmia in these patients.

Another important complication of ASA is its ability to cause arterial embolism. It is reported that ASA causes arterial embolism with various pathophysiologic mechanisms. For example; left atrium may cause left atrium thrombus formation by causing an increase in the stability of blood flow [4-5] or thrombus formed within the aneurysm may directly cause embolization [2] or as a result of atrial arrhythmias [21]. Increased MPV is a useful biochemical indicator of platelet activity in cardiovascular diseases and stroke [22]. Moreover, MPV as a biomarker also predicts the risk of ischemic stroke. The MPV/PC ratio is a new marker and increased MPV/PC ratio is reported to be a better predictor for cardiovascular events than MPV [23]. In our study, MPV/PC ratio was significantly higher in the ASA group compared to the control group, and in the linear regression analysis, an independent relationship was detected between MPV/PC ratio and ASA. High MPV/PC ratio; suggests whether the PC is related to low detection, but it is stated that a low PC can be caused by the most common drug-related immune response or bleeding [24] and in our patient group, patients with chronic disease or drug use for any reason were excluded from the study. Therefore, the mechanism of PC abortion is not fully understood.

In our study, left atrium, LV septum thickness and LV posterior wall thickness were detected higher in the group with ASA. However, in logistic regression analysis, only the thickness of the interventricular septum was found to be associated with the presence of ASA among echocardiographic parameters. Previous studies have shown that increased left ventricular LV wall thickness is a factor that increases the risk of arrhythmia and stroke [25]. We think that this increase in left ventricular LV wall thickness may be another factor increasing the development of complications such as arrhythmia and stroke in patients with ASA. The mechanism of negative relationship between RBC and ASA in the regression analysis was not fully understood.

The most important restriction of this study is retrospective design and the limited number of patients. Moreover, other inflammatory markers such as C-reactive protein, interleukin-6 and tumor necrosis factor-alpha were not evaluated and any comparison between them was not performed; our study doesn't include AF and patients who have had a thromboembolic event or atrial thrombus detected and these patients couldn't be monitored for arrhythmia. In addition, stroke patients are not known because patients are not followed up.

Conclusion

In conclusion, we think that MLR and MPV/PC may be associated with increased thromboembolic status in ASA cases, and we think that this idea should be investigated by prospective studies involving much higher numbered and thromboembolic events.

Acknowledgements
I would like to thank the secretary Seyma Hacioglu who worked in the Cardiology Department of Sakarya Training and Research Hospital.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
The financial support no have.

Ethical approval
This study was approved by University Education and Research Hospital Ethics Committee with decision number 27/3/2019 16214662/050.01.04/48.

References

1. Yetkin E, Atalay H, Ileri M. Ileri. Atrial septal aneurysm: prevalence and covariates in adults. Intern J Cardiol. 2016;223:656-9.
2. Mügge A, Daniel WG, Angermann C, et al: Atrial septal aneurysm in adult patients: A multicenter study using transthoracic and transesophageal echocardiography. Circulation. 1995;91.2785.
3. Hanley PC, Tajik AJ, Hynes JK, et al. Diagnosis and classification of atrial septal aneurysm by two-dimensional echocardiography: report of 80 consecutive cases. J Am Coll Cardiol. 1985;6:1370-138211.
4. Gallet B, Malergue MC, Adam C, et al. Atrial septal aneurysm: a potential cause of systemic embolism. Br Heart J. 1985;53:292-7.
5. Belkin RN, Hurwitz BJ, Kisslo J. Atrial septal aneurysm: association with cerebrovascular and peripheral embolic events. Stroke. 1987;18:856-62.
6. A. Kurtul, Ornek E. Platelet to lymphocyte ratio in cardiovascular diseases: a Platelet to lymphocyte ratio in cardiovascular diseases: a systematic review. Angiology. 2019;70:802-18.
7. C.V. Serrano, F.R. De Mattos, F.G. Pitta, et al. Association between neutrophil-lymphocyte and platelet-lymphocyte ratios and coronary artery calcification score among asymptomatic patients: data from a cross-sectional study. Mediators Inflamm. 2019;2019:6513847.
8. Hammadah M, Hazen SL, Tang WHW. Monocyte to lymphocyte ratio is associated with adverse long term outcomes in patients with heart failure. J Card Fail. 2016;22:32.
9. Ji H, Li Y, Fan Z, et al. Monocyte/lymphocyte ratio predicts the severity of coronary artery disease: a syntax score assessment. BMC Cardiovasc Disord. 2017;17:90.
10. Tian C, Song J, He D, et al. Predictive value of mean platelet volume/ platelet count for prognosis in acute myocardial infarction. Int Heart J. 2018;59:286-92.
11. Elsayed AM, Mohamed GA. Mean platelet volume and mean platelet volume/platelet count ratio as a risk stratification tool in the assessment of severity of acute ischemic stroke. Alex J Med. 2017;53:67–70.
12. Lang RM, Bierig M, Devereux RB, et al: Recommendations for chamber quantification: a report from the american society of echocardiography's guidelines and standards committee and the chamber quantification writing group, developed in conjunction with the european association of echocardiography. J Am Soc Echocardiogr. 2005:18:1440-63

13. Schneider B, Hofmann T, Meinertz T. Is there an association of atrial septal aneurysm with arrhythmias? Cardiology. 1999;91:87-91.

14. Janion M, Kurzawski J. Atrial fibrillation in patients with atrial septal aneurysm. Cardiol J. 2007;14:580-4.

15. Lip GY, Patel JV, Hughes E, Hart RG. High sensitivity C reactive protein and soluble CD40 ligand as indices of inflammation and platelet activation in 880 patients with nonvalvular atrial fibrillation: relationship to stroke risk factors, stroke risk stratification schema, and prognosis. Stroke. 2007;38:1229–37.

16. Shao Q, Chen K, Rha SW, Lim HE, Li G, Liu T. Usefulness of neutrophil/lymphocyte ratio as a predictor of atrial fibrillation: a meta-analysis. Arch Med Res. 2015;46:199-206.

17. Frangogiannis NG. Regulation of the inflammatory response in cardiac repair. Circ Res. 2012;110:159–73.

18. Li D, Fareh S, Leung TK, Nattel S. Promotion of atrial fibrillation by heart failure in dogs: atrial remodeling of a different sort. Circulation. 1999;100:87–95.

19. Li J, Solus J, Chen Q, et al. Role of inflammation and oxidative stress in atrial fibrillation. Heart Rhythm. 2010;7:438–44.

20. Shao Q, Chen K, Rha SW, et al. Usefulness of neutrophil/lymphocyte ratio as a predictor of atrial fibrillation: a meta-analysis. Arch Med Res. 2015;46:199-206.

21. Berthet K, Lavergne T, Cohen A, et al. Significant association of atrial vulnerability with atrial septal abnormalities in young patients with ischemic stroke of unknown cause. Stroke 2000;31:398-403.

22. Akgul O, Uyarel H, Pusuroglu H, et al. Prognostic value of elevated mean platelet volume in patients undergoing primary angioplasty for ST-elevation myocardial infarction. Acta Cardiol. 2013;68:307-14.

23. Azab B, Torbey E, Sıngh J, et al. Mean platelet volume/platelet count ratio as a predictor of long –term mortality after non-ST-elevation myocardial infarction. Platelets. 2011;22:557–66.

24. David Gregg, Pascal J. Goldschmidt-Clermont. Platelets and Cardiovascular Disease. Circulation. 2003;108:e88-e90.

25. Chatterjee S, Bavishi C, Sardar P, et al. Meta-analysis of left ventricular hypertrophy and sustained arrhythmias. Am J Cardiol. 2014; 114:1049.

Available online at www.medicinescience.org

ORIGINAL ARTICLE

Medicine Science International Medical Journal

Medicine Science 2021;10(1):82-7

The relation between the spiritual orientation and quality of life in hemodialysis patients

Seyhan Citlik Saritas[1], Zeliha Buyukbayram[2]

[1]Inonu Univesity Faculty of Nursing, Malatya, Turkey
[2]Siirt University Faculty of Health, Siirt, Turkey

Received 17 July 2020; Accepted 17 September 2020
Available online 17.01.2021 with doi: 10.5455/medscience.2020.07.138

Abstract

The present study was conducted to examine the relation between the spiritual orientation and quality of life of hemodialysis patients. A total of 66 hemodialysis patients were included in this relational and descriptive study. The data of the study were collected by using the Patient Introduction Form, Spiritual Orientation Scale, and Rolls Royce Quality of Life Scale. The mean age of the patients who were included in the study was 55.74 ± 14.86 years, 53% were male, 93.9% were married, 47% were illiterate, 92.4% did not work, 43.9% had income equal to expenses, 48.5% were treated for hemodialysis for 0-5 years, 34.8% were heart failure-hypertension patients. The Rolls Royce Quality of Life Scale total score of the patients was 138.31±21.30, and the mean total score in the Spiritual Orientation Scale was 97.07±11.88. The difference between marital status, learning status, and mean the quality of life total score was found to be statistically significant ($p<0.05$). It was found that there was an important relationship between the mean physical symptom and activity sub-dimension score of the quality of life scale and the mean spiritual orientation scale score. The mean quality of life score of the patients was found to be moderate and the mean spiritual orientation score was high. A positive relation was detected between the mean scores of the physical symptom and activity sub-dimensions of the quality of life scale and the spiritual orientation scale.

Keywords: Hemodialysis, spiritual orientation, quality of life

Introduction

Chronic Renal Failure (CRF) is an important health problem in the whole world and our country depending on its increased incidence [1]. According to the Turkish Nephrology Association (TNA) 2017 data, the total number of patients was 77.311 in our country. A total of 58.635 these patients underwent hemodialysis, 3.346 patients were treated for peritoneal dialysis, and 15.330 patients underwent kidney transplantation [2]. CRF causes loss of workforce and many complications for individuals in all age groups and is life-threatening. Hemodialysis (HD) is the most used treatment method in chronic kidney disease [3-5].

Quality of life includes factors like being able to meet basic needs, being adequate in terms of social behaviors, providing satisfaction from life, normal physical and emotional status, allocating time to have fun, and maintaining interpersonal relations [1,6]. Although the symptoms associated with CRF are controlled by HD treatment, patients face lifelong treatment with HD machines [1,7]. Patients experience many important problems during HD treatment like the restriction of social life, emotional and psychosocial problems, deterioration in physical functionality, and anxiety about losing independence [8,9]. These problems faced during hemodialysis treatment cause negativity in families, and the work and social lives of patients. These negativities can affect the performance of patients and reduce the quality of life [10,11]. In studies conducted on HD patients, it was determined that the quality of life of patients was moderate or low [1,5,12-14]. It was also reported that quality of life is associated with dialysis time and program, social support, anxiety, depression, sleep problems, age, and gender [1,4,6,9,13,15-18].

Spirituality is defined as intangible and spiritual phenomena perceived only with senses. It is an important resource and reference point to deal with the negative consequences of the disease and allow patients to question themselves, their importance, purpose, and personal aspects [19]. Spirituality, which has a meaning for life for patients, is perceived as an "escape door" to find hope in cases of chronic disease like CRF. HD patients can turn to spirituality to improve the quality of life and to think positively. It was found in previous studies that patients moved towards spirituality in their

***Coresponding Author:** Seyhan Citlik Saritas, Inonu Univesity Faculty of Nursing, Malatya, Turkey, E-mail: seyhancitlik@hotmail.com

difficult times and in dealing with diseases [3,20]. Spirituality brings benefits for patients in many ways like making their health better, reducing pain, facilitating the acceptance of the disease, coping with difficulties, improving quality of life, and ensuring that individuals take on social responsibility. For this reason, it is important in nursing practice to address the spiritual needs of patients [1,21,22].

The purpose of the present study was to examine the relations between the spiritual orientation of hemodialysis patients and quality of life.

Material and Methods

The study was conducted in a state hospital dialysis center in a descriptive and cross-sectional design between December 2019 and March 2020. The universe of the study consisted of 80 adult patients who were treated at a state hospital dialysis center. In the sample selection step of the study, all patients were included in the sampling without using any sampling methods. 10 patients who refused to participate in the research and 4 patients who failed to fill in survey forms properly were left out of the research, and so the research was undertaken with the participation of a total of 66 patients (Approximately 83% of the universe).

The inclusion criteria were the absence of a diagnosed psychiatric disease and being able to communicate.

It was approved by the Scientific Research and Ethical Committee of Siirt University with the number 03.12.2019/E.18360. Informed consent was obtained from all participants included in the study.

The data of the study were collected with the Patient Introduction Form, which was prepared by the researchers, the Spiritual Orientation Scale, and Rolls Royce Quality of Life Scale. The data were collected by the researchers by using the face-to-face interview technique. Each meeting lasted approximately 15-20 minutes.

Patient Introduction Form: This form, which was created by the researchers, included questions about the age, gender, marital status, level of education, working status, income status, duration of hemodialysis treatment, and the presence of any comorbidities.

Spiritual Orientation Scale (SOS): The scale was developed by Kasapoglu in 2015 to evaluate the spiritual orientation of individuals. As a result of validity and reliability studies, it was created as 16 items and one dimension. The scale was in a 7-Point Likert design, and the minimum score that can be received is 16, and a maximum of 112. The total score refers to the level of spiritual orientation. Cronbach's Alpha Reliability Coefficient of the scale was found as 0.95 [23]. In this study, Cronbach's alpha value of the scale was found as 0.96.

Rolls Royce Quality of Life Scale: The validity and reliability of the Rolls-Royce Quality of Life scale was conducted by Ozyilkan et al. (1995). The scale consists of 42 questions [24]. The scale was in a 5-Point Likert design, and the minimum score that can be received is 42, and a maximum of 210. High scores received from the scale show that the health-related quality of life is high in a positive way. There are positive and negative statements on the scale. The scale consisted of 8 sub-dimensions as general wellbeing; physical symptoms and activity; sleep disorder; appetite; sexual function; perception function; medical interaction; social relations and job performance. The reliability coefficient of the scale is 0.99 [24]. In this study, the Cronbach's alpha value of the scale was found to be 0.96.

Statistical Analysis

The statistical analysis of the data was made with the SPSS 22 Package Program. Standard deviation, percentage, mean values, and minimum and maximum values were used for demographic data. The t-test, Kruskal Wallis, and Mann Whitney U-test were used in the calculations of the scale scores. The significance level was taken as $p<0.05$.

Results

The mean age of the patients included in the study was 55.74 ± 14.86 years, 53% were male, 93.9% were married, 47% were illiterate, 92.4% were not working, 43.9% had income equal to expenses, 48.5% received hemodialysis treatment for 0-5 years, and 34.8% were heart failure and hypertension patients (Table1).

Table 1. Distribution of Patients by Descriptive Characteristics (n=66)

Descriptive Characteristics	Number	%
Gender		
Female	31	47.0
Male	35	53.0
Marital Status		
Married	62	93.9
Single	4	6.1
Educational Status		
Illiterate	31	47.0
Literate	12	18.2
Primary/High-School	19	28.8
Undergraduate and Postgraduate	4	6.1
Working Status		
Working	5	7.6
Not working	61	92.4
Monthly Income Status		
Income more than expenses	37	40.9
Income equal to expenses	29	43.9
Income less than expenses	10	15.2
HemodialysisTreatment Duration		
0-5 years	32	48.5
6-10 years	23	34.8
11 years and above	11	16.7
Other Chronic Disease		
Diabetes	18	27.3
Heart Failure-Hypertension	23	34.8
COPD-Asthma	8	12.1
No diseases	17	25.8
Age	55.74±14.86	

COPD: Chronic Obstructive Pulmonary Disease

The mean total score of the Rolls Royce Quality of Life Scale of the patients was 138.31±21.30, the mean overall wellbeing sub-dimension score of the Rolls Royce Quality of Life Scale was 23.98±4.20, and the other mean scores were as follows; 23.40±3.46 in physical symptom and activity, 9.30±2.41 in sleep disorder, 6.63±1.62 in appetite, 13.34±2.85 in sexual function, 21.95±3.54 in perception function, 12.28±1.46 in medical interaction, 27.39±4.38 in social relations and work performance, and 97.07±11.88 in Spiritual Orientation Scale (Table 2).

Table 2. Distribution of Mean Scores of the Patients Received from Spiritual Orientation Scale and Rolls Royce Quality of Life Scale (n=66)

Scale and Sub-dimensions	Item count	Min. Max. Values	X±SD
Rolls Royce Quality of Life			
General Wellbeing	7	11-31	23.98±4.20
Physical symptom and activity	8	14-30	23.40±3.46
Sleep disorder	3	4-13	9.30±2.41
Appetite	2	3-9	6.63±1.62
Sexual function	4	6-16	13.34±2.85
Perception function	6	15-28	21.95±3.54
Medical interaction	4	10-16	12.28±1.46
Social relations and job performance	8	14-36	27.39±4.38
Total	42	85-176	138.31±21.30
Spiritual Orientation Total Score	16	64-112	97.07±11.88

It was found in the study that the difference between the total and sub-dimensions of the Rolls Royce Quality of Life Scale according to patients' marital status was statistically significant ($p<0.05$). It was also found that there were statistically significant differences between the averages of total scores in Rolls Royce Quality of Life Scale, sleep disorder, according to the educational status, perception function, social relations, and sub-dimensions of work performance of the patients ($p<0.05$). According to the income status of the patients, there were statistically significant differences between the averages of total scores in the Rolls Royce Quality of Life Scale appetite and social relations and work performance sub-dimensions $p<0.05$). It was also found that there were statistically significant differences between the averages of total scores of the patients in Rolls Royce Quality of Life Scale and appetite sub-dimension ($p<0.05$). It was found that there were no statistically significant differences in the Spiritual Orientation Scale scores according to their demographical characteristics ($p>0.05$) (Table 3).

Table 4. The Relation between Patients' Mean Scores in Rolls Royce Quality of Life Scale Score, Its Sub-Dimensions and Spiritual Orientation Scale (n=66)

Rolls Royce Quality of Life Scale and Sub-dimensions	Spiritual Orientation Scale
General wellbeing	r:0.10 p:039
Physical symptoms and activity	r:0.24 p:0.04
Sleep disorder	r:0.08 p:0.52
Appetite	r:0.14 p:0.25
Sexual function	r:0.16 p:0.19
Perception function	r:0.18 p:0.12
Medical interaction	r:0.19 p:0.11
Social relations and work performance	r:0.21 p:0.08
Scale Total	r:0.19 p:0.12

Discussion

Chronic Renal Failure is a chronic disease, which may affect the quality of life at significant levels. Health-related quality of life is the experience, beliefs, expectations, and perceptions of a person in physical, psychological, and social health areas [4,12]. Dialysis treatment is a repetitive and exhausting routine for CRF patients, and changes in lifestyle and occupational inactivity cause mood changes and emotional stress affecting the mental and physical health of patients [4]. Other factors like addiction and limitations brought by the treatment and changes in bodily appearance, can result in a negative effect in this scenario. These negative factors may affect the spiritual orientation of patients [3,16].

In the present study, the mean SOS total score of the patients was 97.07±11.88. It was determined that the spiritual orientation of the patients who participated in the study was high. In their study, Ottaviani et al. examined the level of spirituality in HD patients and found that patients were directed to spiritual beliefs in difficult times as a method of dealing with their disease [20]. Duran et al. conducted a study and found that HD patients were more inclined to spirituality in the face of difficulties and in dealing with diseases [3]. In their study conducted on hemodialysis patients, Hicdurmaz and Oz found that the coping method used frequently by patients was "turning to religion" [19]. Spiritual needs can come to the forefront in the face of life-threatening diseases, fear of death, stress when hope begins to decrease, and it may be considered that these factors also have effects on similar conditions in high spiritual orientation in HD patients. In this study, the high levels of spiritual orientation in HD patients can be caused by believing in divine power and feeling the need for seeking refuge in a divine power in difficult times.

It was determined that the quality of life of the patients who participated in the present study was at a moderate level (138.31±21.30). In our study, the lowest quality of life was detected in the sub-dimension of appetite (6.63±1.62), and the highest score was found in the quality of life sub-dimension of social relations and work performance (27.39±4.38). Bayoumi et al. found that the quality of life in HD patients was at a moderate level [12]. Some

doi: 10.5455/medscience.2020.07.138

Table 3. Comparison of the Total Scores of Patients in Rolls Royce Quality of Life Scale, its Sub-dimensions and Spiritual Orientation Scale according to Descriptive Characteristics (n=66)

Descriptive Characteristics	General wellbeing X±SD	Physical symptoms and activity X±SD	Sleep disorder X±SD	Appetite X±SD	Sexual function X±SD	Perception function X±SD	Medical interaction X±SD	Social relations and performance X±SD	Total X±SD	Spiritual orientation Total X±SD
Gender										
Female	24.22±3.85	23.22±3.80	9.09±2.39	6.70±1.65	13.54±2.95	21.77±3.53	12.00±1.31	27.19±4.74	137.77±21.31	94.77±13.83
Male	23.77±4.54	23.57±3.18	9.48±2.44	6.57±1.61	13.17±2.79	22.11±3.59	12.54±1.55	27.57±4.09	138.80±21.59	99.11±9.60
Test	t=0.43	t=-0.40	t=-0.65	t=0.34	t=0.53	t=-0.38	t=-1.51	t=-0.34	t=-0.19	t=-1.49
Significance	p=0.66	p=0.68	p=0.51	p=0.73	p=0.59	p=0.70	p=0.13	p=0.72	p=0.84	p=0.14
Marital status										
Married	23.69±4.16	23.14±3.38	9.11±2.36	6.53±1.61	13.17±2.86	21.69±3.49	12.17±1.42	27.00±4.19	136.53±20.67	97.22±11.99
Single	28.50±1.29	27.50±0.50	12.25±0.50	8.25±0.50	16.00±0.00	26.00±0.81	14.00±1.15	33.50±2.38	166±7.11	94.75±11.23
Test	MWU=24.00	MWU=29.50	MWU=26.50	MWU=43.50	MWU=44.00	MWU=30.50	MWU=37.00	MWU=16.00	MWU=16.50	MWU=104.50
Significance	p=0.00	p=0.01	p=0.00	p=0.02	p=0.02	p=0.01	p=0.01	p=0.00	p=0.00	p=0.59
Educational status										
Illiterate	23.09±3.98	22.45±3.44	8.41±2.26	6.25±2.90	12.90±2.90	20.48±2.93	11.90±1.16	25.58±3.97	131.09±18.76	95.45±14.38
Literate	23.41±6.15	23.33±4.11	9.41±2.90	6.41±1.83	13.00±3.76	22.75±4.15	12.50±1.62	27.91±4.54	138.75±28.07	95.50±9.05
Primary school - High-school	25.63±2.87	25.15±2.69	10.47±2.03	7.31±1.20	14.15±2.24	23.47±3.47	12.84±1.77	29.68±4.17	148.73±18.30	100.73±8.12
Undergraduate/post-graduate	24.75±2.98	22.75±2.62	10.25±0.95	7.00±0.81	14.00±1.63	23.75±2.62	12.00±0.81	29.00±2.44	143.50±12.17	97.00±13.14
Test	KW=5.64	KW=6.96	KW=10.09	KW=4.58	KW=2.08	KW=11.62	KW=3.66	KW=12.08	KW=11.59	KW=1.41
Significance	p=0.13	p=0.07	p=0.01	p=0.20	p=0.55	p=0.00	p=0.30	p=0.00	p=0.00	p=0.70
Working status										
Working	24.40±3.36	23.80±4.14	9.60±2.88	6.80±2.16	13.00±3.31	22.20±3.56	13.00±2.82	28.40±6.26	141.20±27.39	102.20±6.01
Not working	23.95±4.29	23.37±3.44	9.27±2.39	6.62±4.59	13.37±2.84	21.93±3.57	12.22±1.32	27.31±4.25	138.08±20.99	96.65±12.17
Test	MWU=151.00	MWU=137.00	MWU=141.50	MWU=136.00	MWU=147.00	MWU=145.00	MWU=126.00	MWU=135.00	MWU=134.00	MWU=108.50
Significance	p=0.97	p=0.70	p=0.78	p=0.67	p=0.89	p=0.86	p=0.51	p=0.97	p=0.65	p=0.28
Income status										
Income more than expenses	22.88±5.08	22.88±3.63	8.74 ±2.72	6.11±185	12.81±3.24	21.48±3.81	12.18±1.54	26.81±4.96	133.92±24.59	97.74±10.72
Income equal to expenses	24.10±3.46	23.24±3.35	9.51±2.02	6.79±1.44	13.31±7.20	21.96±3.38	12.03±1.26	26.89±3.95	137.86±18.70	95.58±13.43
Income less than expenses	26.60±2.11	25.30±2.98	10.20±2.39	7.60±0.96	14.90±1.44	23.20±3.25	13.30±1.49	30.40±2.63	151.50±13.79	99.60±10.52
Test	KW=5.30	KW=4.33	KW=2.39	KW=5.89	KW=53.17		KW=5.48	KW=6.92	KW=5.39	KW=0.22
Significance	p=0.07	p=0.11	p=0.30	p=0.05	p=0.20		p=0.06	p=0.03	p=0.06	p=0.89
Hemodialysis Treatment duration										
0-5 years	24.50±3.61	24.00±3.37	9.34±2.08	6.71±1.48	13.71±2.63	22.62±3.28	12.21±1.53	27.81±4.86	140.93±20.25	97.21±11.98
6-10 years	23.30±4.42	22.78±3.38	9.43±2.51	6.30±1.69	12.82±2.82	21.52±3.62	12.30±1.39	26.95±3.63	135.43±21.24	96.30±14.14
11 and above	23.90±5.44	23.00±3.92	8.90±3.17	7.09±1.86	13.36±3.58	20.90±4.01	12.45±1.50	27.09±4.59	136.72±25.29	98.27±5.49
Test	KW=1.10	KW=1.52	KW=0.23	KW=2.41	KW=2.31	KW=2.35	KW=0.49	KW=0.96	KW=1.19	KW=0.23
Significance	p=0.57	p=0.46	p=0.88	p=0.30	p=0.31	p=0.30	p=0.78	p=0.61	p=0.54	p=0.89
Diagnosis of other chronic diseases (if any)										
Diabetes	22.33±5.42	22.33±4.01	8.50±3.05	5.61±1.88	12.38±3.66	21.22±4.34	11.88±1.49	25.72±5.30	130.00±27.17	98.55±12.82
Heart Failure-Hypertension	24.43±3.25	23.56±2.98	9.34±2.26	7.13±1.17	13.82±1.94	21.78±3.48	12.47±1.23	27.82±2.99	140.39±15.56	98.65±8.36
COPD-Asthma	23.87±4.25	23.62±3.29	9.62±2.19	6.75±1.48	13.00±3.25	21.62±2.19	12.25±1.66	27.87±4.70	138.62±21.39	97.62±11.30
I do not have any disease	25.17±3.64	24.23±3.56	9.94±1.81	7.00±1.54	13.88±2.68	23.11±3.15	12.47±1.66	28.35±4.64	144.17±20.11	93.11±14.97
Test	KW=4.04	KW=2.93	KW=2.35	KW=8.30	KW=1.61	KW=2.69	KW=2.11	KW=3.20	KW=2.85	KW=1.25
Significance	p=0.25	p=0.40	p=0.50	p=0.04	p=0.65	p=0.44	p=0.54	p=0.36	p=0.41	p=0.74

study results were also parallel to our findings [5,25]. Unlike our study results, Moattari et al. found that the quality of life was low in hemodialysis patients [13]. In other studies, conducted by using different quality of life scales, it was determined that the quality of life scores of hemodialysis patients were low [7,14]. The difference in the results of this study may be that the scales with which quality of life was evaluated were different, or that the individual characteristics of patients might have affected the quality of life scores.

In our study, it was found that the spiritual orientations of the male patients were higher than female patients; however, these scores were not statistically significant. Unlike our study, a study that examined the spiritual conditions of patients with renal failure before and after hemodialysis reported that the female HD patients had higher spiritual status [8]. It can be argued that this difference stems from a large number of male patients in our study.

In our study, no statistically significant differences were detected between SOS total scores in terms of the marital status of patients, and the spiritual orientation of married patients was higher. Studies conducted with HD patients reported that marital status did not have significant effects on spirituality [26,27]. The results of the literature and our study results show similarities. Considering life more positively with the support of spouses and feeling psychologically well can positively affect spiritual wellbeing.

In our study, no statistically significant differences were detected between the educational status of patients and the SOS total scores, and the spiritual orientation of the patients who had primary school/high-school education was higher than other groups. Similar to our study results, it was observed in a similar study that the educational status did not affect the level of spirituality in previous studies [28].

In our study, no statistically significant differences were detected between the working status of the patients and the SOS total score, and the average score of the working individuals was higher. Based on the findings, it can be argued that patients are directed to spirituality with the support and strength they receive from their friends in their work lives.

In our study, no statistically significant differences were detected between the income status and SOS total score of patients, and the average score of those who had income less than expenses had higher scores. It may be speculated that HD patients are unable to work or have to resign from their work, and depending on this, economic difficulties are experienced, and patients with low economic levels are more likely to be in spirituality.

In our study, it was determined that there were no statistically significant relations between the treatment durations and SOS total scores, and the mean score of patients with 11 years or more was higher. It may be considered that as the duration of HD treatment increases, the patient has increased symptoms related to his/her disease; and for this reason, move towards spiritual coping methods.

In our study, there were no statistically significant relations between other chronic diseases and SOS total scores; and the heart failure-hypertension patients had higher mean scores. It may be considered that patients with renal failure develop spiritual coping strategies if they have comorbidities.

In our study, no significant differences were detected in terms of the quality of life total scores and gender sub-dimension. Similar to our study, Nazlican et al. examined the quality of life and factors affecting it in hemodialysis patients and found that there was no difference between gender and quality of life [7]. Some study findings are in line with our study results [4,6,17], while some contrast with our results [12,29]. It may be considered that the difference in the results of the present study may be due to the characteristics of the sampling group.

In our study, it was found that patients had a significant difference in total scores and sub-dimension in marital status and quality of life and that the mean scores of single individuals were higher. In some previous studies, no significant differences were reported between married and single individuals in terms of quality of life scores [12,17,30]. It was reported in some studies that there is a significant difference in this respect [4,6]. It can be argued that this difference can affect the quality of life because married people manage the family, which increases financial stress and addiction.

In our study, significant differences were detected in overall scores and sub-dimension of educational status, and the average score of primary school-high-school graduates was higher. It was found that there were also some studies reporting contrasting results to our study [6,14,17]. This difference was considered to be stemming from the sociodemographic characteristics of the patients.

In our study, it was found that there were no significant differences in the overall scores and sub-dimension scores of the patients in terms of working status. There are also some studies reporting contrasting results to our study [6,12,17]. It was considered that this difference stemmed from the sociodemographic characteristics of the patients.

It was found in our study that there were no significant differences in the monthly income levels and quality of life total scores and sub-dimension of the patients. Studies are reporting similar results with our study [6]. Unlike our study, there are also several studies reporting contrasting results [17]. The number of people who do not work due to the disease and the lack of benefits from any other jobs may be among the reasons that were influential in this difference.

In our study, no significant relations were detected between the year of treatment, the quality of life sub-dimensions score, and the total quality of life score. Parallel to our study findings, no significant relations were detected between hemodialysis duration and quality of life scores in the study conducted by Nazlican et al. [7]. In some previous studies, the results were found to be similar to those obtained in our study [17,30]. It can be argued that the quality of life will decrease because of dialysis complications and psychological factors that may occur in patients with more dialysis treatment years.

In our study, a positive and significant relationship was detected between the physical symptom and activity sub-dimension of the quality of life and the Spiritual Orientation Scale score averages of the patients. It can be argued that patients have spiritual orientation because physical activity in dialysis patients improves physical and mental functionality, psychological condition, and quality of life.

Conclusion

It was found that the quality of life of the patients was at a moderate

level and their spiritual orientation was high. It was found that there was a positive and significant relation between the physical symptom and activity sub-dimension of the quality of life scale and spiritual orientation. In the present study, it was found that there was a statistically significant relationship between marital status, learning and income status, and quality of life of the patients. It was found that the relation between descriptive characteristics of the patients and the orientation of spirituality was not statistically significant. In the light of these findings, it is recommended to organize pieces of training for hemodialysis patients to evaluate the quality of life at regular intervals, maintain and improve the quality of life, and evaluate the sense of spirituality to cope with possible health level changes, as well as to conduct studies to increase the awareness of healthcare professionals who provide care to HD patients.

Limitations

The fact that the present study was conducted in one single center was the limitation of the study.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
The financial support no have.

Ethical approval
Ethics Committee approval was received for this study from the Ethics Committee of Siirt University (no. 03.12.2019/E.18360).

References

1. Alemdar H, Cinar Pakyuz S. Hemodiyaliz hastalarında öz bakım gücünün yaşam kalitesine etkisinin değerlendirilmesi. Nefroloji Hemşireliği Dergisi. 2015;10:19-30.
2. Süleymanlar G, Ateş K, Seyahi N: Registry of the nephrology, dialysis and Transplantatıon In Turkey: Ministry of Health and Turkish Society of Nephrology Joint Report. Ankara: Türk Nefroloji Derneği Yayınları, 2017;1-15.
3. Duran S, Gungor E. Diyaliz hastalarının duygusal ve sosyal sorunlarının belirlenmesi. Uludağ Üniversitesi Tıp Fakültesi Dergisi. 2015;41:59–63.
4. Ravindran A, Sunny A, Kunnath RP, et al. Assessment of quality of life among end-stage renal disease patients undergoing maintenance hemodialysis. Indian J Palliat Care. 2020; 26(1):47–53.
5. Kalender N, Tosun N. Determination of the relationship between adequacy of dialysis and quality of life and self-care agency. J Clin Nurs. 2014;23:820-8.
6. Anees M, Muzammil RM, Tanzeel A, et al. Demographic factors affecting the quality of life of hemodialysis patients - Lahore, Pakistan. Pak J Med Sci. 2014;30:1123–7.
7. Nazlican E, Demirhindi H, Akbaba M. Hemodiyalize giren kronik böbrek yetmezliği hastalarında yaşam kalitesi ve etkileyen faktörler. TAF Preventive Medicine Bulletin. 2012;11:383–8.
8. Cheawchanwattana A, Darunee C, Warapond S, et al. Does the spiritual well-being of chronic hemodialysis patients differ from that of pre-dialysis chronic kidney disease patients? Religions. 2015;6:14–23.
9. Shukri M, Mohd AM, Md Aris Md SY, et al. Burden, quality of life, anxiety, and depressive symptoms among caregivers of hemodialysis patients: The role of social support. Int J Psychiatry in Med. 2020;55:397-407.
10. Tuna D, Ovayolu N, Kes D. Hemodiyaliz hastalarında sık karşılaşılan problemler ve çözüm önerileri. Nefroloji Hemşireliği Dergisi 2018;13:17-25.
11. Parvan K, Sima L, Fariborz R, et al. Quality of sleep and its relationship to quality of life in hemodialysis patients. J Caring Sci. 2013;2:295-304.
12. Bayoumi M, Ali AH, Abdulkareem AS, et al. Predictors of quality of life in hemodialysis patients. Saudi J Kidney Dis Transpl. 2013;24:254.
13. Moattari M, Marzieh E, Nasrin S, et al. The effect of empowerment on the self-efficacy, quality of life, and clinical and laboratory indicators of patients treated with hemodialysis: a randomized controlled trial. Health Qual Life Outcomes. 2012;10:115.
14. Theofilou P. Quality of life in patients undergoing hemodialysis or peritoneal dialysis treatment. J Clin Med Res. 2011;3:132-38.
15. Birmelé B, Le Gall A, Sautenet B, et al. Clinical, sociodemographic, and psychological correlates of health-related quality of life in chronic hemodialysis patients. Psychosomatics. 2012;53:30-7.
16. Jesus NMaria, Gracielly FdeSouza, Clesnan MR, et al. Quality of life of individuals with chronic kidney disease on dialysis. J Bras Nefrol. 2019;41:364-74.
17. Joshi U, Roshan S, Prakash P, et al. Assessment of quality of life in patients undergoing hemodialysis using WHOQOL-BREF Questionnaire: A multicenter study. Int J Neph Renovasc Dis. 2017;10:195-203.
18. Landreneau K, Lee K, Landreneau MD. Quality of life in patients undergoing hemodialysis and renal transplantation: A meta-analytic review. Nephrol Nurs J. 2010;37:37-44.
19. Hicdurmaz D, Oz F. Hemodiyaliz ve sürekli ayaktan periton diyalizi uygulanan hastaların stresle başa çıkma biçimleri. H.Ü.S.B.F Hemşirelik Dergisi. 2009;16:1-16.
20. Ottaviani AC, Souza ÉN, Drago Nde C, et al. Hope and spirituality among patients with chronic kidney disease undergoing hemodialysis: A correlational study. Rev Lat Am Enfermagem. 2014;22:248-54.
21. Greenstreet W. From spirituality to coping strategy: Making sense of chronic illness. Br J Nurs. 2006;15:938-42.
22. Reig-Ferrer A, Arenas MD, Ferrer-Cascales R, et al. Evaluation of spiritual well-being in haemodialysis patients. Nefrologia. 2012;32:731-42.
23. Kasapoglu F. Manevi yönelim ölçeği'nin geliştirilmesi: geçerlik ve güvenirlik çalışması. İnönü Üniversitesi Eğitim Fakültesi Dergisi 2015;16:51-68.
24. Ozyilkan O, Karaagaoglu E, Topeli A, et al. A questionnaire for the assessment of the quality of life in cancer patients in Turkey. Mater Med Pol. 1995;27:153-6.
25. Kurbun H, Metin Akten İ. Hemodiyaliz hastalarında öz-bakım gücü ve yaşam kalitesinin değerlendirilmesi. Turk Neph Dial Transpl 2018;27:277-87.
26. Ebrahimi H, Ashrafi Z, Eslampanah G, et al. Relationship between spiritual well-being and quality of life in hemodialysis patients. JNMS. 2014;1:41.
27. Fradelos EC, Konstantinos T, Foteini T, et al. Clinical, social, and demographics factors associated with spiritual wellbeing in end-stage renal disease. Adv Exp Med Biol. 2017;987:77-88.
28. Alradaydeh MF, Khalil AA. The association of spiritual well-being and depression among patients receiving hemodialysis. Perspect Psychiatr Care. 2018;54:341-7.
29. Sathvik BS, Parthasarathi G, Narahari MG, et al. An assessment of the quality of life in hemodialysis patients using the WHOQOL-BREF Questionnaire. Indian J Nephrol. 2008;18:141-9.
30. Gerasimoula K, Lagou L, Lena M, et al. Quality of life in hemodialysis patients. Mater Sociomed. 2015;27:305-9.

Available online at www.medicinescience.org

ORIGINAL ARTICLE

Medicine Science International Medical Journal

Medicine Science 2021;10(1):88-91

Retinal vascular caliber in turkish adolescents with type 1 diabetes mellitus

Alper Halil Bayat[1], Digdem Bezen[2], Akin Cakir[3], Mustafa Nuri Elcioglu[3]

[1]Department of Ophthalmology, Esenler Hospital, Medipol University, Istanbul Turkey
[2]Department of Pediatric Endocrinology, Okmeydanı Research and Traning Hospital, University of Health Sciences, Istanbul, Turkey
[3]Department of Ophthalmology, Okmeydanı Research and Traning Hospital, University of Health Sciences, Istanbul, Turkey

Received 27 July 2020; Accepted 04 November 2020
Available online 17.01.2021 with doi: 10.5455/medscience.2020.07.148

Abstract

Diabetic retinopathy (DR) is a common result of diabetes mellitus (DM). Alterations in retinal vascular caliber may be early finding of diabetic retinopathy. The aim of this study is to demonstrate retinal vascular caliber changes in Turkish adolescents with type 1 diabetes mellitus (T1D). This prospective and cross-sectional study included 108 eyes of the T1D adolescents and 75 eyes of the age-sex matched control group. Fundus images of the both groups were taken with fundus camera system (FA; Visucam500; Carl Zeiss Meditec, Jena, Germany) and were analyzed with IVAN which is a semi-automated system used to measure the width of retinal vessels using a digital retinal image (Nicole J. Ferrier, College of Engineering, Fundus Photography Reading Center, University of Wisconsin, Madison, WI, USA). Central retinal artery equivalent (CRAE), central retinal vein equivalent (CRVE) and artery-vein ratio (AVR) were compared between groups. Both groups were comparable in baseline characteristics ($p>0.05$). The mean CRAE value was higher in T1D group (179.03±29.58 µ in T1D group and 166.64±15.76 µ in control group, $p<0.001$). The mean AVR value was higher in T1D group, too (0.97±0.46 in T1D and 0.84±0.19 in control group, $p=0.01$). There was no statistically significant difference in CRVE value between groups. CRAE was found to be higher in T1D patients. This arteriolar dilation may be the early finding of diabetic retinopathy.
.

Keywords: Retinal vascular caliber, arteriolar dilation, type 1 diabetes mellitus, diabetic retinopathy

Introduction

Diabetes mellitus (DM) is a common disease which effects 366 million people around world, while 20 million to 40 million of these patients is type 1 diabetes mellitus (T1D) [1]. The prevalence of T1D in Turkey is 0.75/1 000 (95% CI 0.74–0.76) [2]. T1D is of the most common chronic disease in adolescents and it can affect both anterior and posterior segment of eyes [3-5]. The diabetic retinopathy (DR) is the most common complication and main reason of vision loss in T1DM [6]. In current literature, some studies showed that measurement of retinal vascular caliber may provide useful information regarding risk of DR in adulthood [7-10]. Vasodilatation which is accepted as a sing of retinal arterial dysfunction were demonstrated in these studies. Most of these studies were in elderly population with type 2 DM which have coexisting disease such as hypertension, hyperlipidemia which can affect retinal vascular caliber. Some studies also showed vasodilatation in children and adults with T1D [11-13]. But there is not any study regarding Turkish adolescents with T1D.

The aim of the current study is to investigate retinal vascular caliber in Turkish adolescents with T1D.

Material and Methods

This prospective and cross-sectional study was conducted in Department of Ophthalmology, - Okmeydanı Research and Traning Hospital, University of Health Sciences, İstanbul, Turkey. Protocol of the study was approved by Ethics Committee of Marmara University (protocol number 09.2018.120). The study was performed in accordance with Declaration of Helsinki. Written informed consent was obtained from all the parents of the children.

The adolescents with T1D were selected among the patients which were referred us for DR screening. The control groups selected among the patients which came to hospital for normal ophthalmic examination. Inclusion criteria was T1DM adolescents (age between 12-20), no systemic disorder than T1DM, normal body-mass index (BMI), no ocular disease, spherical or cylindrical refractive

*Coresponding Author: Alper Halil Bayat, Department of Ophthalmology, Esenler Hospital, Medipol University, Istanbul Turkey,
E-mail: alperhalil76@hotmail.com

errors<1.00 D, no diabetic retinopathy, best-corrected visual acuity (BCVA) ≥ 20/20 at snellen charts. Control group had healthy subjects without any systemic or ocular disease. HbA1C levels, age, gender, duration of DM were noted.

All the patients underwent a complete ophthalmic examination. BCVA, slit-lamb bio-microscopy, intraocular pressure (IOP) values with Goldman applanation tonometry, posterior segments examination with dilated pupillary were performed. Fundus images of the both groups were taken with fundus camera system (FA; Visucam500; Carl Zeiss Meditec, Jena, Germany). Before and after fundus images examination blood pressure of the participants were measured. Only right eyes of the subjects were taken. Retinal vascular caliber was analyzed with IVAN which is a semi-automated system used to measure the width of retinal vessels using a digital retinal image (with permission of Dr. Nicola Ferrier of the University of Wisconsin - Madison School of Engineering and the Department of Ophthalmology and Visual Sciences, University of Wisconsin – Madison) [14-16].

Three concentric rings were placed in images of fundus to determine the vascular measurement field. After ring implantation two zones were formed. The area from the disc margin to half-disc diameter was defined as Zone A, while the area from half-disc diameter to 1 disc diameter was defined as Zone B. Central retinal artery equivalent (CRAE) and central retinal vessel equivalent (CRVE) measurements were performed using the formula created by Hubbard15 and later revised by Knudtson16 (Figure 1).

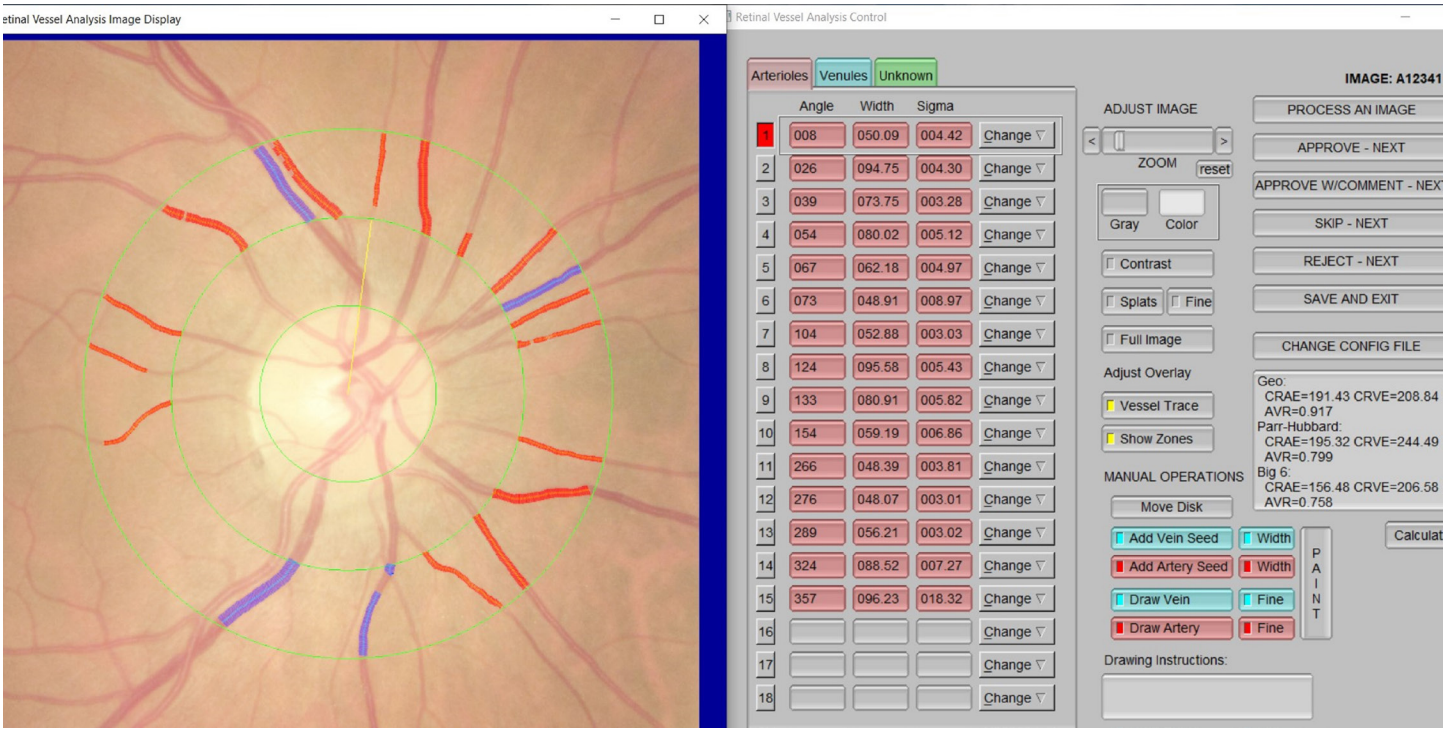


Figure 1. Measurement of retinal vascular caliber in IVAN

Statistical analyses were performed using the SPSS software version 25. Descriptive analyses were presented using means and standard deviations for normally distributed variables. An assessment of normality was done using the Kolmogorov-Smirnov test. The independent-t, Man-Whitney-U, Chi-squared tests were used for analyses. A p-value of less than 0.05 was considered to show a statistically significant result.

Results

One hundred eight eyes of 108 patients were in T1D group, while 75 eyes of healthy subjects were in control groups. The groups were comparable in baseline characteristics. The baseline characteristics of the patients were summarized in table 1.

Table 1. Demographic and clinical characteristics of the patients

	T1D group	Control group	p value
Age, y, mean±SD	14.78±1.96	15.16±2.42	0.261
Gender			
Female (n)	66	42	
Male (n)	42	33	0.489
The duration of DM, y	4.75±1.99		
The mean value of HbA1c, %, mean±SD	7.76±2.17		

SD: Standard deviation, y: years, DM: Diabetes Mellitus, HbA1c: glycated hemoglobin

The mean CRAE value was 179.03±29.58 μ in T1D group, while it was 166.64±15.76 μ in control group (p<0.001) (Figure-2). The mean CRVE value was 206.19±55.57 in T1D group, 205.04±38.45 in control group (p=0.869). AVR was 0.97±0.46 in T1D group and 0.84±0.19 in control group (p=0.01) (Figure-3).

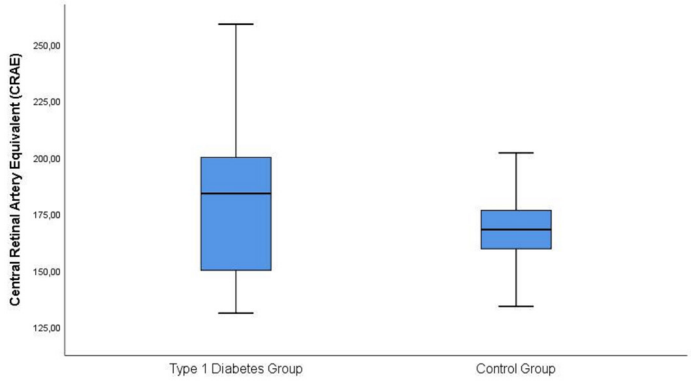


Figure 2. The mean central retinal artery equivalent (CRAE) value in groups

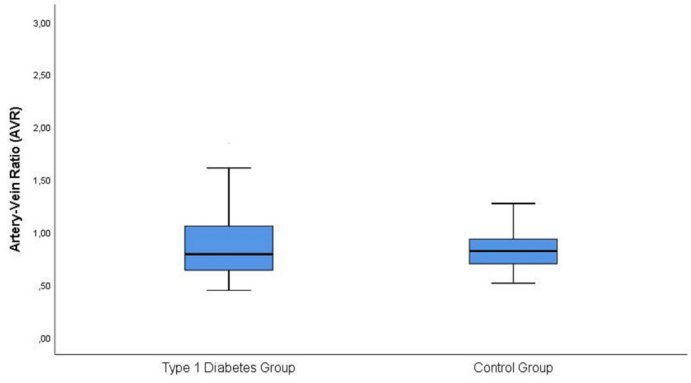


Figure 3. The mean artery-vein ratio (AVR) value in groups

The mean value of CRAE and AVR did not have correlation with age, gender, duration of DM and HbA1c value (p>0.05).

Discussion

Adolescents with T1D have an increasing for vision loss through their lives. The risk of developing DR is associated with duration of DM [17]. It is common knowledge that if DR can be detected in early stages, the risk for vision lose can be reduced with early treatment [18]. Hence, health-care professionals want to develop a noninvasive method to detect complications of DM, especially for children. IVAN is semi-automated system used to measure the width of retinal vessels using digital retinal images. So we used IVAN as a noninvasive method to detect early changes of retinal vessel caliber before developing DR in Turkish adolescent with T1D.

Our study shows that the adolescent with T1D have larger retinal arteriolar caliber and larger arterio/venous ratio. Previous studies have shown that retinal arteriolar dilatation is an indicator of diabetes micro vascular complications [12,19]. In an experimental study, researchers showed that arteriolar vasodilatation and an increase in retinal blood flow are commonly found in eyes of diabetic patients [20]. It is reported that retinal vasodilatation and retinal hyper perfusion which is to cause release of nitric oxide, can be key factors in diabetic retinopathy development [21-23]. Retinal hyper perfusion has been related with micro aneurysm development because it can cause epithelial damage and vascular permeability [21]. With all this information, it is too important to detect early vascular changes in diabetic patients. We aimed to show retinal caliber changes in Turkish adolescent with T1D.

Several studies showed retinal arteriolar dilatation in T1D children. Cheung et al [12] showed that diabetic children have larger retinal vascular caliber than healthy subjects. They also show that the children with larger retinal vascular caliber have higher risk of DR development. Their study demonstrated that each standard deviation increase in retinal vascular caliber was associated with a 46% increase in retinopathy risk [12]. In the Wisconsin Epidemiological Study of Diabetic Retinopathy (WESDR), researchers evaluated that an association of larger retinal vascular caliber with 10 year incident retinopathy risk in type 2 diabetes and 4 year progression of DR risk in type 1 diabetes [8]. While the WESDR show larger retinal arteriolar and venular dilatation in adults with T1D [8]. In our study we did not find any difference in retinal venular caliber. This is probably related to mean age of study population. The Atherosclerosis Risk in Communities study showed that vasodilatation in retinal venular caliber was related to metabolic syndrome components in the middle age person [24].

Conclusion

In conclusion, our study shows that the Turkish adolescent with T1D have larger retinal caliber than healthy people. These patients may have high risk of diabetic retinopathy development. Retinal vascular caliber might be a sensitive biomarker to define early diabetic retinopathy risk. Larger cohort studies in Turkish population are needed to describe early detection of diabetic retinopathy in adolescents and children.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
The financial support no have.

Ethical approval
Protocol of the study was approved by Ethics Committee of Marmara University (protocol number 09.2018.120).

References

1. Rewers M. Challenges in diagnosing type 1 diabetes in different populations. Diabetes Metabolism J. 2012;36:90-7.
2. Yeşilkaya E, Cinaz P, Andıran N, et al. First report on the nationwide incidence and prevalence of Type 1 diabetes among children in Turkey. Diabetic Medicine. 2017;34:405-10.
3. Dhillon N, Karthikeyan A, Castle A, et al. Natural history of retinopathy in children and young people with type 1 diabetes. Eye. 2016;30:987-91.
4. Tekin K, Inanc M, Kurnaz E, et al. Objective evaluation of corneal and lens clarity in children with type 1 diabetes mellitus. Am J Ophthalmol. 2017;179:190-7.
5. Inanc M, Tekin K, Kiziltoprak H, et al. Changes in retinal microcirculation precede the clinical onset of diabetic retinopathy in children with type 1 diabetes mellitus. Am J Ophthalmol. 2019;207:37-44.
6. Geloneck MM, Forbes BJ, Shaffer J, Ying G-s, Binenbaum G. Ocular complications in children with diabetes mellitus. Ophthalmology. 2015;122:2457-64.
7. Cheung N, Wong TY. Diabetic retinopathy and systemic vascular complications. Progress In Retinal Eye Research. 2008;27:161-76.

8. Klein R, Klein BE, Moss SE, et al. The relation of retinal vessel caliber to the incidence and progressionof diabetic retinopathy: Xix: The wisconsin epidemiologic study of diabetic retinopathy. Arch Ophthalmol. 2004;122:76-83.

9. Klein R, Klein BE, Moss SE, et al. Retinal vessel caliber and microvascular and macrovascular disease in type 2 diabetes: XXI: the Wisconsin Epidemiologic Study of Diabetic Retinopathy. Ophthalmology. 2007;114:1884-92.

10. Rogers SL, Tikellis G, Cheung N, et al. Retinal arteriolar caliber predicts incident retinopathy: the Australian Diabetes, Obesity and Lifestyle (AusDiab) study. Diabetes Care. 2008;31(4):761-763.

11. Grauslund J, Hodgson L, Kawasaki R, et al. Retinal vessel calibre and micro-and macrovascular complications in type 1 diabetes. Diabetologia. 2009;52:2213-17.

12. Cheung N, Rogers SL, Donaghue KC, et al. Retinal arteriolar dilation predicts retinopathy in adolescents with type 1 diabetes. Diabetes Care. 2008;31:1842-6.

13. Alibrahim E, Donaghue KC, Rogers S, et al. Retinal vascular caliber and risk of retinopathy in young patients with type 1 diabetes. Ophthalmology. 2006;113:1499-503.

14. Wong TY, Knudtson MD, Klein R, et al. Computer-assisted measurement of retinal vessel diameters in the Beaver Dam Eye Study: methodology, correlation between eyes, and effect of refractive errors. Ophthalmology. 2004;111:1183-90.

15. Hubbard LD, Brothers RJ, King WN, et al. Methods for evaluation of retinal microvascular abnormalities associated with hypertension/sclerosis in the Atherosclerosis Risk in Communities Study. Ophthalmology. 1999;106:2269-80.

16. Knudtson MD, Lee KE, Hubbard LD, et al. Revised formulas for summarizing retinal vessel diameters. Current Eye Research. 2003;27:143-9.

17. Lueder G, Silverstein J. American Academy of Pediatrics Section on Ophthalmology and Section on Endocrinology. Screening for retinopathy in the pediatric patient with type 1 diabetes mellitus. Pediatrics. 2005;116:270-3.

18. Stewart MW. Treatment of diabetic retinopathy: recent advances and unresolved challenges. World J Diabetes. 2016;7:333.

19. Quigley MG. Prognosis and retinal vessel features. Ophthalmology. 2007;114:1796-7.

20. Gardiner TA, Archer DB, Curtis TM, et al. Arteriolar involvement in the microvascular lesions of diabetic retinopathy: implications for pathogenesis. Microcirculation. 2007;14:25-38.

21. Kohner EM, Patel V, Rassam SM. Role of blood flow and impaired autoregulation in the pathogenesis of diabetic retinopathy. Diabetes. 1995;44:603-7.

22. Stefansson E, Landers MB, Wolbarsht ML. Oxygenation and vasodilatation in relation to diabetic and other proliferative retinopathies. Ophthalmic Surgery, Lasers and Imaging Retina. 1983;14:209-26.

23. Scherrer U, Randin D, Vollenweider P, Vollenweider L, Nicod P. Nitric oxide release accounts for insulin's vascular effects in humans. J Clin Investigation. 1994;94:2511-5.

24. Wong TY, Duncan BB, Golden SH, et al. Associations between the metabolic syndrome and retinal microvascular signs: the Atherosclerosis Risk In Communities study. Investigative Ophthalmol Visual Sci. 2004;45:2949-54.

Available online at www.medicinescience.org

ORIGINAL ARTICLE

Medicine Science International Medical Journal

Medicine Science 2021;10(1):92-7

Morphometric measurements in thoracal vertebral fractures

Usame Rakip, Serhat Yildizhan, Mehmet Gazi Boyaci , Adem Aslan

Afyonkarahisar Health Sciences University, Faculty of Medicine, Department of Neurosurgery, Afyonkarahisar, Turkey

Received 12 August 2020; Accepted 14 September 2020
Available online 17.01.2021 with doi: 10.5455/medscience.2020.08.164

Abstract

In this study, we aimed to compare the pedicle morphometric measurements of patients with thoracic vertebral fractures, who were admitted to the emergency department after trauma, and normal population, with the help of tomography. 252 patients with thoracic vertebral fracture between January 2017 and December 2019 were included in the study. The patients were divided into two as operated (Group 1, n: 169) and non-operated (Group 2, n: 83) groups. Transverse and sagittal pedicle diameters of all patients' thoracic vertebrae were measured by computed tomography. These values were compared with the normal population. 252 patients (148 male) were included in the study. Most of the fractures were seen in the T12 vertebrae. The least affected vertebrae were T1 and T2. In males, the thinnest transverse pedicle diameter was measured at the T4 while the thickest transverse pedicle was measured at the T12 level. In females, the thinnest transverse pedicle was measured at the T6 level while the thickest transverse pedicle was measured at the T12 level. In men, the thinnest sagittal pedicle was measured at the T3 level while the thickest sagittal pedicle was measured at the T12 level. The thinnest sagittal pedicle diameter was measured at the T7 vertebra level while the thickest sagittal pedicle was measured at the T12 level. Transverse and sagittal pedicle measurements were found to be higher in males than in females at almost all thoracic vertebra levels. Transverse and sagittal pedicle diameters of patients with thoracic vertebral fracture were significantly lesser than normal population. Pedicle diameter reveals significant individual and segmental differences in the thoracic region. Patients with similar traumas, who also have a pedicle diameter below the mean value, are more likely to develop fractures.

Keywords: Thoracic vertebral fracture, pedicle morphometric measurements, demographic distribution

Introduction

The most common surgical treatment in thoracolumbar trauma is posterior vertebral instrumentation. It was first applied by Raymond Roy-Camille [1] and now occupies an important place in neurosurgical practice [2–4]. After the introduction of computed tomography (CT) and magnetic resonance imaging (MRI) into common practice, the best treatment options for spinal degenerative diseases such as spinal fractures, scoliosis, kyphosis, spondylolisthesis were sought. Wiring, hooks, etc. were tried in this process but did not yield successful results in fusion formation as transpedicular screwing (TPS) [5,6]. In thoracic vertebral fractures, conservative treatment is preferred when there is no neurological deficit and the spine is stable. However, there are indications for surgical treatment in fractures in which the vertebral body height loss is severe with the presence of canal compression, neurological deficit and kyphotic deformity [7]. It is healthy to make surgical decisions based on accepted classifications such as TLICS. The main purpose of the surgical treatment should be to protect or improve the neurological condition, to ensure stability, to correct the deformity and to prepare the ground for early rehabilitation. [8–10]. Nowadays, TPS is the most preferred surgical method. TPS has advantages, but if TPS is performed with wrong methods and the detailed measurements on preoperative images were not made, screwing is insufficient and it can cause distressing results (such as screw loosening). The thoracic vertebrae, especially the upper thoracic (T1-T6), have thinner pedicle diameters in the normal population [11,12] and have a much lower chance of screw revision.

***Coresponding Author:** Usame Rakip, Afyonkarahisar Health Sciences University, Faculty of Medicine, Department of Neurosurgery, Afyonkarahisar, Turkey, E-mail: usamerakip@gmail.com

Material and Methods

This study had been carried out with the decision dated 03.05.2019, and numbered 2019/167 by Afyonkarahisar Health Sciences University Clinical Research Ethical Board, between 01.01.2017-01.07.2019.

252 patients (148 males) who were followed up in our clinic with the diagnosis of thoracic fracture between January 2017 and December

2019 were included in the study. Patients under 15 years old and pathological fractures were not included in the study. Demographic distributions such as age and gender, etiologic factor and treatment modalities were recorded. The patients were divided into two as non-operated (Group 1, n: 83) and operated (Group 2, n: 169) groups. CT was performed on all patients. First, axial images with 2 mm thickness were obtained. Following the reconstruction of the bone window, the thickest section of the pedicle was found. Then the pedicle transverse diameters in this section were digitally measured on the current image (Toshiba CT UK). Afterwards, sagittal images were obtained. Following the reconstruction of the bone window, the thickest section of the pedicle was found. The pedicle sagittal diameters in this section were then measured digitally on the current image. All measurements are indicated in milimeters (Figure 1).

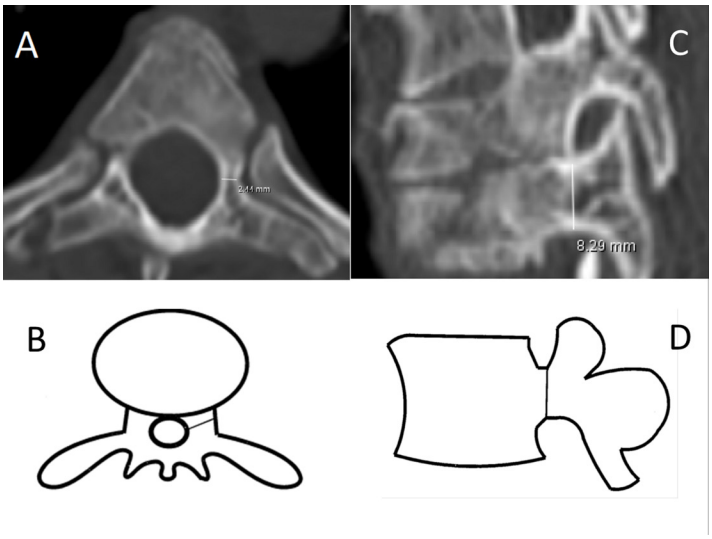


Figure 1. A: Pedicle transverse (PT) diameter in axial section by computed tomography; B: Schematic representation of left pedicle transverse diameter measurement; A: Measurements of pedicle sagittal (PS) diameter are monitored by computed tomography. D: Schematic representation of the sagittal diameter measurement of the pedicle

A total of 1008 morphometric measurements of 504 pedicle transverse diameters and 504 pedicle sagittal diameters were performed. The two groups were compared with each other and normal population values with the guide of literature. Statistical analysis was performed with "IBM SPSS STATISTICS 25". In addition to the standard descriptive calculations (mean ± standard deviation), "Wilcoxon signed ranks test" was used to evaluate the difference between right and left. The $p<0.05$ values were considered statistically significant.

Results

Of the 252 patients included in the study, 148 were male (59%) and 104 were female (41%). Age group to gender distribution was 41 males 14 females between the ages of 15-30, 32 males 14 females between the ages of 31-45, 43 males 32 females between the ages of 46-60, 27 males 32 females between the ages of 61 and 75 years, 5 males and 12 females over the age of 75. While the mean age and standard deviation of male patients were 45.5 ± 16.98 (16-85), the mean age and standard deviation of female patients were 55.2 ± 18.36 (16-84). When a distribution was made according to age groups, while 79% of males were under 60 years of age, 21% were over 60 years of age and while 56% of female patients were under 60 years of age, 32% were over 60 years of age. (Table 1).

Table 1. Distribution of the number of patients by age group

AGE	Male	Female
15-30	41	14
31-45	32	14
46-60	43	32
61-75	27	32
>75	5	12
TOTAL	148	104

The most affected spine was T12, regardless of age, sex and etiology. The least affected were observed to be T1 and T2 (Figure 2).

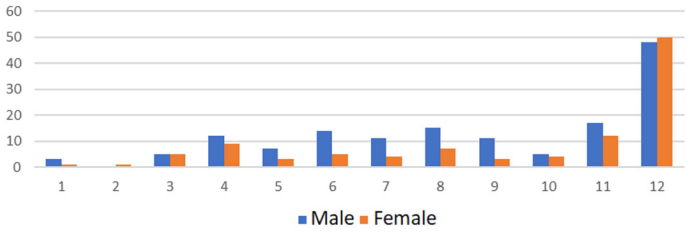


Figure 2. Level distribution of vertebral fracture by age and sex

The most common cause of trauma was falling from height with 62.6% (n: 158), while traffic accidents took the second place with 36.4% (n: 91). The reasons such as beating and being under dent were 1% (n: 3).

When examined separately in males, the thinnest right transverse pedicle diameter (TPD) was measured at the right side of the T4 vertebra with 1.72 mm, while the thinnest mean TPD was measured at the T3 vertebrae with 3.15 mm. When examined separately in males, the thinnest left TPD was measured at the T4 vertebrae level with 1.47 mm, while the thinnest mean TPD was measured at the T3 vertebra with 2.85 mm. In men, the thickest TPD was 8.63 mm on the right and 9.94 mm on the left. When examined separately in women, the thinnest right TPD was measured at the T6 vertebrae level with 2.15 mm, while the mean was measured at the T4 vertebrae level with the thinnest 3.3mm. When examined separately in women, the thinnest left TPD was at the T6 vertebrae level with 2.14 mm, and the mean thickest TPD was measured at T12 levels with 8.81 mm on the right and 9.02 mm on the left. (Table 2- 3)

In males, the thinnest sagittal pedicle diameter (SPD) was measured at the T3 Vertebrae with 5.56 mm and the thickest SPD at the T12 level with 15.20 mm. In women, the thinnest SPD was measured at the T7 Vertebrae with 5.45 mm and the thickest SPD at the T12 with 14.36 mm. (Table 2.)

In determining our treatment strategy, it was decided based on TLICS classification. Of the 252 patients, 67% (n: 169) followed the surgical route and 33% (n: 83) the conservative medical treatment. While the measurements were being made, the average of the pedicles' transverse and sagittal diameters were found to be significantly smaller in the patients who were decided to be operated (group 2). (Table 4- 5)

Table 2. Minimum and maximum of pedicle measurements included in the whole study values and levels

		Male				Female			
Patients		**Min.**	**Level**	**Mac.**	**Level**	**Min.**	**Level**	**Mac.**	**Level**
	PT-R	1.72	T4	8.63	T12	2.15	T6. T7	8.81	T12
PT	PT-L	1.47	T4	9.94	T12	2.44	T6. T7	9.02	T12
	PT Avarage	1.95		9.29		2.3		8.92	
PS		5.56	T3	15.20	T12	5.45	T7	14.36	T12
Group 2 (n: 169) operated		**Min.**	**Level**	**Mac.**	**Level**	**Min.**	**Level**	**Mac.**	**Level**
	PT-R	1.72	T4	8.63	T12	2.44	T4	7.11	T12
PT	PT-L	1.47	T4	8.45	T12	2.44	T4. T7	7.33	T12
	PT Avarage	1.92		8.62		2.44		7.22	
PS		5.56	T3	15.2	T12	5.45	T7	14.36	T12
Group 1 (n: 83) not operated		**Min.**	**Level**	**Mac.**	**Level**	**Min.**	**Level**	**Mac.**	**Level**
	PT-R	2.76	T4	8.21	T12	2.15	T6	8.81	T12
PT	PT-L	2.66	T9	9.94	T12	2.87	T6	9.02	T12
	PT Avarage	2.71		9.07		2.51		8.91	
PS		7.22	T7	15.20	T12	7.23	T6	14.36	T12

Min.: the finest value found, Mac.: the thickest value PT: pedicle transverse diameter, PT-R: right pedicle transverse diameter PT-L: left pedicle transverse diameter, PS: pedicle sagittal diameter

Table 3. Mean pedicle measurements of all patients included in the study

	Pedicle Transvers							**Pedicle Sagittal**			**Number of patients**	
	Male			**Female**								
	Right	**Left**	**Male Avarage**	**Right**	**Left**	**Female Avarage**	**Male and female total Avarage**	**Male**	**Female**	**Avarage**	**Male**	**Female**
T1	4.787±0.23	4.71±0.46	4.75	4.67±0.00	4.67±0.00	4.67	4.71	9.51±1.05	6.65±0.00	8.58	3	1
T2	4.21±0.21	4.32±0.52	4.27	4.28±0.00	4.28±0.00	4.28	4.3	8.62±0.52	7.21±0.00	7.92	2	1
T3	3.51±0.06	3.43±0.36	3.47	3.56±0.6	3.84±0.56	3.7	3.59	8.51±2.83	8.94±0.62	8.73	4	5
T4	3.66±0.89	4.05±1.23	4.08	3.58±0.55	3.63±0.58	3.605	3.82	7.98±0.92	8.02±1.42	8	12	9
T5	3.82±1.05	3.43±0.48	3.63	3.69±0.49	4.77±0.73	4.23	3.93	8.62±0.96	9.89±0.86	9.26	7	3
T6	4.03±1.03	3.79±1.09	4.07	4.5±0.00	3.90±0.28	4.2	4.14	9.10±1.65	9.84±1.91	9.47	14	5
T7	4.54±0.38	4.11±0.93	4.33	4.05±1.36	4.30±0.35	4.18	4.25	8.70±1.81	9.40±4.43	9.05	11	4
T8	4.27±0.48	3.97±1.07	4.12	3.95±0.36	4.02±1.05	3.99	4.06	8.92±1.41	9.15±1.16	9.04	15	7
T9	4.13±1.37	4.50±2.17	4.32	3.31±0.80	3.44±0.61	3.38	3.85	9.38±1.37	8.48±1.59	8.93	11	3
T10	4.58±1.65	4.45±1.05	4.52	4.28±1.38	4.29±0.42	4.29	4.41	11.24±1.14	9.65±0.60	10.45	5	4
T11	5.29±1.80	5.12±1.33	5.21	5.28±0.82	5.53±0.67	5.41	5.31	11.18±1.98	10.28±1.24	10.73	17	12
T12	5.36±1.22	5.40±1.12	5.38	5.26±1.2	5.79±1.20	5.53	5.45	12.42±1.87	11.07±1.78	11.75	48	50

Table 6. Comparison of pt and ps between our groups

Thoracic Vertebra Pedicle Transverse Mean Diameter Measurements												
	T1	**T2**	**T3**	**T4**	**T5**	**T6**	**T7**	**T8**	**T9**	**T10**	**T11**	**T12**
All Patients	4.71	4.3	3.59	3.82	3.93	4.14	4.25	4.06	3.85	4.41	5.31	5.45
1. Group	4.77	4.4	3.81	4.2	4.25	4.24	4.62	4.63	*	5.5	5.34	5.83
2. Group	3.76	4.27	3.3	3.71	3.93	3.54	3.51	3.78	3.90	4.13	5.26	4.99
Mean Thoracic Vertebra Pedicle Sagittal Diameter Measurements												
	T1	**T2**	**T3**	**T4**	**T5**	**T6**	**T7**	**T8**	**T9**	**T10**	**T11**	**T12**
All Patients	8.58	7.92	8.73	8	9.26	9.47	9.05	9.05	8.93	10.45	10.73	11.75
1. Group	8.45	*	9.42	9.39	9.42	9.9	8.8	9.9	10.7	12.25	12.1	12.37
2. Group	8.51	7.21	7.64	7.35	8.54	8.3	8.75	8.9	8.83	11.46	10.43	10.51

PT: Pedicle Transverse Diameter
PS: Pedicle Sagittal Diameter
*: Measurement was not taken as there is no patient.

Table 7. Comparison of our study with the measurements of transverse and sagittal diameters of pedicle made nationally and internationally

Thoracic vertebra pedicle transverse diameters												
	T1	**T2**	**T3**	**T4**	**T5**	**T6**	**T7**	**T8**	**T9**	**T10**	**T11**	**T12**
Our Study Overall Average	4.71	4.3	3.59	3.82	3.93	4.14	4.25	4.06	3.85	4.41	5.31	5.45
Our Study (Group 2)	3.76	4.27	3.3	3.71	3.93	3.54	3.51	3.78	3.90	4.13	5.26	4.99
Baysal (19)	6.75	5.45	4.7	4.25	4	4	4.2	4.55	5	5.6	6.35	6.95
Araz (20)	*	*	*	*	*	*	*	*	5.5	5.9	6.9	6.8
Ugur (21)	6.7	6.2	5.3	4.6	4.7	4.9	5.3	5.7	6.2	6.4	7.8	7.9
Kim (22)	8.1	6.1	4.6	4.2	4.3	4.7	4.8	5.1	5.2	6.3	7.9	7.9
Yu (11.12)	8.7	7	5.8	5.1	5	5.4	5.7	6	6.5	7.8	9.3	9.2
Panjabi (26)	8.1	7.4	5.97	5.2	4.9	5.4	5.9	6.7	7.7	9	9.8	8.7
Vaccaro (23,24)	*	*	*	4.5	4.4	4.6	4.7	5.1	5.8	6.7	8	7.8
Sagittal diameters pedicle of thoracic vertebrae												
	T1	**T2**	**T3**	**T4**	**T5**	**T6**	**T7**	**T8**	**T9**	**T10**	**T11**	**T12**
Our Study Overall Average	8.58	7.92	8.73	8	9.26	9.47	9.05	9.05	8.93	10.45	10.73	11.75
Our Study Group 2	8.51	7.21	7.64	7.35	8.54	8.3	8.75	8.9	8.83	11.46	10.43	10.51
Araz (20)	*	*	*	*	*	*	*	*	14.5	15.4	14.5	15
Panjabi (26)	9.6	11.4	11.9	12.1	11.3	11.8	12	12.5	13.8	15	17.4	16.7
Datir	9.4	12.1	12.2	11.8	11.6	11.7	12.5	13.2	14.4	16.6	17.7	18.7
Yu (11,12)	9.4	11.6	12.2	12.2	12.1	12.1	12.3	12.8	13.5	15.4	17	17.1

PT: Pedicle Transverse Diameter
PS: Pedicle Sagittal Diameter
*: Measurement was not taken as there is no patient.

Discussion

Transpedicular screwing (TPS) has been used reliably by neurosurgeons for many years in spinal traumas, degenerative deformities and diseases such as osteoporotic collapse fracture. The use of TPS in the thoracic region was started a little later due to the existence of important and vital organs and vessels adjacent to the vertebral bodies.[13–17]. Lesser pedicle diameter measurements of the thoracic vertebrae, especially upper thoracic vertebrae, are also one of the reasons.[11,18]. The main aim of our study was to investigate the pedicle morphometric dimensions of thoracic vertebrae with fracture, to compare pedicle morphometric measurements with non-fracture thoracic vertebrae at the same levels and to reveal any significant differences, and to investigate the effect of demographic factors on these dimensions.

In our study, the mean values of the pedicle diameter measurements of the fractured vertebrae of all patients were extracted first. Then, the mean values of non-operated (group 1) and operated (group 2) groups were determined as separate groups. (Table 6)

According to the results of computed tomography measurements in males TPD measurements were found to be higher than women. A statistically significant difference was found. (P = 0.006) SBD measurements were also found to be higher in males. However, no statistically significant difference was found. (P = 0.124)

There was no significant difference between right and left pedicle diameter measurements in both men and women. (Male P = 0.065, female P = 0.110)

A significant difference was found between male and female patients in terms of number (male: female = 59%: 41%). When men and women were compared in terms of the age of trauma, it was found that men were statistically traumatized at a younger age.

When the groups were compared, it was found that the transverse and sagittal diameter measurements of the pedicle were thinner in group 2. There was a significant difference between group 1 and group 2 when compared to each other. (P = 0.008) However, no significant difference was found between the SPD measurements. (P = 0.238)

No similar study was found in the literature. However, many studies have been found regarding the measurements of natural thoracic pedicle diameter without fracture. When our study was compared with those studies, a detailed analysis was performed in terms of both general point of view and the most fractured vertebrae we detected (T4-T6-T8-T11-T12) (Figure 2.) and the values of group 2 were taken as the base values.

Baysal et al[19] found mean TPD values as 4.25 at T4, 4.2 at T6, 4.55 at T8, 6.9 at T11 and 6.8 at T12 level in their study, while we found these values as 3.71 at T4, 3.54 at T6, 3.78 at T8, 5.26 at T11 and 4.99 at T12 level, and TPD measurements in our study were found to be significantly smaller.(Table 7)

While Araz et al.[20]found the mean TPD values 5.508 ± 0.483 at T9, 5.877 ± 0.380 at T10, 6.917 ± 0.411 at T11 and 6.971 ± 0.465 at T12 in their studies, we found 3.90 ± 1.137 at T9, 4.13 ± 1.165 at T10, 5.26 ± 1.20, 4.99±1.120 at T12 in our study. It was found that TPD measurements were significantly smaller in our study. (Table 7)

When Ugur et al.[21], Kim and Arak [22], Vaccaro et al.[23,24] studies were compared with our study, it was found that TPD mean values were significantly smaller in all thoracic levels in our study. (Table 7)

When the detailed measurements of both upper and lower thoracic TPD and SPD in the studies of Datir PS et al.[25]Panjab et al.[26] and Yu et al.[11,12] were compared with our values, it was found that the total TPD and SPD measurements were significantly smaller in all thoracic levels.(Table 7)

Conclusion

Transverse and sagittal pedicle diameters of patients with thoracic vertebral fracture were significantly lesser than normal population. Pedicle diameter reveals significant individual and segmental differences in the thoracic region. Patients with similar traumas, who also have a pedicle diameter below the mean value, are more likely to develop fractures.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
The financial support no have.

Ethical approval
This study had been carried out with the decision dated 03.05.2019, and numbered 2019/167 by Afyonkarahisar Health Sciences University Clinical Research Ethical Board, between 01.01.2017-01.07.2019.

References

1. Roy-Camille R, Saillant G, Berteaux D, et al. Vertebral osteosynthesis using metal plates. Its different uses. Chirurgie. 1979;105:597–603.
2. Ashman RB, Galpin RD, Corin JD, et al. Biomechanical analysis of pedicle screw instrumentation systems in a corpectomy model. Spine. 1989;14:1398–405.
3. Ebraheim NA, Xu R, Ahmad M, et al. Projection of the thoracic pedicle and its morphometric analysis. Spine. 1997;22:233–8.
4. Schizas C, Michel J, Kosmopoulos V, et al. Computer tomography assessment of pedicle screw insertion in percutaneous posterior transpedicular stabilization. Eur Spine J. 2007;16:613–7.
5. Chiba M, McLain RF, Yerby SA, et al. Short-segment pedicle instrumentation. Biomechanical analysis of supplemental hook fixation. Spine. 1996;21:288–94.
6. Liljenqvist U, Hackenberg L, Link T,et al. Pullout strength of pedicle screws versus pedicle and laminar hooks in the thoracic spine. Acta Orthop Belg. 2001;67:157–63.
7. Kemal Koc R. Koç RK. Torakolomber travmalarda cerrahi tedavi.In: Hancı M,Çağlı S (ed), Omurga ve Omurilik Yaralanmaları. TND yayınları. 1997;33-144.
8. Akbarnia BA, Crandall DG, Burkus K, et al. Use of long rods and a short arthrodesis for burst fractures of the thoracolumbar spine. A long-term follow-up study. J Bone Joint Surg Am. 1994;76:1629–35.
9. France JC, Yaszemski MJ, Lauerman WC, et al. A randomized prospective study of posterolateral lumbar fusion. Outcomes with and without pedicle screw instrumentation. Spine. 1999;24:553–60.
10. Islam C, Güzel MB, Sakul BU. Clinical importance of the minimal cancellous diameter of lower thoracic and lumbar vertebral pedicles. Clin Anat. 1996;9:151–4.

11. Yu CC, Bajwa NS, Toy JO, et al. Pedicle morphometry of upper thoracic vertebrae: an anatomic study of 503 cadaveric specimens. Spine. 2014;39:E1201-9.

12. Yu CC, Yuh RT, Bajwa NS, et al. Lower thoracic pedicle morphometry: male, taller, and heavier specimens have bigger pedicles. Spine. 2015;40:E323-31.

13. Chen H-J, Xiao Z-G, Yu R-H, et al. CT measurement and analysis of the target vertebral body in elderly patients with uncompressed osteoporotic thoracolumbar fractures. Eur Rev Med Pharmacol Sci. 2018;22:36–44.

14. Laine T, Mäkitalo K, Schlenzka D, et al. Accuracy of pedicle screw insertion: a prospective CT study in 30 low back patients. Eur Spine J. 1997;6:402–5.

15. Belmont PJ, Klemme WR, Dhawan A, et al. In vivo accuracy of thoracic pedicle screws. Spine. 2001;26:2340–6.

16. Belmont PJ, Klemme WR, Robinson M, et al. Accuracy of thoracic pedicle screws in patients with and without coronal plane spinal deformities. Spine. 2002;27:1558–66.

17. Jones EL, Heller JG, Silcox DH, et al. Cervical pedicle screws versus lateral mass screws. Anatomic feasibility and biomechanical comparison. Spine. 1997;22:977–82.

18. Mohanty SP, Pai Kanhangad M, Bhat SN, et al. Morphometry of the lower thoracic and lumbar pedicles and its relevance in pedicle fixation. Musculoskelet Surg. 2018;102:299–305.

19. Baysal Ö, Baysal T, Elmalı N, et al. Türk Toplumunda Torakal Vertebra Pedikül Çaplarının Bilgisayarlı Tomografi ile Ölçümü. İnönü Üniversitesi Tıp Fakültesi Derg. 2004;11:147-9.

20. Araz N. Alt Torakal ve Üst Lomber Vertebra Pediküllerinde Bilgisayarli Tomografi ile Yapilan Morfometrik Ölçümler. Ph.D. thesis, Mersin University, Mersin, 2014.

21. Ugur HC, Attar A, Uz A, et al. Thoracic pedicle: surgical anatomic evaluation and relations. J Spinal Disord. 2001;14:39–45.

22. Kim NH, Lee HM, Chung IH, et al. Morphometric study of the pedicles of thoracic and lumbar vertebrae in Koreans. Spine. 1994;19:1390–4.

23. Vaccaro AR, Rizzolo SJ, Balderston RA,et al. Placement of pedicle screws in the thoracic spine. Part II: An anatomical and radiographic assessment. J Bone Joint Surg Am. 1995;77:1200–6.

24. Vaccaro AR, Rizzolo SJ, Allardyce TJ,et al. Placement of pedicle screws in the thoracic spine. Part I: Morphometric analysis of the thoracic vertebrae. J Bone Joint Surg Am. 1995;77:1193–9.

25. Datir SP, Mitra SR. Morphometric Study of the Thoracic Vertebral Pedicle in an Indian Population. Spine. 2004;29:1174–81.

26. Panjabi MM, O'Holleran JD, Crisco JJ, et al. Complexity of the thoracic spine pedicle anatomy. Eur Spine J. 1997;6:19–24.

Available online at www.medicinescience.org

ORIGINAL ARTICLE

Medicine Science International Medical Journal

Medicine Science 2021;10(1):98-100

Effect of short-term in vitro antibiotic administration into the human umbilical cord tissue on cfu count and mesenchymal stem cell immunophenotype

Durmus Burgucu

Akdeniz University Teknokent Babylife Cord Blood Bank and Human Cell-Tissue Production Center, Antalya, Turkey

Received 04 August 2020; Accepted 18 October 2020
Available online 17.01.2021 with doi: 10.5455/medscience.2020.08.155

Abstract

Mesenchymal stem cells play important roles in regenerative and reparative medicine applications. Their differentiation and proliferation abilities both in the human body and in the laboratory, environment have been revealed through many clinical and pre-clinical trials. Umbilical cord tissue is an important source of mesenchymal stem cells and has become a popular option in cord blood banking, especially in the last decade. As done for the cord blood, the steps of obtaining, transferring, processing, and cryopreserving umbilical cord tissue are defined by standard procedures. However, there is limited information about the microbiological contamination rate of tissues and their decontamination before the procedure. This study aimed to assess the effect of in vitro short-term antibiotic treatment applied to the umbilical cord tissue obtained via superficial ethanol disinfection immediately after birth on the formation of colony-forming units (CFUs) and immunophenotype of the mesenchymal stem cells. For this purpose, tissues obtained from 10 individuals were evaluated in three different groups that included the control group and groups of tissues with 5- and 10-min antibiotic treatment. There was no significant difference among the groups in the expression levels of CD45, CD34, CD73, CD105, and CD44, which are the markers used in immunophenotyping. Similarly, no difference was found in CFU formation either. The present study has revealed for the first time that an antibiotic preparation used in in vitro cell culture for cord tissue banking can be used safely in tissue preparation and banking stages. Our results show that short-term in vitro antibiotic administration can contribute to the standard formation during decontamination/disinfection stages in cord tissue banking.

Keywords: Umbilical cord, mesenchymal stem cell, cord blood bank

Introduction

Human umbilical cord blood has been successfully used as a source of hematopoietic stem cells from 1988 to the present day [1]. Transplant of more than 40,000 units of cord blood has been successfully performed in both children and adults for the treatment of several diseases, including hematological, metabolic, immunological, neoplastic, and neurological disorders [2]. Also, the number of units within the cord blood banks has reached about 5 million units worldwide, including 800,000 units in state-owned banks and more than 4 million units in private banks [3]. One of the key points in cord blood banking is the microbiological screening of the obtained blood. Studies around the world have shown that the bacterial contamination rate is 1%–2% [4-5]. Just like umbilical cord blood, umbilical cord tissue has also been a popular topic in the studies conducted in the field of cord blood banking, especially in the last decade. Cord tissue is an important source of mesenchymal stem cells [6]. As done for the cord blood, the steps of obtaining, transferring, processing, and cryopreserving the cord tissue are defined by standard procedures [7]. However, there is limited information about the microbiological contamination rate of tissues and their decontamination before the procedure. This study aimed to assess the effect of in vitro short-term antibiotic treatment applied to the umbilical cord tissue obtained via superficial ethanol disinfection immediately after birth on the formation of colony-forming units (CFUs) and immunophenotype of the mesenchymal stem cell.

Material and Methods

This study was approved by the Ethics Committee of the Akdeniz University Faculty of Medicine (decision number: 592-date: 11.10.2017), and volunteer participants signed an informed consent form. Removal, transfer, and decontamination of the tissues: The cord tissues of the subjects who applied to the cord blood bank were cleaned with 70% ethanol and then surgically cut and taken into a

***Coresponding Author:** Durmus Burgucu, Akdeniz University Teknokent Babylife Cord Blood Bank and Human Cell-Tissue Production Center, Antalya, Turkey, E-mail: dburgucu@akdeniz.edu.tr

cord tissue transfer kit immediately after birth and delivered to the GMP laboratory. The tissue was first removed from the transfer kit and then was washed in a sterile petri dish (Falcon 100 mm-353003) with normal saline (0.9% ISOTONIC SODIUM CHLORIDE SOLUTION-Polifarma/c-1911002). Thereafter, it was divided into fragments of 0.3 cm. These fragments were treated with normal saline containing a 4% antibiotic solution (P0781 Sigma-Aldrich Penicillin-Streptomycin). A preliminary study was conducted to determine the concentration of antibiotics. We started with 1% in standard cell culture conditions and increased it up to 4%. As short-term implementation was planned, we decided on 4× standard concentration. We used flow cytometry with 7AAD to test that 5 and 10 minutes of the application did not exhibit a negative effect on cell viability (viability >%95, data not shown). In this preliminary study, mononuclear cells obtained from cord blood were used. In summary, a 4% concentration was considered the safe upper limit for this study. Two groups of tissues were kept in the antibiotic solution: one for 5 min and the other for 10 min. For primary culture, the tissue was cultured for 21 days in a complete medium [Dulbecco's Modified Eagle Medium (DMEM Gibco-11965092) +10% autologous plasma]. At the end of the 21st day, tissue fragments were removed. Samples with 70% confluence were divided into two Petri dishes (100 mm).CFU assay: Cells obtained after the primary culture were transferred into 6-well plates so that there well 5000 cells per well and incubated for 2 weeks in the wells containing 3 ml 0.5% noble agar (A5431 Sigma-Aldrich) (37°C, 5% CO_2). Following incubation, the cells were fixed with 10% formalin (HT501128 Sigma-Aldrich) and dyed with Giemsa (GS500 Sigma-Aldrich). The colonies formed were counted. Mesenchymal stem cell immunophenotyping: After the primary culture, cells were collected into a polystyrene tube of 5 mL (BD 352003) so that there were 100,000 cells in each tube. For each sample, three tubes were prepared. Ten microliters of anti-CD34 (BD Pharmingen PE Mouse Anti-Human CD34 Cat No. 560941) and anti-CD-45 (BD Pharmingen FITC Mouse Anti-Human CD45 Catalog No. 555482) were added to the 1st tube; anti-CD44 (BD Pharmingen FITC Mouse Anti-Human CD44 Catalog No 560977), anti-CD-73 (BD Pharmingen PE Mouse Anti-Human CD73 Cat No 550257), and anti-CD105 (BD Pharmingen APC Mouse Anti-Human CD105 Cat No. 562408) were added to the 2nd tube, and isotypic controls (Mouse IgG1, κ) were added to the 3rd tube for each fluorochrome. These were incubated at room temperature in the dark for 20 min. Following incubation, the cells were washed twice with sterile PBS, and flow cytometry (BD Accuri C6) analysis was performed.

Statistical analysis

SPSS 21 statistical software was used. For intergroup comparisons, Kruskal–Wallis H-test was performed. $P < 0.05$ was considered significant.

Results

The cord tissues obtained from 10 individuals were divided into three fragments, and immunophenotypic analysis and CFU assay were performed in three different groups belonging to the same individual (the control group and the groups with 5- and 10-min antibiotic treatment) after the primary culture process. There was no significant difference among the groups in the primary culture stage and later in the CFU assay (Figure 1). This result shows that short-term antibiotic administration does not harm mesenchymal stem cells in terms of CFU formation. CD45, CD34, CD73, CD44, and CD105 are usually used as markers in the immunophenotyping of mesenchymal stem cells. The expression levels of these markers were assessed as % values in the flow cytometry analysis of mesenchymal stem cells obtained from each group after the primary culture (Figure 2). No significant difference was observed in expression levels when each marker was compared among the groups ($P > 0.05$). This result suggests that antibiotic administration does not affect the immunophenotypic properties of mesenchymal stem cells after the primary culture (Table 1).

Table 1. Immunophenotypic properties of mesenchymal stem cells after the primary culture (n = 10; P > 0.05)

	CD73	CD105	CD44	CD34	CD45
control	99	98.33	97.25	0.51	0.48
Antibiotic (5 min.)	99.15	98.36	97.42	0.52	0.51
Antibiotic (10 min.)	99,1	98.08	97.35	0.57	0.51

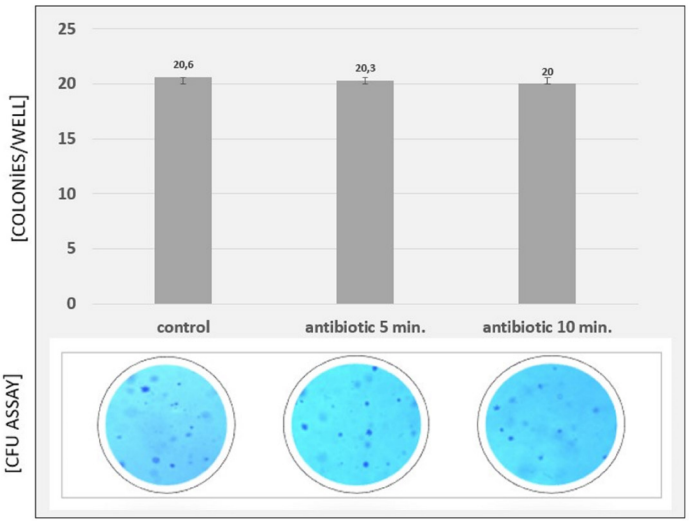


Figure 1. CFU counts: CFU counts of the control group and the groups with 5- and 10-min antibiotic treatment. Values are given as mean values (n = 10; P > 0.05)

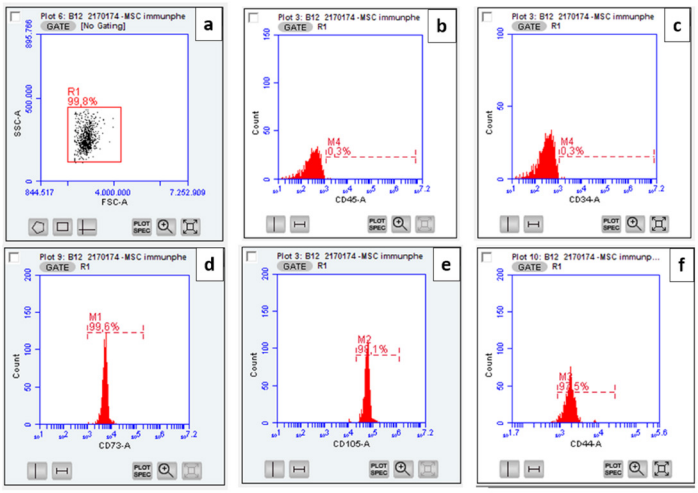


Figure 2. Mesenchymal stem cell immunophenotyping: Flow cytometry histograms

a) SSC/FSC, b) CD45 expression, c) CD34 expression, d) CD73 expression, e) CD105 expression, f) CD44 expression

Discussion

Mesenchymal stem cells play important roles in regenerative and reparative medicine applications. Their differentiation and proliferation abilities both in the human body and in the laboratory, environment have been revealed through many clinical and pre-clinical trials [6-8]. Furthermore, mesenchymal stem cells play important roles in immune system responses via their autocrine and paracrine effects. They exert an immunomodulatory effect, especially in hyperimmune response regulation [9]. Obtaining the cells and storing them under favorable conditions is one of the most important limitations in stem cell and cellular treatments. Successful isolation and reproduction of mesenchymal stem cells in the laboratory is important to produce a cell-based product for therapeutic purposes. Mesenchymal stem cell production is a time-consuming and labor-intensive process. Reproduction time, microbial contamination risks, and possible changes in biological characteristics are processes that need to be managed well. In mesenchymal stem cell production for therapeutic purposes, donor screening and testing, recovery, and safety and efficacy of the cells are important in terms of banking. There are two different studies in the literature regarding cord tissue contamination rate. One of these indicates that the rate is below 1%, especially in cesarean deliveries [10], whereas the other study has reported a contamination rate of 1.22% without indicating the method of delivery [11]. One study has reported in the methodology section that 70% ethanol was used [10], and the other has reported that 75% ethanol was used [11] but no antibiotics were administered. The tissues obtained in the present study were examined in three groups. The tissues obtained from 10 different individuals were grouped into the control group and the groups with 5- and 10-min in vitro antibiotic treatment. To standardize the donors in terms of the method of birth, only those with cesarean deliveries were included in the study. All stages were performed in GMP areas. The reason for this preference was to create a cell bank operating by GMP and to perform the practice according to GMP standards, which is a recommended choice. The approach of using a standard manufacturing process and comprehensive testing guarantees the safety, identity, purity, and strength of the final product [10]. In the present study, it was revealed for the first time that an antibiotic preparation used in in vitro cell culture for cord tissue banking can be safely used in tissue preparation and banking stages. Our results show that short-term in vitro antibiotic administration can contribute to the standard formation in decontamination/disinfection stages of cord tissue banking.

Financial Disclosure

This study was conducted within the scope of the project numbered 2170174 of the Scientific and Technological Research Council of Turkey (TUBITAK)-1512 Individual Entrepreneurship program.

Ethical approval

This study was approved by the Ethics Committee of the Akdeniz University Faculty of Medicine (decision number: 592-date: 11.10.2017).

References

1. Gluckman E, Broxmeyer HA, Auerbach AD, et al. Hematopoietic reconstitution in a patient with Fanconi's anemia by means of umbilical-cord blood from an HLA-identical sibling. N Engl J Med. 1989;321:1174-8.
2. Ballen KK, Gluckman E, Broxmeyer HE. Umbilical cord blood transplantation: the first 25 years and beyond. Blood. 2013;122:491-8.
3. Mayani H, Wagner JE, Broxmeyer HE. Cord blood research, banking, and transplantation: achievements, challenges, and perspectives. Bone Marrow Transplant. 2020;55:48-61.
4. Zhu L, Lv H, Wang Y, et al. Microbial screening of unrelated cord blood units in a Chinese cord blood bank. Transfus Med. 2013;23:438-41.
5. Chen SH, Zheng YJ, Yang SH, et al. Microbial contamination of the Tzu-Chi Cord Blood Bank from 2005 to 2006. Acta Paediatr Taiwan. 2008;49:9-13.
6. Couto PS, Shatirishvili G, Bersenev A, et al. First decade of clinical trials and published studies with mesenchymal stromal cells from umbilical cord tissue. Regen Med. 2019;14:309-19.
7. Dulugiac M, Moldovan L, Zarnescu O. Comparative studies of mesenchymal stem cells derived from different cord tissue compartments - The influence of cryopreservation and growth media. Placenta. 2015;36:1192-203.
8. Dominici M, Le Blanc K, Mueller I, et al. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Cytotherapy. 2006;8:315-7.
9. Gao F, Chiu SM, Motan DA, et al. Mesenchymal stem cells and immunomodulation: current status and future prospects. Cell Death Dis. 2016;7(1): e2062. Published 2016 Jan 21.
10. Gong W, Han Z, Zhao H, et al. Banking human umbilical cord-derived mesenchymal stromal cells for clinical use. Cell Transplant. 2012;21:207-16.
11. Ganesh Kumar Sarvesa, Chirayu Padhiar, Ashika Asha. Comparison study of 70% ethanol effect on direct and retrival culture of contaminated umbilical cord tissue for expansion of msc at lifecell. Cytotherapy volume 17, issue 6, supplement, s36, June 01, 2015

Available online at www.medicinescience.org

ORIGINAL ARTICLE

Medicine Science International Medical Journal

Medicine Science 2021;10(1):101-5

Paranasal sinus mucucele; clinical presentations and surgical management

Ozer Erdem Gur, Nevreste Didem Sonbay Yilmaz

Antalya Training and Research Hospital, Depatment of Otolaryngology, Antalya, Turkey

Received 04 August 2020; Accepted 13 September 2020
Available online 17.01.2021 with doi: 10.5455/medscience.2020.08.154

Abstract

Mucoceles of the paranasal sinus are benign expandable lesions that primarily occur between the fourth and seventh decades of life. In this study, the cases diagnosed with paranasal sinus mucocele who were operated by a single surgeon between 2002 and 2019 were evaluated in terms of symptoms, surgical technique, complications, and recurrence and discussed in the light of the literature. In this study, we retrospectively analyzed 75 patients, 76 mucoceles who underwent operations due to paranasal sinus mucoceles between January 2002 and December 2019. In the patients diagnosed with a mucocele, the mucocele was removed surgically. Of the 75 patients, 36 were female and 40 were male. All the patients were between the ages of 21 and 85, with an average age of 56.9 years old. Mucocele formation occurred in the frontal sinus in 46 (61%) patients, the maxillary sinus in 16 (21%) patients the ethmoid sinus in 11 (14%) patients, and the sphenoid sinus in 3 (4%). 1 patient had both frontal and maxillary sinus mucocele. 15 underwent surgery using external approach. All patients were followed-up with endoscopic examinations for 13 months to 4 years. 4 of 76 mucoceles (5,3%) experienced recurrence Treatment of paranasal sinus mucoceles is surgical and usually simple drainage and marsupialization of mucoceles is sufficient. The endoscopic approach in the treatment of sphenoid, maxillary and ethmoid mucoceles is the surgical method of choice without question. However, in frontal sinus mucocele surgery, external surgery is still valid as much as endoscopic sinus surgery.

Keywords: Mucocele, endoscopic sinus surgery, external approach

Introduction

Mucoceles of the paranasal sinus are benign expandable lesions that primarily occur between the fourth and seventh decades of life [1]. Sinus mucoceles may develop due to obstruction of the sinus outflow resulting from anatomical obstruction, mucosal hyperplasia, mass lesion or other mechanical factors. Previous operation and trauma, chronic sinusitis, tumor, nasal polyps, and RT are the main etiological factors [1,2].

The frontal sinus is the most common site of mucocele formation, followed by the ethmoidal, maxillary, and sphenoid sinuses [3-6].

Mucoceles are slow-growing mucosa-filled cysts lined with pseudo-columnar epithelium [3,5]. Although they grow slowly, they may extrude from the sinus from which they originate because of the bone erosion caused by the pressure they exert on the sinus wall and the cytokines they secrete. If the mucocele advances into the nasal passage, it causes nasal symptoms such as nasal congestion.

If it advances towards the orbital wall it causes orbital symptoms, such as proptosis, diplopia, epiphora, visual loss, and orbital cellulitis [1,4]. Frontal sinus mucoceles can cause intracranial symptoms, such as brain abscess, subdural abscess, and meningitis or they can cause cosmetic complaints because of swelling in the cheek or front and facial asymmetry due to expansion into the skin anteriorly [2,5]. Additionally, mucoceles may sometimes become infected and transform into a mucopyocele, causing symptoms such as osteomyelitis, orbital cellulitis and meningitis [1,7]. Therefore, when a mucocele that affects the sinus is detected, it must certainly be treated to prevent irreversible complications.

Diagnosis is made on imaging [8]. Computed tomography may illustrate an expansile remodeling-thinning and often sufficient for diagnosis. Magnetic resonance imaging (MRI) delineate the relationship among the mucocele, brain tissue, the orbit, and other soft tissues [1,8].

***Coresponding Author:** Nevreste Didem Sonbay, Antalya Training and Research Hospital, Depatment of Otolaryngology, Antalya, Turkey
E-mail: didem_ece@yahoo.com

The treatment method of mucoceles is surgery [1,3,9,10]. Endoscopic sinus surgery is the gold standard in paranasal sinus mucocele treatment [9]. Nowadays, only endoscopic sinus surgery is preferred for maxillary, ethmoid and sphenoid sinus mucoceles. However, although endoscopic sinus surgery is the first choice in frontal sinus mucocele, open technique surgery can still be used today when there is frontal sinus anterior wall defect, intracranial or intraorbital extension.

In this study, cases diagnosed with paranasal sinus mucocele who were operated by a single surgeon between 2002 and 2019 were evaluated in terms of symptoms, surgical technique, complications, and recurrence and discussed in the light of the literature.

Materials and Methods

In this study, we retrospectively analyzed 75 patients, 76 mucoceles who underwent operations due to paranasal sinus mucoceles between January 2002 and December 2019. Approval for the study was granted by the Local Ethics Committee of Antalya Training and Research Hospital (30/05/2019-14/12). Age, sex, sinonasal symptoms, facial deformity and visual changes were noted. All the patients were assessed with endoscopic inspection followed by a paranasal sinus computed tomography (PNS CT) scan. In cases of cranial or orbital extension, magnetic resonance imaging (MRI) was performed for additional evaluation. In the patients diagnosed with a mucocele, it was removed surgically. All the patients underwent surgery by the same team. The patients with a postoperative pathological diagnosis of a mucocele were included in the study.

Results

Of the 75 patients, 35 were female and 40 were male. All these patients were between the ages of 21 and 85, with an average age of 56.9. Mucocele formation occurred in the frontal sinus in 46 (61%) patients, the maxillary sinus in 16 (21%) patients the ethmoid sinus in 11 (14%) patients, and the sphenoid sinus in 3 (4%). 1 patient had both frontal and maxillary sinus mucocele (Figure 1).

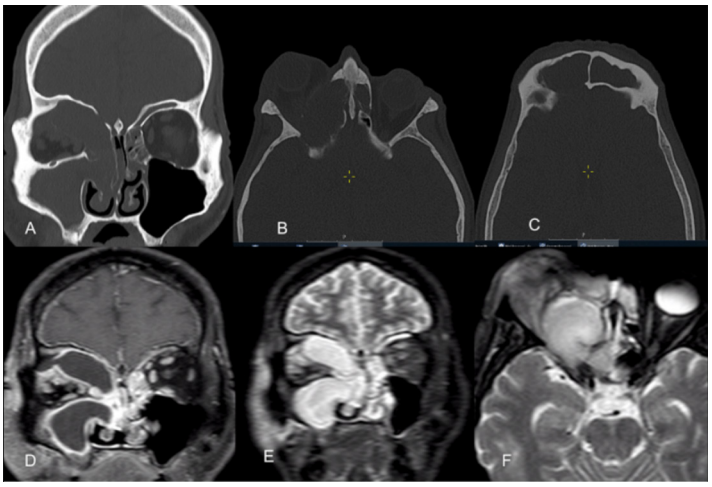


Figure 1. Ethmoid and frontal sinus mucocele (Preoperative PNS CT A.Coronal Plane B.Axial Plane C.Involvement of the right orbit. Preoperative MRI D. Coronal Plane T2 Hyperintens İmage E. Coronal Plane T1 Hypointens Image. F Axial Image)

Of the 75 patients, 76 paranasal sinus mucoceles, 19 (25%) had a history of FESC or nasal surgery and 18 (24%) had a history of chronic sinusitis, 11 (15%) had a history of allergy, 5 (7%) had a history of trauma, 4 (%5) patients had both frontal mucoceles and nasal polyposis. In 19 (25%) patients, no etiological factor was determined.

The most common symptom was nasal obstruction, which was exhibited by all patients with maxillary sinus mucoceles. Proptosis was the second most common symptom; total vision loss was present only in 1 patient with a frontal mucocele. In the preoperative assessment, a mucocele that invaded the superior orbital wall in the right frontal region and a 2/10 vision loss in the right eye was found. Vision in the left eye was 10/10. The patient was treated with the endoscopic approach, and in the postoperative assessment, the vision in the right eye was 10/10. Swelling was most frequently observed in the frontal sinus mucocele patients, and visual symptoms were exhibited by the sphenoid and ethmoid sinus mucocele patients. Headache was present in 38% of the patients. CSF fistula, meningitis and brain abscess are rare but serious complications due to frontal pyocele. The distribution of the sinus symptoms is provided in (Table 1).

Table 1. Distribution of the sinus symptoms

		Frontal (46 /61%)	Ethmoid (11/14%)	Maxillary (16/21%)	Sphenoid (3/4%)	Total
Nasal Symptoms	Nasal Obstrictions	11(24%)	7(63%)	16(100%)	0	34(45%)
	Nasal Congestion	4(8.6%)	2(18.1%)	4(25%)	0	10 (21%)
Orbital Symptoms	Proptosis	25(54,3%)	4(36%)	0	0	29(38%)
	Visual Symptoms	5(10%)	4(36%)	0	1(50%)	10 (21%)
	Orbital Wall Defects	16(34%)	2(18%)	0	0	18 (23%)
Cranial Symptoms	Headache	14(30%)	3(27%)	2(12%)	1(33%)	20 (26%)
	CSF Fistula	2 (4%)	0	0	0	2 (2.6%)
	Menengitis	2(4%)	0	0	0	2 (2.6%)
	Apscess	1 (2%)				1 (1%)
Cosmetic Symptoms	Facial Asymmetry	6(13%)	0	1(6%)	0	7 (%9)
	Bone Defect	4(8%)	0	0	0	4 (5%)

Maxillary, ethmoid, sphenoid sinus mucoceles were all treated with the endoscopic approach (Figure 2). Of the 46 patients with frontal sinus mucoceles, 31 underwent surgery underwent ESC (Figure 3). 15 underwent surgery using external approach (Figure 4). We performed osteoplastic frontal sinus surgery in 14 of these patients, and trephination was performed in the 1 remaining patient. The characteristics of the patients who underwent external approach and had frontal sinus mucocele are shown in (Table 2).

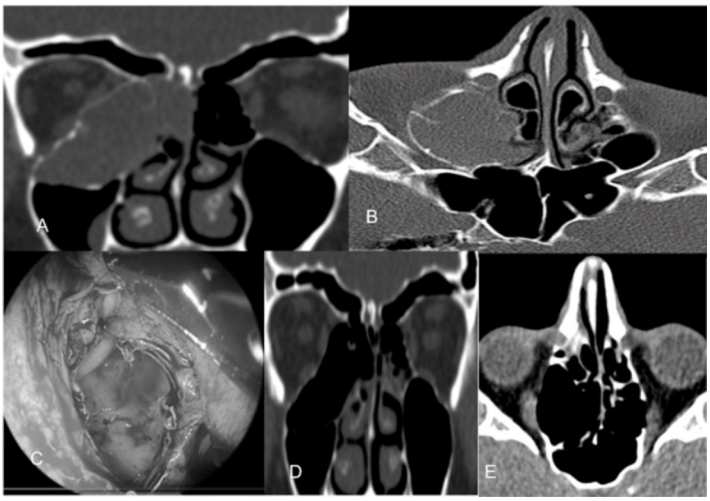


Figure 2. Ethmoid sinus mucocele is involvement of the right orbit (Preoperative PNS CT A.Coronal Plane B.Axial Plane, C. Intraoperetive Imaging Postoperative PNS CT D.Coronal Plane E.Axial Plane

All patients were followed-up with endoscopic examinations for 13 months to 4 years. 4 of 76 mucoceles (5,3%) experienced recurrence. The recurrent patients were those who had previously been operated for chronic sinusitis (3 patients with polyps, 1 patient with chronic sinusitis without polyps).

Table 2. Causes of External Surgery Preference in Patients Diagnosed with Frontal Sinus Mucocele

Anterior Wall Defect	5
Frontal Lobe Abscess	1
Dura Defect	2
Intracranial Expansion	2
Orbital Oomplications	5
Not Being Able to Get General Anesthesia	1

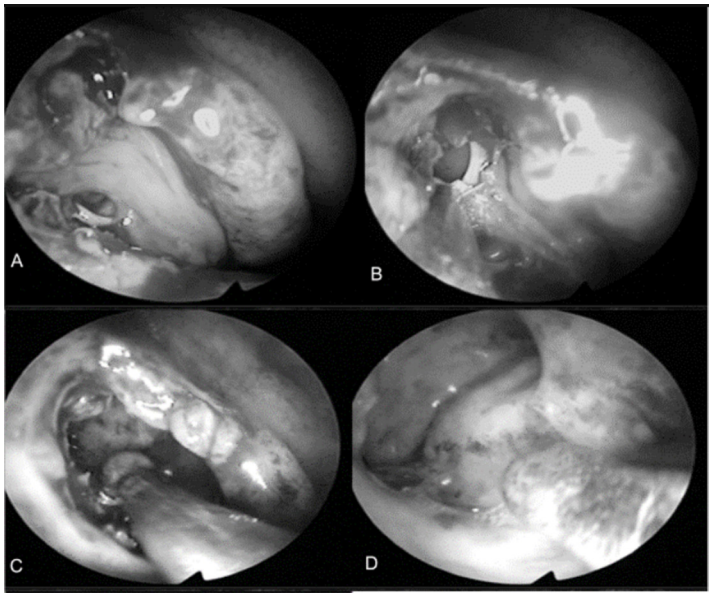


Figure 3. Frontal sinus mucocele intraoperative image. A. Drainage of the mucocele. B.After marsupialization of frontal mucocele, C-D:Frontal sinus

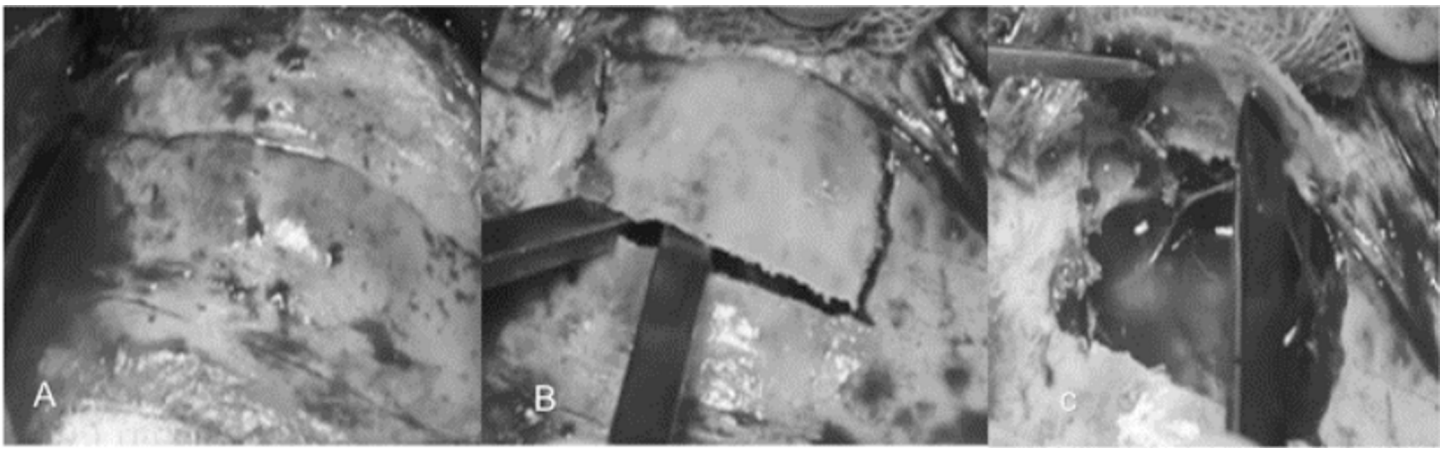


Figure 4. External Approach. A.Expansion of the frontal sinus mucocele on the anterior wall. B.Osteoplactic flap elevation. C.Frontal sinus mucucele

Discussion

Mucoceles are cystic, benign expansile masses [3,8]. Mucoceles may give different symptoms depending on the area they affect. Depending on the size of the lesion, bone resorption and remodeling may be seen [2,4]. Visual disturbances due to orbital displacement or optic nerve compression may also lead to facial deformities due to bone expansion or defect. When mucoceles become infected and form pyomucocele formation, orbital cellulitis, orbital abscess, and intracranial spread may cause complications such as meningitis and brain abscess that require urgent intervention [9,10].

In our study, the 3 most common symptoms in paranasal sinus mucoceles were nasal obstriction (45%), proptosis (38%), and

Headage (20%). Plainter et al (78) reported that the most common symptom was pain before surgery. Fhu et al [1], on the other hand, reported the most common symptom in patients with primary and secondary mucocele as nasal obstruction. Proptosis is the 2 most common symptoms and was more common in frontal sinus mucoceles (54%) and ethmoid sinus mucoceles (36%), which are closely related to the orbit.

The treatment of paranasal sinus mucoceles is surgical and simple drainage and marsupialization of mucoceles is usually sufficient [8,9]. The endoscopic approach in the treatment of sphenoid, maxillary and ethmoid mucoceles is the surgical method of choice without question. Especially in ethmoid and sphenoid sinus mucoceles, endoscopy provides the same field of vision as in the external approach, and the morbidity rate is much lower [11].

In frontal sinus surgery, as a result of the magnificent development of endoscopic sinus surgery, the area of use of the external approach is gradually narrowing. However, it still has a place in some pathologies of the frontal sinus. In the literature, there are many authors who support the use of external approach in frontal sinus anterior wall effects, pathologies with excessive lateral localization, presence of pathology in type 3 frontal cells, and lesions with intracranial extension leading to the dura effect [2,11,12]. However, there are also publications treated with endoscopic approaches in many similar pathologies [3,6,10]. In our series, 16 of 46 patients with frontal sinus mucocele were treated using an external approach. Since 1 patient could not receive general anesthesia, trephination with LAA was performed, and 2 patients underwent craniotomy for frontal lobe abscess. Endoscopic surgery was unlikely to be performed in these cases. An external approach was applied to 5 patients with anterior wall defect in order to perform reconstruction. In these cases, the external approach is required for reconstruction (bone cement, titanium rapier). External approach was applied to 2 patients due to dura defect. There are patients treated with both methods in the literature. In these cases, the surgeon's facilities and experience are the most important factors in decision-making. A meta-analysis evaluating the development and use of endoscopic sinus surgery and techniques applied according to the surgeon's experience was conducted by Courson et al [13]. The studies examined in this meta-analysis are divided into 2 groups. The surgeries performed between 2002-2012 were collected in the first group, and the studies performed between 1975-2001 in the second group. It is seen that the rate of endoscopic surgery has increased in the second group. Again, in the same meta-analysis, in the comparison between the senior surgeons and others, it is seen that the senior surgeons solved the problems endoscopically at a much higher rate. In our study, 15 of 46 frontal sinus mucoceles and 31 external ones were treated by endoscopic approach. When we evaluate the development of our own surgical experience, we think that 5 cases that cause orbital complications can be performed endoscopically.

If the external approach is applied in the frontal sinus surgery, another discussion point is the obliteration of the frontal sinus. Some authors claim that the obliteration of the sinus after the complete removal of the frontal mucocele decreases the rate of recurrence [5,9]. Others defend the position that the sinus must be left open because obliteration damages the physiology of the frontal sinus [1,3]. Although we support the view that unless there is an underlying pathology, marsupialization of the mucocele is sufficient to protect the drainage and physiology of the frontal sinus, we also claim that for the patients who have dura defects, there is a need for obliteration to support the fascia that we use to repair the defect.

Another topic of discussion in the treatment of frontal mucoceles is whether to place a stent in the frontal ostium. Har-El G et al [10] placed stents in the cavity when they endoscopically performed small unilateral marsupialization and removed the stents after 8-12 weeks; they observed no recurrence in the follow-ups. On the other hand, we did not place stents in any of our patients. In the only patient who had recurrence, the real reason for the recurrence was that a nasal polyp obliterated the frontal recess; however, the recurrence occurred on postoperative month 41. As a result, we maintain that even a 12-week stent would not have been able to prevent recurrence in this patient. Even though the treatment for sinus mucoceles is surgery, it must be kept in mind that past surgical operations are also important in the etiology of mucoceles. The formation of a scar that blocks the sinus ostium after the surgery speeds up the formation of mucoceles [1,3]. Recurrence in the surgery operations due to nasal polyps or chronic rhinosinusitis may be caused because the ostium was not enlarged enough, and blockage of the ostium due to the recurrence of the primary pathology or excessive deformation of the nasal physiology during the surgery. The recurrence after the mucocele surgery occurs due to the same reasons. Especially in the frontal mucoceles, more frequent obliteration due to the anatomy of the frontal recess increases the recurrence rate [14]. However, in the surveys on mucocele surgery in the literature, it was observed that recurrence rates were very low (0-13%). In our study, the recurrence rate was 5%. However, we maintain that these recurrence rates do not reflect the reality because the follow-up periods did not exceed 10 years in any of these studies. However, mucoceles are cysts that grow very slowly. Meetze et al [15] retrospectively surveyed the frontal sinus complications in patients who underwent frontal craniotomy and found that frontoethmoidal mucoceles developed 14.8 years (1-39 years) after the operation on average. If recurrence can develop 39 years after a previous operation, we believe it is also possible for it to develop many years after mucocele surgery due to the trauma caused by the operation. We maintain that with longer-running studies, the recurrence rates may increase even more.

Conclusion

Paranasal sinus mucoceles can lead to serious complications such as orbital cellulitis, brain abscess and meningitis, especially when they are infected, that is, when they form a pyomucocele formation.

Endoscopic sinus surgery has emerged as the preferred surgical method for ethmoid, maxillary and sphenoid mucoceles. It is also the best treatment approach for frontal sinus mucoceles. In frontal sinus mucoceles, the limits of endoscopic sinus surgery are determined by the experience of the surgeon and the characteristics of the mucocele. Mucoceles that cause anterior wall defect and cause intracranial complications are the most important candidates for open surgery.

Conflict of interests

The authors declare that they have no competing interests.

Financial Disclosure
All authors declare no financial support.

Ethical approval
Local Ethics Committee of Antalya Training and Research Hospital (30/05/2019-14/12).

References

1. Fu CH, Chang KP, Lee TJ. The difference in anatomical and invasive characteristics between primary and secondary paranasal sinus mucoceles. Otolaryngol Head Neck Surg. 2007;136:621-5.
2. Bockhmul U. Osteoplastic frontal sinusotomy and reconstruction of frontal defects. In: Kountakis S, Senior B, Draf W (eds) The frontal sinus. Springer, Berlin, 2005;281-9.
3. Har-El G. Endoscopic management of 108 sinus mucoceles. Laryngoscope 2001;111:2131-4.
4. Stienberg CM, Bailey BJ, Calhoun KH, et al. Management of invasive frontoetmoidal sinus mucoceles. Am J Otolaryngol. 2007;28:145-7.
5. Soon SR, Lim CM, Singh H et al. Sphenoid sinus mucocele: 10 cases and literature review. J Laryngol Otol. 2010;124:44-7.
6. Herndon M, McMains KC, Kountakis SE. Presentation and management of extensive fronto-orbital-ethmoid mucoceles. Am J Otolaryngol. 2007;28:145-7.
7. 7. Zukin LM, Hink EM, Liao S, et al. Endoscopic Management of Paranasal Sinus Mucoceles: Meta-analysis of Visual Outcomes. Otolaryngol Head Neck Surg. 2017;157:760-6.
8. 8. Plantier DB, Neto DB, Pinna FR, et al. Mucocele: Clinical Characteristics and Outcomes in 46 Operated Patients. Int Arch Otorhinolaryngol. 2019;23:88-91.
9. 9. Khong JJ, Malhotra R, Wormald PJ et al. Endoscopic sinus surgery for paranasal sinus mucocoele with orbital involvement. Eye 2004,18:877-81.
10. 10.Har-El G. Transnasal endoscopic management of frontal mucoceles. Otolaryngol Clin North Am. 2001;34:243-51.
11. 11.Haug GA, Dortzbach RK, Brandenburg J. Tretament of frontal sinus mucoceles with the osteoplastic flap technique. Ophtalmic Surg. 1978 ;9:40-66.
12. 12. Park CM, Stoffella E, Gile J, et al. Osteoplasty Flap Technique for Repair of Latent (30-Year) Post-Traumatic Frontal Sinus Mucocele: Case Report and Review of the Literature J Oral Maxillofac Surg. 2012;70:2092-6.
13. 13.Courson AM, Stankiewicz JA, Lal D Contemporary Management of Frontal Sinus Mucoceles: A Meta-Analysis. Laryngoscope. 2014;124:378-86.
14. 14.Serrano E, Klossek JM, Percodani J, et al. Surgical management of paranasal sinus mucoceles: a long term study of 60 cases. Otolaryngol Head Neck Surg. 2004;131:133–40.
15. 15.Meetze K, Palmer JN, Schlosser RJ. Frontal sinus complications after frontal craniotomy. Laryngoscope. 2004;114:945-8.

Available online at www.medicinescience.org

ORIGINAL ARTICLE

Medicine Science International Medical Journal

Medicine Science 2021;10(1):106-10

Effects of sugammadex on platelet levels and platelet-to-lymphocyte ratio in morbidly obese patients undergoing sleeve gastrectomy

Ozkan Gorgulu[1], Mehmet Nuri Kosar[2]

[1]*Antalya Training and Research Hospital, Department of Anesthesiology and Reanimation, Antalya, Turkey*
[2]*Antalya Training and Research Hospital, Department of General Surgery, Antalya, Turkey*

Received 10 August 2020; Accepted 06 October 2020
Available online 17.01.2020 with doi: 10.5455/medscience.2020.08.160

Abstract

Sugammadex is known to have minimal effects on coagulopathy. The aim of this study was to analyse the changes in platelet levels and platelet-to-lymphocyte ratio (PLR) in preoperative and postoperative periods in morbidly obese patients. This retrospective study included a total of 86 morbidly obese patients with a Body Mass Index (BMI) of >40 kg/m^2 and with an American Society of Anaesthesiologists Classification score (ASA) III undergoing elective laparoscopic sleeve gastrectomy (LSG). Patient data were obtained from patient files and electronic health records system (SARUS). The patients were allocated into two groups namely sugammadex (Group S) and neostigmine (Group N). Preoperative and postoperative (12th hour) hemogram recordings of the patients were examined. Compared to preoperative levels, there was a significant decrease in the postoperative platelet and lymphocyte values of patients in Group S ($p<0.001$) whereas postoperative PLR values were significantly increased ($p<0.001$). The comparison of the preoperative and postoperative values of patients in Group S according to gender showed no significant difference ($p>0.05$). Although sugammadex causes a decrease in the platelet and lymphocyte levels in the postoperative period similar to neostigmine, a relatively higher decrease in lymphocyte levels caused an increase in PLR values. None of the morbidly obese patients, who were administrated sugammadexn (2 mg kg^{-1}) via intravenous administration, underwent reoperation in the postoperative period due to coagulopathy.

Keywords: Sugammadex; platelet count; lymphocyte count; platelet-to-lymphocyte ratio; blood coagulation disorders

Introduction

Sugammadex is a new selective medication with a structure of modified gamma cyclodextrin that is used to reverse neuromuscular blockade caused by aminosteroid muscle relaxants [1]. Gamma cyclodextrin in its structure is a cyclic oligosaccharide formed by bacterial digestion of starch and used as solubilizers and stabilizers in various pharmaceutical and food products [2]. Oligosaccharides have various effects on blood components [3]. Oligosaccharides are known to inhibit platelet aggregation as well as exhibiting a mild anticoagulation effect by blocking the intrinsic coagulation pathway [3]. Furthermore, oligosaccharides have no effect on such complement activation and platelet activation as C3a and C5a [3]. There are also studies reporting that sugammadex prolongs prothrombin time (PT) and activated partial thromboplastin time (APTT) [4,5]. Sugammadex has been shown not to cause any major and minor bleeding in the postoperative period in morbidly obese patients [5].

***Coresponding Author:** Ozkan Gorgulu, Antalya Training and Research Hospital, Department of Anesthesiology and Reanimation, Antalya, Turkey.
E-mail: drozkangorgulu@hotmail.com

Although platelet-to-lymphocyte ratio (PLR) has been used in studies to estimate the prognosis of some cancer diseases such as nasopharyngeal carcinoma [6], urothelial carcinoma [7], small cell lung cancer [8], laryngeal squamous cell carcinoma [9], and hepatocellular carcinoma [10] in the literature, the number of studies investigating its effect on coagulopathy is limited. In light of all this information, we aimed to compare the preoperative and postoperative platelet levels and PLR according to gender to examine the effect of sugammadex on coagulopathy in morbidly obese patients who underwent sleeve gastrectomy.

Materials and Methods

Study Population

This retrospective study study was performed in compliance with the Declaration of Helsinki in the period from the year 2017 to 2018 and the Antalya Training and Research Hospital Ethics Committee Approval was obtained from our tertiary hospital before starting the study (Date of Approval-Protocol No: 2018-9/2). Patient data were obtained from patient files and electronic health records system (SARUS). Data of a total of 95 patients were analyzed. The study included a total of 86 morbidly obese patients with a Body

Mass Index (BMI) of >40 kg/m^2 and with an American Society of Anesthesiologists Classification score (ASA) III undergoing elective laparoscopic sleeve gastrectomy (LSG) (mean ± SD: 35.12±12.7 years, 75.6% were females). Patients with systemic disease other than morbid obesity were excluded from the study. The patients were allocated into two groups namely sugammadex (Group S) and neostigmine (Group N).

In our retrospective study, it was determined that 0.05 mg kg^{-1} neostigmine and 0.02 mg kg^{-1} atropine were administered intravenously to the patients in Group N, and 2 mg kg^{-1} sugammadex was administered to the patients in Group S to reverse neuromuscular blockade. In 5 patients, the drug used to reversal of the neuromuscular block was excluded because the drug was unknown. Since 4 mg kg^{-1} sugammadex was used in 4 patients, it was not included in the study.

Anesthesia Technique

After electrocardiography (ECG) and peripheral oxygen saturation (SpO_2) monitoring, general anesthesia was induced through the intravenous administration of 2% lidocaine (1mg/kg) to reduce the propofol-induced pain. After induction with propofol (3mg/kg) and fentanyl (1µg/kg), rocuronium (0.6mg/kg) was administered for muscle relaxation. A 50% air-oxygen, remifentanil infusion (0.5 µg/kg/min) and desflurane inhalation (1 MAC) were applied to maintain anesthesia. After inserting the orogastric catheter, end-tidal carbon dioxide ($EtCO_2$) was monitored using capnography. The patients were given the reverse-Trendelenburg position when the bispectral index (BIS) was 40–60 and 15 mmHg intra-abdominal insufflation pressure was applied. All patients received an intravenous infusion of Ringer's lactate (1000–1500 mL) throughout the surgery. This protocol was applied to all patients by the same surgical and anesthesia team.

Surgical Technique

In the sleeve gastrectomy technique that was used in the first group operated in 2017-2018, the patient was placed in the French (European) position, the surgeon stood between the legs in abduction, the first assistant stood on the left of the patient and the cameraman on the right of the patient, and entering the abdomen by a Veress needle at the distance of approximately 8-14 cm from the sternum xiphoid notch (depending on the distance between the umbilicus and xiphoid) and 1 cm left lateral of the linea alba, 14 mmHg intraperitoneal insufflation was achieved. An 36-Fr silicone bougie was inserted into the stomach under vision, passed through the pylorus and ensured to fit properly in the lesser curvature. The first 4.1mm (green) 60-mm linear stapler was placed at a distance of 2 cm to the pylorus by giving a 15-25 degree external angle through the 12-mm trocar on the right side of the patient not to create a stricture in the incisura and fit the base of the stapler in 2 cm to the pylorus. The second stapler was placed again through the right trocar as 4.1 mm (green) with an internal angle of 45 degrees. The third stapler 3.8mm (gold), 4th and if necessary 5th-6th cartridges as 3.5 mm (blue) were placed through the 12-mm trocar without angulation. Fundus resection was performed by preserving 1 cm HIS angle in the gastroesophageal junction. After the resection, the 36-Fr bougie was pulled out under vision and the presence of any twisting was checked. The mean operative time of the patients was 55 minutes.

Assessments

Age, sex, preoperative and postoperative (12 hours) platelet (low: 0-150 10^3 / mm³, high:> 450 10^3 / mm³) and lymphocyte levels (low: 0-1.16 10^3 / mm³, high:> 3.18 10^3 / mm³) and PLR values were calculated, and intragroup and intergroup comparisons were recorded. Power analysis could not be performed since there is no study in the literature investigating the side effects of sugammadex on platelets.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 23.0 (IBM Corporation, Armonk, NY, USA). Pearson chi-square test was used for categorical variables. The conformity of the data to normal distribution was evaluated with the Shapiro-Wilk test. The Mann–Whitney U test and Student's t test were used for the analysis of non-normally and normally distributed numerical data, respectively. Postoperative and preoperative parameters were compared using the Wilcoxon signed-rank test. Data were expressed as number (n), percentages (%), mean±standard deviation (SD) or median (min-max). A p value of <0.05 was considered statistically significant.

Results

There was no statistically significant difference between the gender distribution, age and mean BMI and ringer's lactate values of the groups (p>0.05) (Table 1).

Compared to preoperative levels(platelets count:300 10^3/mm³) lymphocytes count: 2.6 10^3/mm³), there was a significant decrease in the postoperative platelet and lymphocyte values(platelet count: 276.5 10^2, lymphocytes count: 1.7 10^3/mm³) of patients in Group S (p<0.001) whereas postoperative PLR(115108.7- 139722.2, respectively) values were significantly increased (p<0.001). Similarly, compared to preoperative levels(platelet count: 293.5 10^2, lymphocytes count: 2.3 10^3/mm³), there was a significant decrease in the postoperative platelet and lymphocyte values (260.5 10^2, 1.8 10^3/mm³, respectively) of patients in Group N (p<0.05) whereas postoperative PLR(123009.05-160573.5 respectively) values were significantly increased (p=0.018) (Table 2).

The decrease in the lymphocyte levels(-1 10^3/mm³ (-3.1-0.8)) in Group S was found to be higher than Group N(-0.5 10^3/mm³ (-2.3-1.4)) (p=0.041, p<0.05) (Table 3).

A significant decrease was observed in postoperative platelet and lymphocyte levels(291 10^3/mm³, 1.7 10^3/mm³ respectively) of female patients compared to preoperative levels(306 10^3/mm³, 2.6 10^3/mm³ respectively) (p<0.05) whereas PLR(121560.46, 175087.72 respectively) was found to significantly increase after the surgery (p=0.001, p<0.05). Similarly, a significant decrease was observed in postoperative platelet and lymphocyte levels(247 10^3/mm³, 2 10^3/mm³ respectively) of male patients compared to preoperative levels(274 10^3/mm³, 3.4 10^3/mm³ respectively) (p<0.05) whereas PLR was found to significantly increase after the surgery (p=0.028) (Table 4).

The comparison of the preoperative and postoperative values of patients in Group S according to gender showed no significant difference (p>0.05). (Table 5).

Table 1. Comparison of the demographic data of the patients

	Total (n=86)	Group S (n=42)	Group N (n=44)	p
Age	35.2±12.7(17–70)	33.2±10.8(19–60)	37.1±14.2(17–70)	0.152
Gender (Male/Female)	21(24.4)/65(75.6)	12(28.6)/30(71.4)	9(20.5)/35(79.5)	0.381
BMI	45.3±5.7(35–62.5)	45.7±5.9(37–62.5)	44.9±5.5(35–60.6)	0.491
Ringer's lactate (ml)	1250±75(1.175-1.325)	1243±78(1.165-1.321)	1252±45(1.207-1.297)	0.258

Data are presented as n (%), mean±SD (min-max). SD: standard deviation, BMI: Body Mass Index Student's t-test, Pearson's chi-square test

Table 2. Intergroup comparison of preoperative and postoperative values

	Group S (n=42)	Group N (n=44)	p
Preop Platelet	30010^3/mm³(152000–550000)	293500(186000–564000)	0.269
Postop Platelet	276.510^2/mm³(68000–418000)	260.510^2/mm³(162000–455000)	0.574
p	<0.001	<0.001	
Preop Lymphocyte	$2.6\ 10^3$/mm³ (1.7–5)	2.310^3/mm³ (1.5–4.4)	0.069
Postop Lymphocyte	1.710^3/mm³ (0.9–3.2)	1.810^3/mm³ (0.6–4)	0.527
p	<0.001	0.001	
Preop PLR	115108.7(44705.88–220000)	123009.05(64137.93–245217.39)	0.586
Postop PLR	139722.2(52631.6–360000)	160573.5(59428.6–338333.3)	0.931
p	<0.001	0.018	

Preop:Preoperative Postop:Postoperative Data are presented as median (min- max). PLR: platelet-to-lymphocyte ratio Wilcoxon signed-rank test, Mann-Whitney U test. PLR: Platelet-to-lymphocyte ratio.

Table 3. Intragroup comparison of the differences in the parameters

	Group S (n=42)	Group N (n=44)	p
Platelet difference	-3910^3/mm³(-254000–147000)	-310^3/mm³(-121000–60000)	0.163
Lymphocyte difference	-110^3/mm³(-3.1–0.8)	-0.510^3/mm³(-2.3–1.4)	0.041
PLR difference	43923.38(-105037.04–205384.62)	23090.08(-97238.1–219833.33)	0.308

Data are presented as median (min- max). PLR: platelet-to-lymphocyte ratio Mann-Whitney U test.

Table 4. Comparison of preoperative and postoperative values between genders in Group S

	Female (n=30)	Male (n=12)	p
Preop Platelet	30610^3/mm³(208000–550000)	27410^3/mm³(152000–356000)	0.010
Postop Platelet	29110^3/mm³(102000–418000)	24710^3/mm³(68000–301000)	0.028
p	0.001	0.023	
Preop Lymphocyte	2.610^3/mm³ (1.7–4.9)	3.410^3/mm³ (2.1–5)	0.034
Postop Lymphocyte	1.710^3/mm³ (0.9–3.2)	210^3/mm³ (0.9–2.7)	0.276
p	<0.001	0.002	
Preop PLR	121560.46(51224.49–220000)	84232.46(44705.88–125217.39)	0.004
Postop PLR	175087.72(78461.54–360000)	130113.64(52631.58–229230.77)	0.024
p	0.001	0.028	

Preop:Preoperative Postop:Postoperative Data are presented as median (min- max). PLR: platelet-to-lymphocyte ratio Wilcoxon signed-rank test, Mann-Whitney U test.

Table 5. Comparison of the differences in the parameters between genders in Group S

	Female (n=30)	Male (n=12)	p
Platelet difference	-3910^3/mm³(-254000–147000)	-4310^3/mm³(-152000–20000)	0.717
Lymphocyte difference	-0.95 (-2.8–0.8)	-1.1(-3.1–-0.2)	0.139
PLR difference	44432.9(-105037.04–205384.62)	38439.12(-67368.42–104013.38)	0.597

Data are presented as median (min- max). PLR: platelet-to-lymphocyte ratio Mann-Whitney U test.

Discussion

In the literature, the studies investigating the effect of sugammadex and neostigmine on platelet levels and PLR, which are among coagulation parameters, is very rare. In this retrospective cohort study, although postoperative platelet and lymphocyte levels were lower than the preoperative levels, an increase has been observed in the PLR values in both patient groups undergoing sleeve gastrectomy for morbid obesity, who were given sugammadex and neostigmine to reverse neuromuscular blockade. In a study investigating the effect of sugammadex and pyridostigmine on coagulation parameters, no difference was reported between the two drugs in terms of the decrease in postoperative platelet levels, similar to our study [11]. The significant increase in postoperative PLR values may be due to the fact that the decrease in lymphocyte levels is higher than the decrease in platelet levels. In comparative studies using different doses of sugammadex (2 mg kg^{-1} and 4mg kg^{-1}), no significant coagulopathy was reported and none of the patients were re-operated due to postoperative bleeding [11,12]. Similarly, none of our patients receiving sugammadex via intravenous administration were re-operated due to coagulopathy in the postoperative period. In patients who undergo anesthesia, lymphopenia and immunosuppression due to surgical stress may be observed [13]. In the present study, the decrease in the lymphocyte levels in Group S was found to be higher than Group N. Surgery has no effect on acute coagulopathy in rats [14]. In rats, the decrease in the release of neutrophils and platelets into the circulation after laparotomy has been reported to cause a 45% decrease in lymphocytes [14]. There are studies in the literature showing that clinical doses of desflurane have no effect on platelets[15]. In studies conducted in the literature, it was found that the antithrombotic effects of desflurane did not persist 1 hour after surgery [16]. In the present study, the relative decrease in the lymphocyte levels due to decreased platelet and lymphocyte levels has been found to cause increases in PLR values. In our study, the comparison of both groups in terms of gender has shown similar results. There was a significant decrease in the postoperative platelet and lymphocyte levels compared to preoperative levels whereas there was a significant increase in the postoperative PLR values. In a randomized prospective study comparing PT and aPTT values of neostigmine and Sugammadex, no statistically significant difference was observed between the results [17]. In a publication examining the interaction of sugammadex with various anticoagulants, it was concluded that sugammadex has a temporary effect on coagulation and is unlikely to increase the risk of bleeding [18]. In our study, anticoagulant medication was not administered to the patients in the first 12 hours postoperatively. In an observational study, the use of 2 and 4 mg kg^{-1} sugammadex was not associated with longer clotting time or decreased hemoglobin concentrations [11,12,19]. However, results in patients administered 16 mg kg^{-1} sugammadex are uncertain. [19]. In the light of these findings, the effects of sugammadex on thrombocyte and lymphocyte levels in morbidly obese patients who underwent sleeve gastrectomy are similar to those in the neostigmine group. The limitation of our study is that it is retrospective and the patient population is not large number. Although sugammadex has limited effects on platelet volume and coagulopathy, there is a need for studies that compare the thromboelastogram analysis and changes in the platelet levels in a larger population. The administration of sugammadex in doses higher than 2 mg kg^{-1} may increase the risk of lymphopenia in addition to the current surgical stress, and may predispose to infection in the postoperative period.

Conclusion

Although sugammadex causes a decrease in the platelet and lymphocyte levels in the postoperative period similar to neostigmine, a relatively higher decrease in lymphocyte levels caused an increase in PLR values. None of the morbidly obese patients, who were administrated sugammadex(2 mg kg^{-1}) via intravenous administration, underwent reoperation in the postoperative period due to coagulopathy. Prospective randomized controlled studies are needed to evaluate the effect of sugammadex on platelet values and coagulopathy.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
All authors declare no financial support.

Ethical approval
This study was conducted in accordance with the ethical principles stated in the "Declaration of Helsinki" and permission was obtained from Ethics Committee of Antalya Training and Research Hospital for the use of patient data for publication purposes (Date of Approval-Protocol No: 2018-9/2).

References

1. Hawkins J, Khanna S, Argalious M. Sugammadex for Reversal of neuromuscular blockade: uses and limitations. Curr Pharm Des. 2019;25:2140-8.
2. Saokham P, Loftsson T. γ-Cyclodextrin. Int J Pharm. 2017;516:278-92.
3. Guo X, Sun T, Zhong R et al. Effects of chitosan oligosaccharides on human blood components. Front Pharmacol. 2018;9:1412.
4. Lee IO, Kim YS, Chang HW et al. In vitro investigation of the effects of exogenous sugammadex on coagulation in orthopedic surgical patients. BMC Anesthesiol. 2018;18:56
5. Carron M, Bertini D, Prandini T et al. Effect of sugammadex on coagulation as detected by rotational thromboelastometry in morbidly obese patients. Minerva Anestesiol. 2018;84:178-88.
6. Zhang J, Feng W, Ye Z et al. Prognostic significance of platelet-to-lymphocyte ratio in patients with nasopharyngeal carcinoma: a meta-analysis. Future Oncol. 2019
7. Bao Y, Wang Y, Li X et al. Prognostic significance of platelet-to-lymphocyte ratio in urothelial carcinoma patients: a meta-analysis. Cancer Cell Int. 2019;19:315.
8. Shen XB, Wang Y, Shan BJ et al. Prognostic significance of platelet-to-lymphocyte ratio (plr) and mean platelet volume (mpv) during etoposide-based first-line treatment in small cell lung cancer patients. Cancer Manag Res. 2019;11:8965-75.
9. Zhong B, Gu DY, Du JT et al. Correction: May the change of platelet to lymphocyte ratio be a prognostic factor for T3-T4 laryngeal squamous cell carcinoma: A retrospective study. PLoS One. 2019;14:0226383.
10. Lin WF, Zhong MF, Zhang YR et al. Prognostic role of platelet-to-lymphocyte ratio in hepatocellular carcinoma with different BCLC stages: a systematic review and meta-analysis. Gastroenterol Res Pract. 2018;2018:5670949.
11. Moon YJ, Kim SH, Kim JW et al. Comparison of postoperative coagulation profiles and outcome for sugammadex versus pyridostigmine in 992 living donors after living-donor hepatectomy. Medicine (Baltimore). 2018;97:0129.
12. Raft J, Betala Belinga JF, Jurkolow G et al. Clinical evaluation of post-surgical bleeding after a sugammadex injection. Ann Fr Anesth Reanim. 2011;30:714-7.
13. Kitamura T, Ohno N, Bougaki M et al. [Comparison of the effects of

sevoflurane and propofol on changes in leukocyte-count induced by surgical stress]. Masui. 2008;57:968-72.

14. Davenport L, Letson HL, Dobson GP. Immune-inflammatory activation after a single laparotomy in a rat model: effect of adenosine, lidocaine and Mg_2+ infusion to dampen the stress response. Innate Immun. 2017;23:482 94.

15. Türkan H, Beyan C, Karabiyik L et al. The effects of desflurane on human platelet aggregation in vitro. Int J Hematol. 2004;80:91-3.

16. Bozdogan N, Madenoglu H, Dogru K et al. Effects of isoflurane, sevoflurane, and desflurane on platelet function: A prospective, randomized, single-blind, in vivo study. Curr Ther Res Clin Exp. 2005;66:375-84.

17. Taş N, Korkmaz H, Yağan Ö et al. Effect of sugammadex on postoperative bleeding and coagulation parameters after septoplasty: a randomized prospective study. Med Sci Monit. 2015;21:2382-6.

18. Kruithof CA, Kluft C, Kam PJ et al. Interactions of sugammadex with various anticoagulants. Int J Clin Pharmacol Ther. 2020 Jul;58:395-403.

19. Raft J, Guerci P, Harter V et al. Biological evaluation of the effect of sugammadex on hemostasis and bleeding. Korean J Anesthesiol. 2015;68:17–21.

Available online at www.medicinescience.org

ORIGINAL ARTICLE

Medicine Science International Medical Journal

Medicine Science 2021;10(1):111-7

Can Google® trends predict emergency department admissions in pandemic periods?

Serkan Emre Eroglu, Gokhan Aksel, Ibrahim Altunok, Serdar Ozdemir, Abdullah Algin, Hatice Seyma Akca, Kamil Kokulu

University of Health Sciences, Umraniye Research and Training Hospital, Department of Emergency Medicine, Istanbul, Turkey

Received 12 August 2020; Accepted 03 September 2020
Available online 17.01.2020 with doi: 10.5455/medscience.2020.08.162

Abstract

Currently, individual sharing and emotions can affect health behaviors and admissions to hospitals. Google Trends created from Google search can use for screening mood changes associated with people's daily lives. We aimed to investigate the association between emergency department (ED) admissions and Covid-19-associated search engine use. This cross-sectional observational study was carried out in the ED between 2018 to 2020. Since the Covid-19 disease is specific to this year, Google Trends analysis was done between December 31, 2019 and March 31, 2020. However, ED admissions data for the same period were also compared with the data of 2018 and 2019 to observe the change from previous years. The correlation between the IOTs (a kind of search data score defined by google trends) term and the number of admissions to ED were evaluated. A total of 118,765 patients admitted from December 31, 2019 to March 31, 2020. Out of these ED visits, 34.830(29.3%) were admitted by Covid-like symptoms. The average rate of patients with these symptoms in the same periods of the last 3 years was 24%. We discovered that the IOTs for the term 'corona', which has the greatest IOTs among other terms, was positively correlated with the ratio of patients with coronavirus-like symptoms to all patients ($r = 0.249$, $p < 0.001$) and negatively correlated with the ratio of patients with other symptoms to all patients ($r = -0.249$, $p < 0.001$). Contrary to the expectations,the pandemic situation, a decrease in the number of cases should make us question a patients' urgency. Because of the association between search engine using and patient admissions during the coronavirus pandemic, our study is the first study to predict emergency crowding. Due to this characteristic, our research can provide important data for forecasting health system management.

Keywords: Emergency departments, patient admission, search engine, pandemics, Covid-19, Covid-19 symptoms, coronavirus, pneumonia.

Introduction

Currently, people can easily follow global health issues via newspaper articles and advertisements, radio and television messages, and social media outlets (i.e., Twitter and Facebook) [1,2]. With the information disseminated via these channels, information can quickly reach a large population and create curiosity, excitement, anxiety and even fear. With the effect of these feelings and situations, people often need to research various issues to a greater extent and use internet search engines for this aim. This intense information mobility can also affect patients' hospital admission behaviors. In this context, in the last few months, we observe that the most important situation that has affected people is Covid-19, which originated in China in December 2019 and caused a pandemic.

This current coronavirus pandemic situation affects the whole world, is at the top of the global agenda and creates anxiety in every layer of society.

***Coresponding Author:** Hatice Seyma Akca. University of Health Sciences, Umraniye Research and Training Hospital, Department of Emergency Medicine, Istanbul, Turkey, E-mail: haticeseymaakca@gmail.com

People worry and search for information about the pandemic on the internet. Mood changes may affect current admissions to hospitals. Many studies have revealed a significant number of non-urgent admissions to emergency departments (EDs) on routine working days [3,5]. If this situation continues during the pandemic, the healthcare systems struggling with the pandemic will be influenced by this group of patients, who create additional burden on healthcare workers.

The aim of this study was to investigate the association between ED admissions and Covid-19-associated search engine use and thus, the effect of mood changes in people's daily lives on their ED admissions was observed.

Materials and Methods

This study is a cross-sectional observational study that was conducted in the ED of the Training and Research Hospital in University of Health Sciences Umraniye Research and Training Hospital, (Istanbul, Turkey), which has approximately 580,000 visits annually. The study began after the Institutional Review Board approved it with number B.10.1.TKH.4.34.H.GP.0.01/75.

The months of January, February, March of 2018 - 2019 and the same months of 2020 were the time period of datacollection of the study.

Our study was conducted by using two sets of independent data: the number of ED admissions obtained from hospital information management system and Google Trends data obtained from https://trends.google.com/. Because of the Covid-19 disease is specific to this year, Google Trends analysis was only done between December 31, 2019 and March 31, 2020. In addition to this, ED admissions data for the same period were also compared with the data of 2018 and 2019 to observe the change from previous years. So, the sample size was 119.422 patients for 2018, 128.317 patients for 2019, and 118.765 patients for 2020.Then, the number of ED admissionsand Google Trends search term data were analyzed using a time-series analysis. Non-traumatic patients over the age of 18 and trauma patients of all ages were included in the study. Despite their visit to the ED, patient files that belonged to patients that were discharged without examination were not included in the analysis.

Study Center Description

According to the statistics of 2019, the population of Istanbul was 15,519,267. The hospital where our study is conducted is located in University of HealthSciences Umraniye Research and Training Hospital, district; its population was 710,280. When the population of the 5 districts surrounding this district is included, the total population of the regions under the responsibility of our hospital was 2,616,700[6]. Because of the surrounding population density is high, our ED is considered to be one of the most crowded emergency services in Turkey. In addition to this, ED overcrowding is an issue not only in University of Health Sciences Umraniye Research and Training Hospital, Istanbul but also all EDs in Turkey [7]. The Ministry of Health reported that the number of ED admissions in Turkey were more than five times the Istanbul population in the first 10 months of 2017(n = 76,834,439;25.97%) [8].

In the triage system used in our ED, patients are categorized by a triage nurse firstly and then grouped as green, yellow or red. While the green code states the lowest level of urgency, red code states the highest. Then, all of the patients grouped are taken care in specialized ED areas such as green area for green code, red code for red area, yellow code for yellow area. In addition to this, trauma area is structured for noncritical green code trauma patients and injection room is also structured for the prescribed IV/IM administrations.

Data Pre-processing

Patient admission and epidemiological data, which includes the emergency patient's digital records, were obtained from the hospital information management system, whereas Google Trends data were obtained from https://trends.google.com/.

The patients were divided into two groups: the first group (Covid-19-like symptoms) consisted of patients who present with symptoms that could be associated either with Covid-19 or other flu-like infections (symptoms of upper and lower respiratory tract infection), while the second group (other symptoms) consisted of other patients. In our search, we chose Covid-19-related English/Turkish terms that are used frequently by the World Health Organization (WHO), Health Ministry and the public. The terms “coronavirus”, “covid”, “COVID19”, “SARS-Cov-2”, “corona”, “korona” and “Koronavirüs” were searched (Figure 1). First, these words were searched in separated groups because the Google Trends application does not allow word combinations and more than 5 calls at once. Second, comparative analyses were performed according to one term (term “corona”), which had the highest IOTs.

Google Trends

Google Trends is a search trends feature that shows how frequently a given search term is entered into Google’s search engine relative to the site’s total search volume over a given period of time. Google Trends was created from Google search and other sites affiliated with Google [9]. The popularity of a search term is represented as a number defined as an IOTs. The peak popularity of a search term is defined by 100 points. An IOTs of 50 points means that the searched term has half the popularity. A score of 0 means that the data for this term is insufficient [10].

Statistical Analysis

Statistical analysis was performed using SPSS v25.0 for Mac OS X (Chicago, IL, USA). Patient data were obtained from the hospital information management system. The normality of the data distribution was determined by the Shapiro-Wilk test. The categorical values of the patients were expressed as a number and a percentage and continued values were presented as a mean standard deviation (SD) or median values and an inter-quartile range (IQR) of 25%–75% according to the distribution of variables. Because the variables were not normally distributed, Spearman’s correlation was performed to calculate the correlation of Covid-19-related IOTs (“corona”) with the number of emergency admissions.

P value ≤ 0.05 were admitted statistically significant.

Results

A total of 366,504 patients admitted to ED over the 3-month period (from the last day of December to the last day of March) for 2018, 2019 and 2020 were enrolled. The median age was 39 years (IQR, 26 to 54), and 48.9 percent were men. While 118,765 patient encounters occurred from December 31, 2019 to March 31, 2020, out of these ED visits, 34.830 (29.3%) were admitted by Covid-like symptoms. The average number of patients with these symptoms in the same periods of the last 3 years was 88,127 (24%) [Table 1].

Google Trends analysis was shown that the topic word that yielded the greatest IOTs was "corona", which was searched using the "search term" option [figure 1].Thus, we used this term for statistical analysis in our study.

According to our study, while Over the 3-month period for 2020, the median number of patient encounters was 1,368.5 patients per day (IQR: 1272.0 – 1481.75), The median IOTs for the same period of the patient encounters was 9 (IQR: 2 – 24).

Google Trends analysis was shown that the highest IOTs of 100 was obtained on March 11, 2020: on this day, the first Covid-19

case in Turkey was reported. A second peak was observed on March 16, 2020 (IOTs = 86/100), which coincides with the day after the first death was reported in Turkey. Our study clearly demonstrated that ED admissions decreased, especially in contrast to the increase in Covid-19-associated search starting from March 11, 2020. Accordingly, the IOTs for the term "corona", which has the greatest IOTs among other terms, was positively correlated with the ratio of patients with coronavirus-like symptoms to all patients ($r = 0.249$, $p < 0.001$) and negatively correlated with the ratio of patients with other symptoms to all patients ($r = -0.249$, $p < 0.001$). The association between patients' behaviors of ED admissions and Google Trends IOTs during the first 3 months of the Covid-19 pandemic is shown in figure 2.

According to our study, when patient admissions according to the triage code were evaluated, most of the patients were assigned a green triage code for all three years [figure 3].

Table 1. The demographic and clinical characteristics & emergency department admission areas of patients by years

		2018	2019	2020	Total
Age (median)		39.0 (27.0 – 55.0)	39.0 (26.0 – 55.0)	38.0 (26.0 – 53.0)	39.0 (26.0 – 54.0)
Gender (n(%))	Male	58575 (49.0)	61706 (48.1)	58836 (49.5)	179117 (48.9)
	Female	60847 (51.1)	66611 (51.9)	59929 (50.5)	187387 (51.1)
Emergency Department Admission Area (n(%))	Green Area	64417 (53.9)	71496 (55.7)	71732 (60.4)	207645 (56.7)
	Trauma Area	23249 (19.5)	23107 (18.0)	18672 (15.7)	65028 (17.7)
	Injection Room	15441 (12.9)	16706 (13.0)	16034 (13.5)	48181 (13.1)
	Yellow Area	11062 (9.3)	11487 (9.0)	7769 (6.5)	30318 (8.3)
	Red Area	5253 (4.4)	5521 (4.3)	4558 (3.8)	15332 (4.2)
	Total	119422	128317	118765	366504
The Most Common Reasons of Admission	Acute upper respiratory infections	20140	27891	31615	79646
	Prescribed treatment	15441	16706	16034	48181
	Soft tissue disorders	12059	14032	10084	36175
	Falls	8744	8382	6019	23145
	Digestive system and abdomen	7684	7785	6745	22214
	Circulatory and respiratory systems	3981	4281	5422	13684
	Exposure to inanimate mechanical forces	5108	4375	3524	13007
	Non-infective enteritis and colitis	2297	3333	3243	8873
	Dorsopathies	2403	1778	2218	6399
	Other diseases of urinary system	1995	1952	1493	5440
	Exposure to animate mechanical forces	1880	1622	1771	5273
	Hypertensive urgency	1428	1627	1352	4407
	Acute lower respiratory infections	1492	846	878	3216
	Other	34770	33707	28367	96844
Outcome (n(%))	Discharged	117206 (98.1)	125429 (97.7)	115551 (97.3)	358186 (97.7)
	Hospitalized to clinic	1755 (1.5)	2453 (1.9)	2577 (2.2)	6785 (1.9)
	Referred to another center	347 (0.3)	198 (0.2)	304 (0.3)	849 (0.2)
	Hospitalized to ICU*	49 (0.0)	185 (0.1)	225 (0.2)	459 (0.1)
	Died within ER**	65 (0.1)	52 (0.0)	108 (0.1)	225 (0.1)
Patients with Covid-like symptoms (n(%))	Other symptoms	96681 (81.0)	97761 (76.2)	83935 (70.7)	278377 (76.0)
	Covid-like symptoms	22741 (19.0)	30556 (23.8)	34830 (29.3)	88127 (24.0)
Total (n(%))		119422 (32.6)	128317 (35.0)	118765 (32.4)	366504 (100.0)

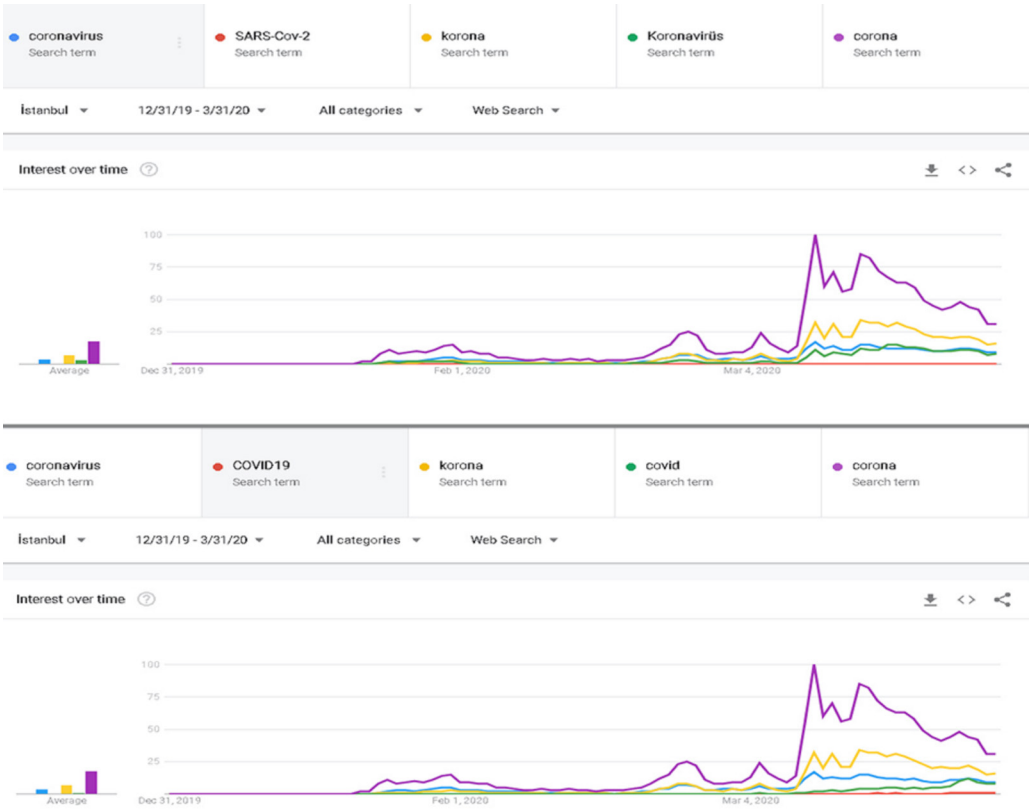


Figure 1. The terms searched in Google Trends

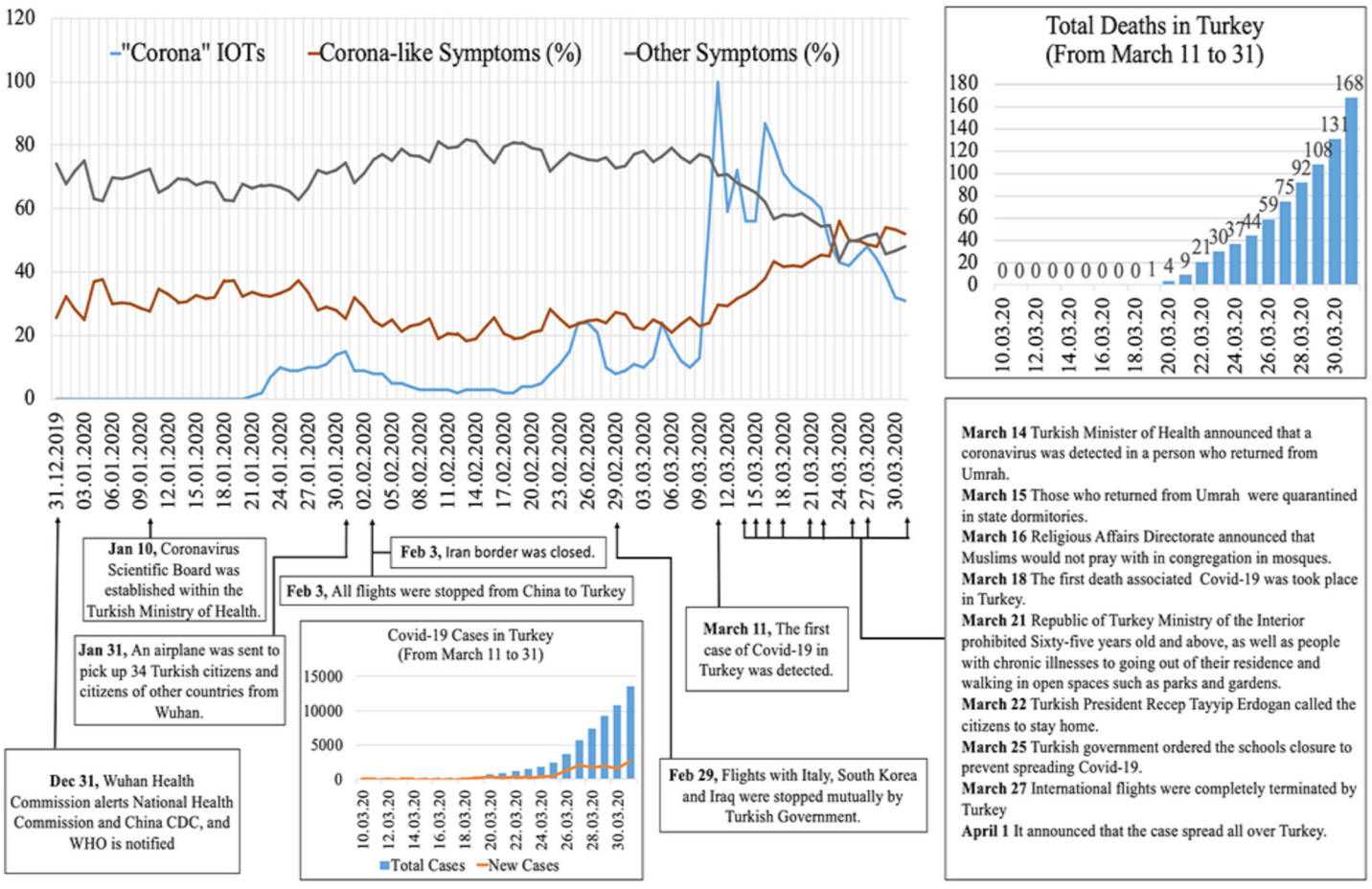


Figure 2. The association between patients' behavior of emergency department admissions and Google Trends-IOTs during the first months of the Covid-19 Pandemic

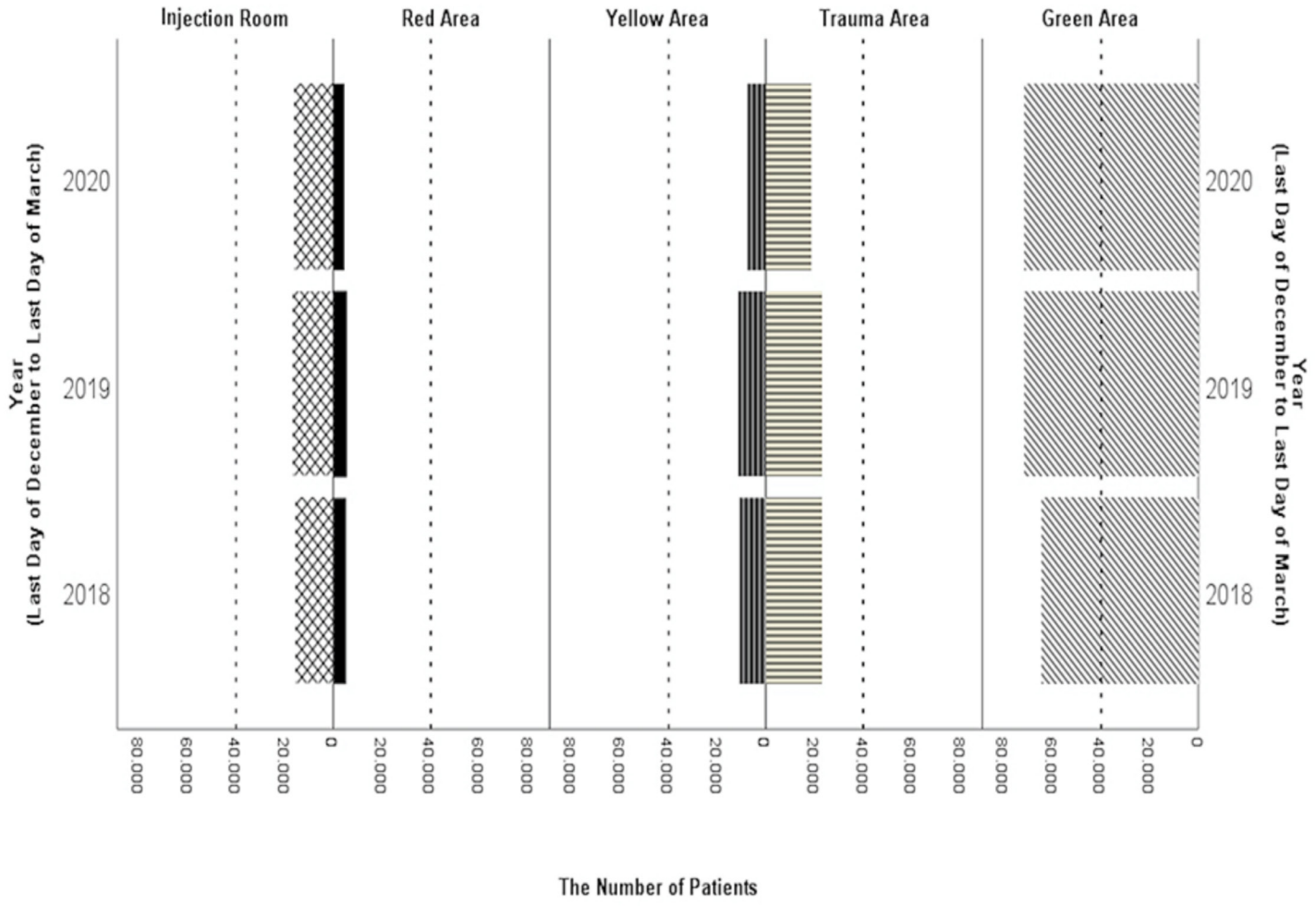


Figure 3. Emergency Department admission areas of the patients

In all, there were 53.9%, 55.7% and 60.4% patient admission who were evaluated with green triage code in 2018, 2019 and 2020, respectively.

Discussion

Coronaviruses are non-segmented, positive-sense RNA viruses that were first described in 1966 [11]. These viruses infect humans and many animal species [12].In the past 20 years, two major outbreaks associated with coronavirus, SARS-CoV and MERS-CoV, occurred. At the end of 2019, a new type of coronavirus named SARS-COV2 caused a severe respiratory illness, Covid-19, with a global impact. Depending on the magnitude of the impact, Covid-19 term may be used more than in daily speech and practice.

In our study, the IOTs of the term "corona", which has the greatest IOTs among other terms, was positively correlated with the ratio of patients with coronavirus-like symptoms to all patients and was negatively correlated with the ratio of patients with other symptoms to all patients. In summary, according to our study, patients do not visit the EDs due to their non-flu-like symptoms during the Covid-19 pandemic. This result may suggested that fear and anxiety directly affect the ED admissions especially the nonurgents.

With the exception of our study, no other study has investigated the association between ED admissions and Covid-19-associated search engine use other. In a study by Alicino et al. which was published in 2015, a significant correlation between Google Trends activities and epidemiologic data during the 2014 Ebola outbreak in western Africa was identified [13]. In another study, Malik et al. discovered that syndromic indicators based on Google Flu Trends (GFT) and ED data were strongly correlated with each other and virologic data during both waves of the 2009 H1N1 pandemic in Manitoba [14].

Some articles have addressed the use of internet search engine data to monitor infectious disease activity, outbreaks, mental health and substance abuse [13,15-19]. Our study is similar to these studies due to the use of Google Trends analysis in the methodology.

A study published in 2018 revealed that population size affected the flu spread [20]. The current pandemic situation in our country also supports this result. Most cases (approximately 60% of all confirmed Covid-19 cases in Turkey) are observed in Istanbul, which is the largest city in Turkey. In their 2012 study, Dugas et al. reported a positive correlation between flu incidents and ED overcrowding [18].

Turkey has been known as an upper-middle income country with a population of 83.2 million people [6]. According to the Turkey Electronic Communication Sector report, Turkey has 77.1 million

broadband internet subscribers [21]. Considered the largest and most developed city in the country, Istanbul is one of the cities where this technology is extensively employed. Because our study was conducted in Istanbul, future evaluations of ED admissions is important.

Covid-19 is transmitted from one person to another person by droplet transmission. Recent WHO reports have concluded that 3,759,967 confirmed patients worldwide have been exposed to SARS-CoV-2. These reports also indicated 259,474 deaths [22]. Thus, social isolation is considered the determinant of this pandemic. In the current situation, people use social media, the internet, TV, and radio. We can assume that the probability of "stay home" announcements were heard by the population more and the number of ED visits decreased due to its effect. The decrease in the number of emergency admissions during the pandemic in our study warrants further investigation of the urgency of emergency admissions during the pre-pandemic period.

Due to the Turkish Health Ministry's triage system suggestion, emergency service admissions are separated into green, yellow and red, which represent the lowest level of urgency to the highest level of urgency. In our study, 60.4% of the cases were assigned green triage in the main study period. Therefore, non-urgent cases were high in this period.

According to a study published in 2018 in Turkey, the most common complaints of non-urgent patients were musculoskeletal system pain (25.2%) and symptoms of upper respiratory tract infections (URTI) (19.7%) [4]. In another study, 6,254 (37.5%) patients admitted to the ED with a total of 23,424 admissions were diagnosed with upper respiratory tract infections [23]. In a different study conducted in the United States, it was concluded that anxiety during the pandemic period is related to google trends [24]. In this study, 31,615 (26%) patients admitted to the ED with a total of 118765 admissions were diagnosed with upper respiratory tract infections. In previous studies, the application density was different from our study. The pandemic, which is effective all over the world, caused us to get different results from other google trends studies. Hospital admissions made due to Covid-19 symptoms during the pandemic were different from those due to other symptoms. Similar studies conducted in countries affected by the pandemic, though our study is the first study conducted in Turkey on this issue.

A study conducted in Turkey reported that approximately 22% of the ED admissions involved pregnancy tests, testing for job applications, wound dressing, and suture removal. Inappropriate ED use hinders its use for real emergency cases, decreases readiness for care, produces a negative spillover effect on the quality of emergency services, and raises overall costs [3].

Limitations

The main limitation of this study is that it was conducted in a single center in one city. Emergency department admissions made with subjective symptoms could vary according to patient psychology and social conditions. This situation could cause differences in sample size.

Conclusio

It is known that Google trends will change during the pandemic. Communication systems need to reach people with correct information and avoid panic. In emergency service admissions, patients should be aware of the risk of infection due to infection in the hospital

In our era, digitalization has reached great dimensions and has been adopted by a large population. Because of the availability of internet services, people strongly influence the volume of search engines during panic-inducing events, such as the Covid-19 pandemic. Governments and health managers should employ these interactions to guide their Emergency Health Care plans.

Nevertheless, healthcare systems should reveal the reasons for non-urgent admissions to the ED and provide solutions.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
All authors declare no financial support.

Ethical approval
The study began after the Institutional Review Board approved it with number B.10.1.TKH.4.34.H.GP.0.01/75.

References

1. Zhao Y, Zhang J. Consumer health ınformation seeking in social media: a literature review. Health Info Libr J. 2017;34:268-83.
2. Bastani P, Bahrami MA. COVID-19 related misinformation on social media: a qualitative study from Iran. J Med Internet Res. 2020.
3. Eroglu SE, Toprak SN, Urgan O, et al. Evaluation of non-urgent visits to a busy urban emergency. Saudi Med J. 2012;33:967-72.
4. Idil H, Kilic TY, Toker I et al. Non-urgent adult patients in the emergency department: Causes and patient characteristics. Turk J Emerg Med. 2018;18:71-4.
5. Di Somma S, Paladino L, Vaughan L et al. Overcrowding in emergency department: an international issue. Intern Emerg Med. 2015;10:171-5.
6. Address Based Population Registration System, Turkish Statistical Institute. https://biruni.tuik.gov.tr/medas/?kn=95&locale=tr access date. 16.02.2020.
7. Aksel G, Bildik F, Demircan A, et al. Effects of fast-track in a university emergency department through the National Emergency Department Overcrowding Study. J Pak Med Assoc. 2014;64:791-7.
8. Health Statistics. Turkish ministry of health. https://dosyahastane.saglik.gov.tr/Eklenti/9300,2017-ocak-ekim-donemi-poliklinik-yatis-ve-yogun-bakim-ve-acil-servis-verileri-baglaminda-her-bransta-ilk-100-hastanepdf.pdf?0 accessed date. 08.05.2020.
9. Elhussein M, Brahimi S, Alreedy A, et al. Google trends identifying seasons of religious gathering: applied to investigate the correlation between crowding and flu outbreak. Inf process Manag. 2020;3:102208.
10. Google Trends: What Is Google Trends? https://www.wordstream.com/google-trends accessed date. 01.05.2020.
11. Tyrrell DA, Bynoe ML. Cultivation of viruses from a high proportion of patients with colds. Lancet. 1966:1:76-7.
12. Velavan TP, Meyer CG. The COVID-19 epidemic. Trop Med Int Health. 2020;25:278-80.
13. Alicino C, Bragazzi NL, Faccio V, et al. Assessing Ebola related web search behaviour: Insights and implications from an analytical study of Google trends-based query volumes. Infect Dis Poverty. 2015;4:54.
14. Malik MT, Gumel A, Thompson LH, et al. "Google flu trends" and emergency department triage data predicted the 2009 pandemic H1N1 waves in Manitoba. Can J Public Health. 2011;102:294-7.
15. Ginsberg J, Mohebbi MH, Patel RS et al. Detecting influenza epidemics using search engine query data. Nature. 2009;457:1012-4.

16. Nuti SV, Wayda B, Ranasinghe I, et al, The use of Google trends in health care research: A systematic review. Plos One. 2014;9:109583.

17. Cho S, Sohn CH, Jo MW, et al. Correlation between national influenza surveillance data and google trends in South Korea. Plos One. 2013;8:81422.

18. Dugas AF, Hsieh YH, Levin SR, et al. Google flu trends: Correlation with emergency department influenza rates and crowding metrics. Clin Infect Dis. 2012:54:463–9.

19. Bragazzi NL, Barberis, I, Rosselli R, et al. How often people google for vaccination: Qualitative and quantitative insights from a systematic search of the web-based activities using Google trends. Hum Vaccin Immunother. 2017;13:464-9.

20. Dalziel BD, Kissler S, Gog JR et al. Urbanization and humidity shape the intensity of influenza epidemics in U.S. cities. Science. 2018;362:75-9.

21. Turkey Electronic Communication Sector Quarterly Market Data Report. https://www.btk.gov.tr/uploads/pages/pazar-verileri/3-ceyrekraporu-2019.pdf accessed date 16.02.2020.

22. World Health Organization Coronavirus disease (COVID-19) Situation Report – 109. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports accessed date 08.05.2020.

23. Ozdemir S, Cimilli Ozturk T, et al. Evaluation of the prescriptions written for upper respiratory tract infections. North Clin Istanbul. 2015; 2:107-14.

24. Hoerger M, Alonzi S, Perry L M, et al. Impact of the COVID-19 pandemic on mental health: Real-time surveillance using Google Trends. Psychological Trauma: Theory, Research, Practice, and Policy. 2020;12:567-8.

Available online at www.medicinescience.org

ORIGINAL ARTICLE

Medicine Science International Medical Journal

Medicine Science 2021;10(1):118-24

Relationships between quality of life and the idea of undergoing anesthesia in patients scheduled for elective surgery

Muhammet Korkusuz[1], Tugsan Egemen Bilgin[2]

[1]Karaman Training and Research Hospital, Depatment Anesthesiology and Reanimation, Karaman, Turkey
[2]Mersin University, Faculty of Medicine, Mersin, Turkey

Received 10 September 2020; Accepted 04 November 2020
Available online 20.01.2021 with doi: 10.5455/medscience.2020.09.183

Abstract

Preoperative anesthesia-related anxiety is a major problem. Our aim was to investigate the effect of the idea of undergoing anesthesia on the quality of life of patients scheduled for elective surgery by evaluating preoperatively and postoperatively. All patients who were referred to the outpatient clinic of the Anesthesiology and Reanimation Department for preoperative assessment from May 2011 to December 2011 were informed about the study plan. Patients were evaluated with the SF-36 scale during their final examination and also after surgery. We found that the postoperative Mental Component Summary (MCS) domain demonstrated statistically significant increase compared to preoperative scores (51.3 ± 12.0 and 50.6 ± 12.7 respectively, p = 0.014). There were no significant differences between the preoperative and postoperative periods in terms of the Physical Component Summary (PCS) domain or any other subdimensions (p>0.005). When evaluated according to age groups, preoperative and postoperative PCS and MCS scores were found to be consistently higher in the 18–35 age group compared to older groups (p <0.05 for all). Higher level of education was also found to be associated with better SF-36 scores in all preoperative and postoperative comparisons of PCS and MCS scores (p <0.001 for all). Patients with physical disability had significantly lower PCS and MCS scores (preoperative and postoperative) compared to those without physical disability (p<0.01 for all). Patients without prior anesthesia experience had significantly higher postoperative PCS scores compared to those who had undergone anesthesia before this study (p = 0.021); all other comparisons were similar.

Keywords: Elective surgery, anesthesia, quality of life

Introduction

Patients scheduled for surgery can experience various types of psychological problems in the preoperative period, including anxiety about receiving anesthesia, worries about the risk of death, fear of disability and being unable to work, fear of losing control over their body, and fear of losing sexual competence. Studies have reported that around 60–80% of patients are anxious in the preoperative period [1, 2].

Informing patients about the anesthesia and intervention to be applied facilitates adaptation and increases coping by providing insight. Many studies have shown that patients feel happier and more peaceful when they are informed in detail about their disease and its treatment. Providing sufficient information also leads to reduced analgesic need, shorter hospital stay and accelerated rehabilitation [3].

***Coresponding Author:** Muhammet Korkusuz, Karaman Training and Research Hospital, Depatment Anesthesiology and Reanimation, Karaman, Turkey.
E-mail: drmuhammetkorkusuz@gmail.com

Alone with other reasons, anxiety about receiving anesthesia also increases anxiety and affects the quality of life of patients.

Although survey studies have been conducted to reveal preoperative causes for anxiety and its severity, the effect of the idea of receiving anesthesia on quality of life has not been investigated. Quality of life is a combination of a person's physical, social, psychological, emotional or mental state and is of great importance in health and disease [4]. The World Health Organization (WHO) defines quality of life as a concept that includes the psychological and social functions of the individual as well as physical functions [5]. Due to the increase in life expectancy and the fact that longer life often translates to living longer with chronic diseases, the assessment of quality of life in disease-related conditions has become crucial.

Previous studies have examined the effect of surgical interventions on quality of life. Although there are many studies that have investigated the anesthesia-related concerns of patients, the effect of being scheduled for anesthesia due to a planned elective surgery on patients' quality of life has not been studied. Therefore, here we aimed to investigate the effects of the idea of receiving anesthesia on quality of life in patients scheduled for elective surgery by

evaluating the preoperatively and postoperatively.

Materials and Methods

Approval for the study was obtained from the Ethics Committee of Mersin University Medical Faculty Hospital (Date: 22.04.2011, decision no: 2011/85). All patients that had been scheduled for elective surgeries and were evaluated in the outpatient clinic of our Anesthesiology and Reanimation Department between May 2011 and December 2011 were evaluated for inclusion in the study. A total of 1050 individuals accepted to participate after they were provided with detailed information about the study.

Inclusion criteria were: being aged between 18–75 years, being literate and agreeing to participate. Exclusion criteria were: undergoing non-elective surgery, having any maxillofacial anomaly that would complicate anesthesia, being diagnosed with any major psychiatric disorder (depressive, anxiety-related, bipolar) at any time in their life, having cardiac or neurological diseases that could adversely effect the outcome of surgery or anesthesia, being allergic to any type of anesthetic, having neurological damage (cerebrovascular event, traumatic injury etc.), and being pregnant or continuing to breastfeed.

A standard form, containing information such as, age, gender, educational status, occupation, previous anesthesia experience, presence of psychiatric disease, was filled routinely by patients in the outpatient clinic. In the physical examination of the patients; cervical lordosis, paravertebral muscle spasm and tenderness, tenderness at Arnold points, and range of motion (ROM) were evaluated. Compression test, distraction test and spurling test were applied. Cases with physical disability were recorded. Preoperative ASA (American Society Anesthesiologist) classification of the patients was performed and results were recorded. This classification system that was developed by the American Society of Anesthesiologists is frequently used to determine anesthesia-related risks in combination with other factors, since it enables the prediction of perioperative risks [6]. In our study, this evaluation was performed on the day of anesthesia.

Quality of life assessment

The Short Form-36 (SF-36) was used to measure the general quality of life of the patients. The SF-36 Quality of Life Scale is a short questionnaire with 36 items that can be used for the assessment of individuals with and without disease. This scale evaluates 8 dimensions which can be listed as follows: physical function (PF), social function (SF), physical role (PR), bodily pain (BP), mental health (MH), emotional role (ER), vitality (VT), and general health (GH). The questions of the subscales are weighted and summed and the physical component summary (PCS) and mental component summary (MCS) scores are obtained. All scores range from zero to one hundred. Lower scores correspond to lower health status, while higher scores indicate better health [7]. The SF-36 is a self-assessment scale and its Turkish reliability and validity study has been conducted [8]. The patients were asked to fill the SF-36 questionnaire preoperatively (before the day of admittance for surgery) and postoperatively (immediately before discharge).

Statistical analysis

All analyses were performed on SPSS v21 (SPSS Inc., Chicago, IL, USA). For the normality check, the Shapiro-Wilk test was used. Data are given as mean ± standard deviation for continuous variables. Normally distributed variables were analyzed with two-way repeated measures analysis of variances (ANOVA). Non-normally distributed variables were analyzed with the Wilcoxon Signed Ranks test for repeated measurements. Between-group comparisons of these variables were performed by the Mann Whitney U test or Kruskall Wallis test –depending on the number of groups compared. Pairwise comparisons were performed with the Bonferroni correction method. Analyses with $p<0.05$ values were accepted as statistically significant.

Results

Among the 1050 participants, 54.7% (n=574) were women, 84.1% (n=883) were between the ages of 18–55 years. More than half (57%, n=599) had previous experience with anesthesia. General anesthesia was applied in 94.4% of the cases. The leading clinics in terms of number of surgeries performed on subjects included in this study were: Obstetrics and Gynecology (21.2%), General Surgery (18.5%), Otorhinolaryngology (18.5) and Urology (16%). Together, these clinics were responsible for almost 75% of the surgeries. The summary of patients' characteristics is shown in Table 1.

When comparisons with regard to the quality of life were performed, we found that the postoperative MCS domain (including vitality, social functioning, emotional role, and mental health subdimensions) demonstrated a marginal but statistically significant increase compared to preoperative scores (51.3 ± 12.0 and 50.6 ± 12.7 respectively, $p = 0.014$). There were no significant differences between the preoperative and postoperative periods in terms of the PCS domain or any other subdimensions. Preoperative and postoperative SF-36 scale scores are shown in Table 2.

Next, we evaluated and compared domain scores (PCS and MCS) based on patient characteristics. The results demonstrated that all subgroups were similar when preoperative scores were compared to postoperative scores. This was especially interesting for the fact that patients who did not have prior anesthesia experience also did not have any significant changes in time-bound comparisons ($p = 0.250$ for PCS and $p = 0.509$ for MCS) (Table 3).

There were no gender-related differences in terms of preoperative or postoperative PCS or MCS scores in any comparison. When evaluated according to age groups, preoperative and postoperative PCS and MCS scores were found to be consistently higher in the 18–35 age group compared to older groups ($p <0.05$ for all). There was no significant difference between the 56-75 age group and the 36-75 age group in terms of preoperative and postoperative PCS and MCS scores ($p>0.05$ for all) (Table 3). Higher level of education was also found to be associated with better SF-36 scores in all preoperative and postoperative comparisons of PCS and MCS scores ($p <0.001$ for all). Additionally, although the number of patients with physical disability was comparatively very low (n=50), they had significantly lower PCS and MCS scores (preoperative and postoperative) compared to those without physical disability ($p<0.01$ for all). Patients without prior anesthesia experience had significantly higher postoperative PCS scores compared to those who had undergone anesthesia before this study ($p = 0.021$); all other comparisons were similar. Finally, we also found no differences in any comparison of MCS and PCS scores with regard to the type of anesthesia (Table 3)

Table 1. Summary of patients' characteristics

Gender	Female	574 (54.7)
	Male	476 (45.3)
Age (years)	18-35	421 (40.1)
	36-55	462 (44.0)
	56-75	167 (15.9)
Education	Literate	38 (3.6)
	Primary school	478 (45.6)
	Secondary school	288 (27.4)
	High school or higher	246 (23.4)
Experience of anesthesia	Yes	599 (57.0)
	No	451 (43.0)
Physical problem	Yes	50 (4.8)
	No	1000 (95.2)
ASA classification	1	594 (56.6)
	2	406 (38.7)
	3	49 (4.7)
	4	1 (0.1)
Type of anesthesia	General	991 (94.4)
	Regional	59 (5.6)
Surgical clinic	General surgery	194 (18.5)
	Urology	168 (16.0)
	Cardiovascular surgery	10 (1.0)
	Otorhinolaryngology	194 (18.5)
	Orthopedics and traumatology	106 (10.1)
	Plastic and reconstructive surgery	99 (9.4)
	Neurosurgery	25 (2.4)
	Ophthalmology	22 (2.1)
	Obstetrics and gynecology	223 (21.2)
	Thoracic Surgery	9 (0.9)

Data are given as frequency (percentage)
ASA: American Society of Anesthesiologists

Table 2. SF-36 subscale scores before and after operations.

QoL domains	Period		
	Preoperative	**Postoperative**	**p**
Physical functioning	70.5 ± 27.3	68.6 ± 28.5	0.111
Physical role	56.2 ± 41.7	58.1 ± 40.4	0.289
Bodily pain	36.7 ± 25.5	38.1 ± 28.2	0.212
General health	51.1 ± 12.1	51.6 ± 14.8	0.426
Physical component summary (PCS)	53.6 ± 13.5	54.1 ± 13.5	0.125
Vitality	50.6 ± 12.7	51.1 ± 13.6	0.381
Social functioning	45.0 ± 18.4	43.9 ± 14.7	0.133
Emotional role	54.6 ± 42.0	57.9 ± 40.3	0.067
Mental health	52.1 ± 12.2	52.3 ± 12.1	0.721
Mental component summary (MCS)	50.6 ± 12.7	51.3 ± 12.0	0.014

Data are given as mean ± standard deviation
QoL: Quality of life

Table 3. Comparison of PCS and MCS domain scores based on patient characteristics and time-bound analysis.

		SF-36 QoL domains					
		PCS			MCS		
		Preop	Postop	p-value	Preop	Postop	p-value
Gender	Female (n=574)	53.4 ± 12.7	53.7 ± 13.0	0.693	50.8 ± 12.9	51.1 ± 12.0	0.694
	Male (n=476)	53.8 ± 12.7	54.5 ± 14.1	0.421	50.3 ± 12.6	51.6 ± 11.9	0.102
	p-value	0.634	0.326		0.511	0.506	
Age (years)	18-35 (n=421)	55.7 ± 11.2	56.0 ± 11.9	0.707	51.9 ± 11.8	52.6 ± 11.6	0.386
	36-55 (n=437)	53.1 ± 13.3	53.5 ± 14.0	0.589	49.6 ± 12.8	50.3 ± 11.8	0.401
	56-75 (n=192)	50.2 ± 13.6	51.2 ± 14.8	0.491	49.9 ± 14.3	50.6 ± 12.8	0.614
	p-value	p1<0.001 p2<0.001 p4=0.058	p1=0.002 p2<0.001 p4=0.190		p1=0.017 p2=0.051 p4=0.058	p1=0.015 p2=0.051 p4=1.0	
Education	Literate (n=38)	46.4 ± 11.5	46.0 ± 12.5	0.885	46.0 ± 10.5	43.7 ± 13.0	0.399
	Primary (n=478)	51.2 ± 13.4	52.2 ± 14.8	0.274	48.5 ± 13.4	49.5 ± 12.1	0.226
	Secondary (n=288)	55.5 ± 12.0	55.3 ± 12.1	0.842	50.9 ± 11.9	51.9 ± 11.3	0.302
	High (n=246)	57.2 ± 11.0	57.7 ± 11.2	0.618	54.8 ± 11.6	55.1 ± 11.1	0.770
	p-value	p1=0.147 p2<0.001 p3<0.001 p4<0.001 p5<0.001 p6=0.424	p1=0.051 p2<0.001 p3<0.001 p4=0.003 p5<0.001 p6=0.162		p1=1.0 p2=0.077 p3<0.001 p4=0.031 p5<0.001 p6=0.001	p1=0.045 p2=0.001 p3<0.001 p4=0.031 p5<0.001 p6=0.008	
Experience of anesthesia	Yes (n=599)	53.2 ± 13.0	53.3 ± 13.2	0.895	50.5 ± 13.1	50.9 ± 12.0	0.683
	No (n=451)	54.1 ± 12.3	55.2 ± 13.8	0.250	50.7 ± 12.3	51.8 ± 12.0	0.509
	p-value	0.267	0.021		0.143	0.250	
Physical disability	Yes (n=50)	46.2 ± 11.6	46.2 ± 12.7	1.000	45.1 ± 10.4	46.3 ± 12.0	0.651
	No (n=1000)	54.0 ± 12.7	54.5 ± 13.4	0.074	50.8 ± 12.8	51.5 ± 11.9	0.089
	p-value	<0.001	<0.001		<0.001	0.003	
Type of anesthesia	General (n=991)	53.7 ± 12.8	54.2 ± 13.5	0.088	50.5 ± 12.7	51.3 ± 11.9	0.373
	Regional (n=59)	52.4 ± 11.4	52.4 ± 13.0	1.000	51.3 ± 13.5	51.6 ± 12.8	1.000
	p-value	0.448	0.333		0.637	0.842	

Data are given as mean ± standard deviation. QoL: Quality of life, PCS: Physical component summary, MCS: Mental component summary
Comparisons: p1; category 1 vs category 2, p2; category 1 vs category 3, p3; category 1 vs category 4, p4; category 2 vs category 3, p5; category 2 vs category 4, p6; category 3 vs category 4

Discussion

Pre-anesthetic anxiety is a condition that can negatively affect the quality of life of patients. In this study, in which the preoperative and postoperative quality of life of the patients were examined, it was found that age, educational status and physical disabilities affected the quality of life in both periods. Among these, age and physical disabilities may be factors that are inherently associated with quality of life, but the fact that receiving a higher level of education is also greatly associated with higher quality of life is an important result. The type of anesthesia had no effect on the quality of life.

Although there are many studies examining the preoperative anesthesia concerns of patients, there is very little data on the effect of being subject to anesthesia on the quality of life of patients (regardless of the type of surgery) both in the preoperative and postoperative periods. Therefore, there was very little information in the literature that could be compared with our findings. In previous studies, the quality of life before and after different types of surgeries was examined. Kuan et al. reported that there was no significant change in any of the SF-36 domains before and after endoscopic pituitary surgery. In addition, they reported that tumor size was the only variable that showed a significant relationship with postoperative quality of life scores [9]. Another study reported that the postoperative quality of life of patients reached similar levels with the general population [10]. Mousavi et al. showed that, after rhinoplasty surgery, all scores of the patients except physical functioning and physical role had improved significantly [11]. Shamsaeefar et al. reported that all SF-36 domains, except general health, were significantly improved postoperatively in patients who had undergone liver transplantation [12]. Dacha et al. reported a significant improvement in all dimensions of the SF-36 after pyloromyotomy [13]. Netto et al. showed a significant improvement in all dimensions except for general health and mental health after lumbar spine surgery [14]. Erdivanli et al. reported that all domains except social function and bodily pain improved significantly after septoplasty [15]. When the studies are examined overall, features such as the size and region of the surgical operation to be performed, what it means to the patient, the level of well-being that the operation will provide to the patient, expectations, mood states of the patients, and anxiety levels seem to be the important determinants of quality of life before and after surgery. In our study, the results of all patients undergoing anesthesia were examined without classification according to these variables, since our aim was to determine whether the idea of being subject to anesthesia (with the surgery as an unavoidable confounding effect) had an impact on quality of life. Based on the studies conducted in the literature, and with the guidance of the results of our study, regardless of the type of surgical operation, it is expected that the quality of life will improve, albeit marginally, in the postoperative period compared to the preoperative period.

Age is an important variable that affects almost every aspect of quality of life. In our study, a statistically significant difference was found in the comparison of PCS and MCS scores between age groups, both preoperatively and postoperatively. SF-36 scale scores decreased as age increased, meaning the quality of life was decreasing. According to the results of the Turkish validity and reliability study of WHO Quality of Life Module for the Elderly, the lower quality of life results of elderly people was expected. This may be associated with loss of sensory functions and the inability to perform daily activities, as shown previously [16]. Quality of life studies in healthy individuals or chronic patients also indicate that the quality of life decreases with increasing age [17]. Although there are few studies evaluating the quality of life according to age classification, there is no study examining the effect of anesthesia on the quality of life in the elderly. Although the lower levels of quality of life was apparent in the elderly, their results were consistent at preoperative and postoperative analysis –similar to younger groups.

In our study, no statistically significant difference was found in the comparisons of preoperative and postoperative PCS and MCS scores by gender. In different studies conducted in Finland, Taiwan, Poland, Croatia, Japan and Iran, it was determined that women have lower health-related quality of life compared to men [18-22]. Younossi et al. and Van der Plas et al. stated that the quality of life in patients with liver transplantation does not differ according to gender [23, 24]. From an epidemiological standpoint, the fact that women generally have higher frequency of depression and anxiety disorders than men may result in lower quality of life in women. While Badner et al. attributed this difference to the higher anxiety of women due to separation from their families in surgery [1], Shevde and Panagopoulos and Domar et al. attributed this difference to women's ability to express their surgical concerns more easily than men [25, 26]. In another study, although male patients stated that they felt better emotionally (compared to female patients), vasovagal syncope was found more frequently in men during spinal anesthesia [27]. This may be due to the fact that men do not fully express their feelings in order to show that they are more resilient. There are also studies showing that hormonal differences between genders affect the level of anxiety [28].

Another feature examined in our study was the effect of educational status on quality of life. Both preoperative and postoperative PCS and MCS scores were statistically significantly different according to educational status. As the education level increased, the quality of life of the patients increased. In studies conducted with patients who underwent surgery for renal transplantation, Muehrer and Becker and Matas et al. reported that the quality of life significantly increased with the increase in education level, but no significant relationship was found between educational status and quality of life [29, 30]. On the other hand, Yıldırım determined that there was a significant relationship between education level and quality of life [31]. Different results found in the studies suggested that the personal characteristics of the individual affect the quality of life together with the level of education. However, our results that demonstrate consistently higher levels of quality of life among patients with higher education indicate that individuals with lower education must receive more detailed information in order to reduce peroperative anxiety.

Anxiety associated with various events may decrease when people re-experience such events. In our study, a statistically significant difference was found in the comparison of postoperative PCS scores according to the anesthesia experience of the patients; however, this effect was not present among individuals when MCS scores were compared. However, surprisingly, postoperative PCS scores were higher in patients without prior anesthesia experience.

We attributed this difference to the perception of anesthesia-related outcomes among individuals who had not undergone anesthesia before. In other words, patients who had not undergone anesthesia before could have been expecting worse outcomes, which may have resulted in higher scores when such adverse results were not experienced.

Physical disabilities can also negatively affect quality of life independently. In our study, both preoperative and postoperative PCS and MCS scores were significantly different between groups determined according to the presence/absence of physical disability. Ambulatory difficulties, dependence in daily activities, activity limitation due to chronic pain, and social isolation occur in individuals with chronic physical disabilities, causing a decrease in life satisfaction and quality of life [32, 33]. As expected, in our study, the quality of life determined according to both the PCS score and the MCS score in the preoperative and postoperative period was higher in the patient group without any physical disabilities.

In some other studies, it has been reported that mood states and waiting time before surgery affect the quality of life. Netto et al. reported that patients with postoperative depression symptoms have significantly worse quality of life [14]. In a similar study, Katz et al. also showed that patients with depression symptoms after surgery had more negative results [34]. Desmeules et al. reported that waiting time before knee replacement surgery significantly affected the physical function score [35]. In our study, various such features that may influence quality of life before and after surgery were not examined. The omission of these variables may have led to the selection of patients with more positive or negative characteristics and could have indirectly caused selection bias. However, since the attending physicians of these patients were from other departments before being referred to us for pre-surgical assessment, we could not control or directly assess some of these characteristics, and no additional analysis was performed in our study to rule out these situations.

Although the anxiety levels of the patients were not examined in our study, it was assumed that anxiety was effective in the change in the quality of life before and after anesthesia. As a matter of fact, it has been shown in different studies that anxiety increases before anesthesia [36, 37]. Anxiety, which occurs with the idea of surgical intervention and anesthesia in the preoperative period, can affect the quality of life of patients by negatively influencing vital functions and activities. In a study examining the causes of anesthesia-related anxiety of patients, Shevde and Panagopoulos reported that patients' fear of anesthesiologist's lack of knowledge (45%), lack of experience (43%), the possibility of not waking up (37%) and postoperative pain (34%) were effective on anxiety [25]. While Chew et al. reported pain (39.4%) and not being able to wake up after surgery (18.9%) as the most frequent anxiety-inducing causes before anesthesia [38], another study, by Zvara et al. reported that the most common causes of anxiety were awakening during surgery (51.8%), not being able to wake up after surgery (43.4%) and pain (38%) [39]. Based on the results of these studies and our study, it can be said that anesthesia-related anxiety could have important effects on quality of life, especially in the preoperative period. However, this result was not evident in the MCS scores of patients in the current study. It may be advisable to perform further studies with the addition of state and trait anxiety analysis (via the STAI scale).

Although the effect of the anxiety of anesthesia on quality of life was examined in our study, anxiety-specific results could not be obtained because the anxiety level of the individuals was not examined. The size of the surgical operation, the waiting time for this surgical operation, and the postoperative advantages (life standards, daily activities, socialization, etc.) may have affected both preoperative and postoperative results. These were not examined in our study. Although we attributed the results to the idea of undergoing anesthesia, the idea of undergoing surgery might also have affected the results. Additionaly, we compared only preoperative and early postoperative results. The effects of the idea of receiving anesthesia and surgery on quality of life would probably affect all perioperative period. A comparison of the preoperative scores with late postoperative scores might give different results. We recommend examining the possible effect on all perioperative period in future studies.

Conclusion

Age, educational status and physical disabilities affect both preoperative and postoperative quality of life. Anesthesia experience only affected postoperative PCS scores. The type of anesthesia applied is not associated with any of the domains of quality of life. Although the results of our study are not surprising, it can be said that more accurate and valid results can be obtained by examining the relationship between the type of surgery (minor surgery, major surgery, tumor surgery, any surgery that will result in organ-tissue loss, etc.) and the quality of life in future studies. The addition of anxiety scales may also be beneficial in future studies.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
All authors declare no financial support.

Ethical approval
Approval for the study was obtained from the Ethics Committee of Mersin University Medical Faculty Hospital (Date: 22.04.2011, Decision no: 2011/85).

References

1. Badner NH, Nielson WR, Munk S, et al. Preoperative anxiety: detection and contributing factors. Can J Anaesth. 1990;37:444.
2. Lichtor JL, Johanson CE, Mhoon D, et al. Preoperative AnxietyDoes Anxiety Level the Afternoon Before Surgery Predict Anxiety Level Just Before Surgery? Anesthesiology: Anesthesiology. 1987;67:595-8.
3. Johnson JE. Psychological interventions and coping with surgery. Handbook of psychology and health. 1984;4:167-87.
4. Ching S, Thoma A, Mccabe RE, et al. Measuring outcomes in aesthetic surgery: a comprehensive review of the literature. Plast Reconstr Surg. 2003;111:469-82.
5. Srouji IA, Andrews P, Edwards C, et al. General and rhinosinusitis-related quality of life in patients with Wegener's granulomatosis. The Laryngoscope. 2006;116:1621-5.
6. Mayhew D, Mendonca V, Murthy B. A review of ASA physical status–historical perspectives and modern developments. Anaesthesia. 2019;74:373-9.
7. Ware Jr JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36): I. Conceptual framework and item selection. Med Care. 1992:473-83.

8. Pinar R. Reliability and construct validity of the SF-36 in Turkish cancer patients. Qual Life Res. 2005;14:259-64.
9. Kuan EC, Yoo F, Chyu J, et al. Quality of life before and after endoscopic pituitary surgery as measured by the short-form-36. Journal of neurological surgery Part B, Skull base. 2018;79:314.
10. Karabatsou K, O'kelly C, Ganna A, et al. Outcomes and quality of life assessment in patients undergoing endoscopic surgery for pituitary adenomas. Br J Neurosurg. 2008;22:630-5.
11. Mousavi SJ, Aramideh JA, Fattahi SS, et al. Quality of life before and after rhinoplasty surgery measured with SF-36, RSES, and WHOQOL-BREF. Eur J Plast Surg. 2018;41:535-42.
12. Shamsaeefar A, Nikeghbalian S, Kazemi K, et al. Quality of life among liver transplantation recipients before and after surgery: A single-center longitudinal study. Indian J. Trans. 2020;14:48.
13. Dacha S, Mekaroonkamol P, Li L, et al. Outcomes and quality-of-life assessment after gastric per-oral endoscopic pyloromyotomy (with video). Gastrointest Endosc. 2017;86:282-9.
14. Netto MB, Barranco ABS, De Oliveira KWK, et al. Influence of anxiety and depression symptoms on the quality of life in patients undergoing lumbar spine surgery. Rev Bras Ortop. 2018;53:38-44.
15. Erdivanli OC, Coskun ZO, Ozgur A, et al. Comparison of Quality of Life Before and After Septoplasty With Short Form-36. J Craniofac Surg. 2020;31:832-5.
16. Power M, Quinn K, Schmidt S. Development of the WHOQOL-old module. Qual Life Res. 2005;14:2197-214.
17. Gelling L. Quality of life following liver transplantation: physical and functional recovery. J Adv Nurs. 1998;28:779-85.
18. Noro A, Aro S. Comparison of health and functional ability between noninstitutionalized and least dependent institutionalized elderly in Finland. The Gerontologist. 1997;37:374-83.
19. Tajvar M, Arab M, Montazeri A. Determinants of health-related quality of life in elderly in Tehran, Iran. BMC Public Health. 2008;8:323.
20. Tsai S-Y, Chi L-Y, Lee L-S, et al. Health-related quality of life among urban, rural, and island community elderly in Taiwan. Journal of the Formosan Medical Association= Taiwan yi zhi. 2004;103:196-204.
21. Knurowski T, Lazic D, Van Dijk JP, et al. Survey of health status and quality of life of the elderly in Poland and Croatia. Croat Med J. 2004;45:750-6.
22. Lee Y, Shinkai S. A comparison of correlates of self-rated health and functional disability of older persons in the Far East: Japan and Korea. Arch Gerontol Geriatr. 2003;37:63-76.
23. Younossi ZM, Mccormick M, Price LL, et al. Impact of liver transplantation on health-related quality of life. Liver Transpl. 2000;6:779-83.
24. Van Der Plas SM, Hansen BE, De Boer JB, et al. Generic and disease-specific health related quality of life in non-cirrhotic, cirrhotic and transplanted liver patients: a cross-sectional study. BMC Gastroenterol. 2003;3:33.
25. Shevde K, Panagopoulos G. A survey of 800 patients' knowledge, attitudes, and concerns regarding anesthesia. Anesth Analg. 1991;73:190-8.
26. Domar AD, Everett LL, Keller MG. Preoperative anxiety: is it a predictable entity? Anesth Analg. 1989;69:763-7.
27. Boeke S, Jelicic M, Bonke B. Pre-operative anxiety variables as possible predictors of post-operative stay in hospital. Br J Clin Psychol. 1992;31:366-8.
28. Caumo W, Schmidt AP, Schneider CN, et al. Risk factors for preoperative anxiety in adults. Acta Anaesthesiol Scand. 2001;45:298-307.
29. Muehrer RJ, Becker BN. Psychosocial factors in patients with chronic kidney disease: life after transplantation: new transitions in quality of life and psychological distress. Seminars in Dialysis: Wiley Online Library; 2005. p. 124-31.
30. Matas AJ, Halbert R, Barr ML, et al. Life satisfaction and adverse effects in renal transplant recipients: a longitudinal analysis. Clin Transplant. 2002;16:113-21.
31. Yildirim A. The importance of patient satisfaction and health-related quality of life after renal transplantation. Transplant Proc: Elsevier; 2006. p. 2831-4.
32. Budh CN, Österåker A-L. Life satisfaction in individuals with a spinal cord injury and pain. Clin Rehabil. 2007;21:89-96.
33. Ravenscroft A, Ahmed Y, Burnside I. Chronic pain after SCI. A patient survey. Spinal Cord. 2000;38:611-4.
34. Katz JN, Stucki G, Lipson SJ, et al. Predictors of surgical outcome in degenerative lumbar spinal stenosis. Spine (Phila Pa 1976). 1999;24:2229.
35. Desmeules F, Dionne CE, Belzile E, et al. The burden of wait for knee replacement surgery: effects on pain, function and health-related quality of life at the time of surgery. Rheumatology. 2010;49:945-54.
36. Celik F, Edipoglu IS. Evaluation of preoperative anxiety and fear of anesthesia using APAIS score. Eur J Med Res. 2018;23:41.
37. Ahmetovic-Djug J, Hasukic S, Djug H, et al. Impact of Preoperative Anxiety in Patients on Hemodynamic Changes and a Dose of Anesthetic During Induction of Anesthesia. Med Arch. 2017;71:330-3.
38. Care SI, Chew S, Tan T, et al. A survey of patients' knowledge of anaesthesia and perioperative care. Orthopaedics. 1998;23:74.
39. Zvara D, Manning M, Stewart T, et al. Preoperative anesthetic concerns: perceptions versus reality in men and women. Anesthesiology. 1994;81.

Available online at www.medicinescience.org

ORIGINAL ARTICLE

Medicine Science International Medical Journal

Medicine Science 2021;10(1):125-31

Comparison of complete blood count parameters of panic attack and panic disorder

Mehmet Hamdi Orum

Kahta State Hospital, Depatment of Psychiatry Clinic, Adiyaman, Turkey

Received 25 September 2020; Accepted 08 October 2020
Available online 17.01.01.2021 with doi: 10.5455/medscience.2020.09.201

Abstract

Although complete blood count (CBC) parameters in panic disorder (PD) are frequently studied, there is no data on panic attacks (PA). In this retrospective study, CBC parameters of patients diagnosed with PD (n=63) and PA (n=61) were compared with the data of healthy subjects (n=41). The groups were similar in terms of age (p=0.395) and gender (p=0.567). There were significant differences between the PD and the PA groups in terms of percentage of lymphocyte (p<0.001), lymphocyte count (p<0.001), neutrophil to lymphocyte ratio (p<0.001), platelet to lymphocyte ratio (p<0.001), basophil to lymphocyte ratio (BLR) (p<0.001), and monocyte to lymphocyte ratio (MLR) (p<0.001). Our findings suggested that the lymphocyte parameters were significantly higher and lymphocyte-related ratios were significantly lower in the PA group compared to the control and PD groups. Low basophil parameters were suggested to be significantly associated with PA, while neutrophil-related parameters were significantly increased in PD.

Keywords: Panic attack, panic disorder, lymphocyte, neutrophil, complete blood count

Introduction

The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) defines a panic attack (PA) as "an abrupt surge of intense fear or intense discomfort that reaches a peak within minutes." DSM-5 criteria for panic disorder (PD) include the experiencing of recurrent PAs, with one or more attacks followed by at least one month of fear of another PA or significant maladaptive behavior related to the attacks [1]. The lifetime prevalence of PAs is 13.2%. Among persons that ever had a PA, the majority had recurrent PAs, while only 12.8% fulfilled DSM-5 criteria for PD. Lifetime prevalence estimates were 1.7% for PD [2]. PA is one of the most often forms of anxiety, while PD is often a chronic condition. There may be differences between the complete blood count (CBC) parameters of acute and chronic diseases [3-6].

CBC is the most common laboratory test performed today [7]. It gives information about the production of all blood cells [8]. As with other psychiatric disorders [9-11], CBC parameters in PD were frequently studied [12-19].

***Coresponding Author:** Mehmet Hamdi Orum, Kahta State Hospital, Depatment of Psychiatry Clinic, Adiyaman, Turkey. E-mail: mhorum@hotmail.com

Red blood cell distribution width_coefficent of variation (RDW_CV) is the most emphasized parameter in these studies [16,17]. While Hamzekolaei et al. [17], Ransing et al. [18], and Asoglu et al. [16] reported an increase in RDW_CV, Gunduz et al. [19] and Gogcegoz-Gul et al. [14] did not report any significant alterations. Mean platelet volume (MPV) is another frequently studied marker in PD [14,15]. Some studies reported a significant decrease in PD compared to the control group [14,17,18], while others reported a significant increase [15,16]. According to the majority of studies, there is no significant difference between PD and healthy controls in terms of hemoglobin (HGB), platelet count (PLT), and mean corpuscular volume (MCV) values [12,14,19]. Studies on immune cell and lymphocyte-related ratios are limited. Gunduz et al. [19] reported that the lymphocyte count (LYM) increased in PD compared to the control group, Gurok et al. [12] reported that the LYM decreased. Both studies [12,19] stated that the neutrophil count (NEU) was similar between the PD and the control groups. Gunduz et al. [19] also did not find significance between the groups in terms of neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR). When studies investigating the relationship between PD and CBC are examined, it is seen that various findings are noticeable, and some CBC parameters have not been studied yet. According to our best knowledge, there are no studies on immune cell percentages, monocyte to lymphocyte ratio (MLR), eosinophil to lymphocyte ratio (ELR), basophil to

lymphocyte ratio (BLR). Also, considering that PD is a psychiatric disorder with high chronicity, and PA is an acute condition seen in PD, the hypothesis that CBC parameters will differ between these two conditions has come to mind. It was hypothesized that the differences between CBC values in PD reported in the literature may be due to the blood of attack or non-attack period. In this study, we aimed to compare the CBC parameters of PA, PD, and healthy control groups, especially lymphocyte-related ratios, percentages of immune cells.

Materials and Methods

Study Population

In this retrospective study, CBC parameters, especially white blood cell (WBC), red blood cell (RBC), HGB, hematocrit (HTC), MCV, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), RDW_CV, PLT, platelet distribution width (PDW), plateletcrit (PCT), MPV, NEU, LYM, and lymphocyte-related ratios, of patients diagnosed with PD and PA, were compared with the data of healthy subjects who were similarly distributed regarding age and gender. The control group consisted of healthy volunteers without a history of a PA and PD who were recruited from the hospital staff. When the number of cases in both patient groups reached 60's, a power analysis was performed, and the study was terminated because it was over 80.0%. This study was conducted in the psychiatry outpatient clinic of Kahta State Hospital. All the data of the study were obtained by the sole author. Consulted patients are also evaluated by the same physician. The interviews were conducted in an environment suitable for psychiatric examination. The diagnosis was made by the sole physician/author who conducted the interview. Panic attack and panic disorder states were determined according to DSM-5. Although the interviews did not include a structured scale, they included a detailed mental state examination. In addition to clinical judgment, patients with additional psychiatric disorders according to DSM-5 were not included in the study. Local ethics committee approval was obtained, and all study participants provided written informed consent (2020/3-23).

Inclusion Criteria

Patients with PD and PA who were diagnosed according to the DSM-5 [1] criteria were included. According to verbal statements and the ministry of health (e-Nabız) records, individuals who had not received long-term medical treatment for any condition in the past were included in the study. The entire PA group had the first attack and the PA group was directed from the emergency department. The blood of PA patients was taken before any treatment intervention in the first half-hour of the attack. PD group consisted of patients who applied directly to the psychiatric outpatient clinic. PD patients who had their most recent attack one week earlier were included in the study.,

Exclusion Criteria

Twenty-two patients with a benzodiazepine (BZD), 27 patients with an antidepressant (AD), 2 patients with antipsychotic (AP), 9 patients with AD plus AP, 7 patients with BZD plus AD, 1 patient with AD plus AP plus BZD, 3 patients with illicit drug use, 2 patients with ethyl alcohol use, and 15 patients with non-psychotropic drug use were excluded from the study. Individuals who had incomplete CBC information according to the patient registry system, patients with recurrent attacks were not included in the study. In this way, 21 patients were excluded from the study. Eight PD patients with attack symptoms were excluded. Patients –in total, 12 patients– who had a comorbid additional psychiatric diagnosis, hypertension, diabetes mellitus, severe neurological, immunological or systemic diseases, asthma, chronic obstructive lung diseases, cardiovascular disease, malign conditions according to the patient registry system were excluded. The group of healthy controls did not have any psychiatric diagnosis and systemic diseases which may affect the results. For the control group, in addition to the verbal statement, their consent was obtained and e-Nabız records were reached; It was confirmed that there was no previous chronic disease history. The physician who conducted the study confirmed that there was no infection, especially an upper respiratory tract infection, at present.

Statistical Analysis

Group sample sizes of 63 and 61 achieve 99.999% power to detect a difference of $\mu1 - \mu2 = 29.0 – 35.7 = -6.7$ using a two-sided Mann-Whitney U or Wilcoxon Rank-Sum test assuming that the actual data distribution is double exponential when the significance level (alpha) of the test is 0.150 and the standard deviation is 8.0 in both groups. Version 22.0 of SPSS (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp) was used for all statistical analyses.

The numerical data were expressed as means and standard deviations, and the categorical data were expressed as frequencies and percentages. Normal distribution suitability was assessed using visual and analytical methods (Kolmogorov–Smirnov/Shapiro–Wilk test). Student's t-test was used for normal distributions, and one-way ANOVA was used for three independent groups. Mann–Whitney U test and Kruskal Wallis test was used for those with no normal distribution. A posthoc Tukey Honestly Significant Difference test was used when a significant difference was found between the three independent groups.

The relationship between the variables was assessed by the Spearman correlation test. Receiver operating characteristic (ROC) curve analysis was used to measure the diagnostic value of LYM, RDW_CV, NEU. Binary logistic regression analysis was used. A value of less than 0.05 was considered statistically significant.

Results

PD group consisted of 63 (38 females, 25 males) subjects, PA group 61 (31 females, 30 males) subjects, and the control group consisted of 41 (23 females, 18 males) subjects (p=0.567). The mean age was 32.77 ± 9.19 years in the PD group, 30.54 ± 8.75 years in the PA group, and 32.02 ± 9.42 years in the control group (p=0.395). A comparison of the CBC values of the PD, PA, and control groups were given in Table 1. In Table 1, the groups that led to significant differences were specified (e.g., while there were significant differences between PD and control groups –expressed with the exponential numeral of "1"– and between PA and control groups –expressed with the exponential numeral of "2"– in terms of WBC, there is no significant difference between PD and PA groups.).

Table 1. Comparison of CBC Values of PD, PA, and Healthy Control Groups

	PD (n=63) Mean ± SD	PA (n=61) Mean ± SD	Control (n=41) Mean ± SD	p-value	η^2
Age (years)	32.78 ± 9.19	30.54 ± 8.75	32.02 ± 9.42	0.395	0.012
WBC (103/uL)	8.82 ± 2.58[1]	9.41 ± 2.71[2]	7.24 ± 1.31[1,2]	<0.001*	0.113
RBC (106/uL)	5.39 ± 0.52[1]	5.69 ± 0.68[1]	5.43 ± 0.91	0.036*	0.039
HGB (g/dL)	14.12 ± 2.13	13.58 ± 2.17	13.81 ± 2.31	0.345	0.012
HTC (%)	43.91 ± 6.38	45.34 ± 6.00	44.75 ± 6.15	0.602	0.010
MCV (fL)	81.99 ± 6.63	79.26 ± 6.11	80.95 ± 6.22	0.023*	0.035
MCH (pg)	25.85 ± 3.10[1]	23.51 ± 2.89[1]	24.70 ± 3.43	<0.001*	0.097
MCHC (g/dL)	31.38 ± 2.08[1]	29.45 ± 1.92[1]	30.47 ± 2.32	<0.001*	0.141
RDW_CV (%)	11.84 ± 1.69[1,2]	11.05 ± 1.33[1]	11.07 ± 0.82[2]	<0.001*	0.071
PLT (103/uL)	272.56 ± 73.94	266.96 ± 72.66	255.95 ± 78.08	0.265	0.008
PDW (fL)	19.80 ± 1.27[1]	19.20 ± 1.11[1]	19.74 ± 1.13	0.006*	0.054
PCT (%)	0.21 ± 0.04	0.20 ± 0.05	0.20 ± 0.04	0.149	0.021
MPV (fL)	8.11 ± 1.34	7.89 ± 1.59	7.98 ± 1.38	0.441	0.005
NEU (106/uL)	5.42 ± 2.19[1]	5.21 ± 1.99[2]	4.06 ± 1.24[1,2]	0.002*	0.077
LYM (103/uL)	2.53 ± 1.05[1]	3.27 ± 1.05[1,2]	2.32 ± 0.45[2]	<0.001*	0.159
MONO (103/uL)	0.53 ± 0.15	0.53 ± 0.29	0.48 ± 0.14	0.296	0.011
BASO (103/uL)	0.07 ± 0.04[1]	0.05 ± 0.05[1]	0.07 ± 0.03	<0.001*	0.040
EOS (103/uL)	0.17 ± 0.14	0.21 ± 0.22	0.18 ± 0.11	0.659	0.015
NEU%	60.93 ± 9.42[1,2]	54.60 ± 10.52[1]	56.64 ± 7.49[2]	0.001*	0.082
LYM%	29.02 ± 7.98[1]	35.70 ± 9.17[1,2]	31.98 ± 5.71[2]	<0.001*	0.118
MONO%	6.34 ± 1.70	5.89 ± 2.48	6.86 ± 2.17	0.061	0.031
BASO%	1.04 ± 0.83[1]	0.60 ± 0.53[1,2]	1.13 ± 0.87[2]	<0.001*	0.089
EOS%	2.04 ± 1.48	2.34 ± 2.06	2.57 ± 1.64	0.277	0.015
NLR	2.47 ± 1.89[1,2]	1.74 ± 0.96[1]	1.80 ± 0.62[2]	<0.001*	0.063
PLR	121.72 ± 55.90[1]	89.11 ± 37.14[1,2]	114.13 ± 46.36[2]	<0.001*	0.088
MLR	0.23 ± 0.08[1]	0.17 ± 0.09[1,2]	0.21 ± 0.07[2]	<0.001*	0.079
BLR	0.03 ± 0.02[1]	0.01 ± 0.01[1,2]	0.03 ± 0.01[2]	<0.001*	0.106
ELR	0.06 ± 0.04	0.06 ± 0.05	0.07 ± 0.04	0.224	0.010

*p<0.05, **p<0.001, Kruskal Wallis Test was used. Degree of Freedom (df, within groups) was 164. Exponential Arabic numerals in "Mean±SD" indicate a significant difference concerning p-value.

A comparison of PD and control groups was shown in Table 2.

ROC analysis was performed based on 104 subjects (63 PD, 41 control). The area under the ROC curve of RDW_CV for PD was 0.682 (p=0.002; 95% CI (0.572-0.791)); neutrophil count for PD was 0.697 (p=0.001; 95% CI (0.598-0.797)). The optimal cut-off score for RDW_CV was 11.12, and its sensitivity and specificity for the diagnosis of PD were 71.4% and 78.0%, respectively. The optimal cut-off score for the neutrophil count was 5.90, and its sensitivity and specificity for the diagnosis of PD were 36.5% and 97.6%, respectively (Figure 1).

ROC analysis was performed based on 102 subjects (61 PA, 41 control). The area under the ROC curve of PLR for PA was 0.714 (p<0.000; 95% CI (0.612-0.815)); BLR for PA was 0.713 (p<0.000; 95% CI (0.611-0.814)); BASO% for PA was 0.718 (p<0.000; 95% CI (0.615-0.822)); lymphocyte count for PA was 0.805 (p<0.000; 95% CI (0.722-0.889)). The optimal cut-off score for PLR was 107.35, and its sensitivity and specificity for the diagnosis of PA were 65.9% and 75.4%, respectively. The optimal cut-off score for BLR was 0.0337, and its sensitivity and specificity for the diagnosis of PA were 51.2% and 83.6%, respectively. The optimal cut-off score for BASO% was 1.2550, and its sensitivity and specificity for the diagnosis of PA were 41.5% and 86.9%, respectively. The optimal cut-off score for lymphocyte count was 0.4307, and its sensitivity and specificity for the diagnosis of PA were 53.7% and 86.9%, respectively (Figure 1).

According to the binary logistic regression analysis, the sensitivity of RDW_CV plus neutrophil count related to the diagnosis of PD was 53.7 percent and the specificity was 79.4 percent (Nagelkerke R2=0.282; -2 Log Likelihood (a): 115.199; [for RDW_CV, p=0.008, Exp(B) 0.504, 95% CI for EXP(B) 0.303-0.838] [for neutrophil count, p=0.001, Exp(B) 0.581, 95% CI for EXP(B) 0.421-0.801].

According to the binary logistic regression analysis, the sensitivity of lymphocyte count related to the diagnosis of PA was 65.9 percent and the specificity was 77.0 percent (Nagelkerke R2=0.363; -2 Log-Likelihood (a): 105.538; p<0.001, Exp(B) 0.163, 95% CI for EXP(B) 0.070-0.378).

Spearman's correlation test results were given in Table 3. There was only significant in the values expressed in Table 3; other correlations were not significant.

Table 2. Comparison of CBC Parameters of PD and Control Groups

Parameters	PD (n=63) Mean ± SD	Control (n=41) Mean ± SD	Cohen's d	Glass's delta	Hedges' g	p
WBC (103/uL)	8.82 ± 2.58	7.24 ± 1.31	0.77	0.61	0.72	<0.001**
RBC (106/uL)	5.39 ± 0.52	5.43 ± 0.91	0.05	0.07	0.05	0.216
HGB (g/dL)	14.12 ± 2.13	13.81 ± 2.31	0.13	0.14	0.14	0.556
HTC (%)	43.91 ± 6.38	44.75 ± 6.15	0.13	0.13	0.13	0.417
MCV (fL)	81.99 ±6.63	80.95 ± 6.22	0.16	0.15	0.16	0.378
MCH (pg)	25.85 ± 3.10	24.70 ± 3.43	0.35	0.37	0.35	0.082
MCHC (g/dL)	31.38 ± 2.08	30.47 ± 2.32	0.41	0.43	0.41	0.056
RDW_CV (%)	11.84 ± 1.69	11.07 ± 0.82	0.57	0.45	0.54	0.002*
PLT (103/uL)	272.56 ± 73.94	255.95 ± 78.08	0.21	0.22	0.21	0.120
PDW (fL)	19.80 ± 1.27	19.74 ± 1.13	0.04	0.04	0.04	0.855
PCT (%)	0.21 ± 0.04	0.20 ± 0.04	0.25	0.25	0.25	0.048*
MPV (fL)	8.11 ± 1.34	7.98 ± 1.38	0.09	0.09	0.09	0.545
NEU (106/uL)	5.42 ± 2.19	4.06 ± 1.24	0.76	0.62	0.72	0.001*
LYM (103/uL)	2.53 ± 1.05	2.32 ± 0.45	0.25	0.20	0.24	0.547
MONO (103/uL)	0.53 ± 0.15	0.48 ± 0.14	0.34	0.33	0.34	0.113
BASO (103/uL)	0.0790 ±0.0419	0.0716 ± 0.0394	0.18	0.17	0.18	0.167
EOS (103/uL)	0.17 ± 0.14	0.18 ± 0.11	0.07	0.07	0.07	0.517
NEU%	60.93 ± 9.42	56.64 ± 7.49	0.50	0.45	0.49	0.015*
LYM%	29.02 ± 7.98	31.98 ± 5.71	0.42	0.37	0.41	0.028*
MONO%	6.34 ± 1.70	6.86 ± 2.17	0.26	0.30	0.27	0.374
BASO%	1.04 ± 0.83	1.13 ± 0.87	0.10	0.10	0.10	0.345
EOS%	2.04 ±1.48	2.57 ±1.64	0.33	0.35	0.34	0.134
NLR	2.47 ± 1.89	1.80 ± 0.62	0.47	0.35	0.43	0.008*
PLR	121.72 ± 55.90	114.13 ± 46.36	0.14	0.13	0.14	0.367
MLR	0.23 ± 0.08	0.21 ± 0.07	0.26	0.25	0.26	0.530
BLR	0.0353 ± 0.0264	0.0317 ± 0.0165	0.16	0.13	0.15	0.834
ELR	0.0674 ±0.0463	0.0776 ± 0.0466	0.21	0.22	0.21	0.265

*p<0.05, **p<0.001, Mann-Whitney U Test was used.

Table 3. The Correlation Between Age and CBC Parameters of Three Groups

Parameters	PD (n=63) (r, p)	PA (n=61) (r, p)	Control (n=41) (r, p)
MCH	-0.142, 0.267	-0.009, 0.945	-0.362, 0.020*
RBC	-0.197, 0.123	-0.121, 0.351	0.532, <0.001**
BASO%	0.094, 0.462	-0.033, 0.803	-0.336, 0.032*
LYM	0.021, 0.871	0.381, 0.002**	-0.142, 0.377
EOS	-0.088, 0.494	0.319, 0.012*	0.041, 0.797
BASO	0.125, 0.329	0.023, 0.860	-0.496, 0.001**

*p<0.05, **p<0.001, Spearmen's Correlation Test was used.

Table 4. The Studies of CBC Parameters in PD

Studies	Diagnosis	RDW_CV	MPV	PDW	HGB	PLT	WBC	RBC	MCHC	PCT	MCV	L	M	E	B	N
This study (for PD, 38 females, 25 males)	DSM-5	↑	↔	↔	↔	↔	↑	↔	↔	↑	↔	↔	↔	↔	↔	↑
Gurok et al.12 (The year 2019; 25 females, 15 males)	DSM-IV-TR				↔	↔	↔	↔	↔		↔	↓	↔	↑	↑	↔
Asoglu et al.16 (The year 2016; 16 females, 14 males)	DSM-5	↑	↑			↔	↑									
Ransing et al.13 (The year 2017; 81 females, 52 males)	DSM-IV	↑	↓	↑	↔	↑	↔	↑	↓	↔	↔					
Hamzekolaei et al.17 (Year 2020; 31 females, 29 males)		↑	↓	↑		↓	↔	↓	↓		↔					
Gunduz et al.19 (Year 2018; 20 females, 19 males)	DSM-5	↔			↔	↔	↔				↔	↑				↔
Gökcegoz Gul et al.14 (Year 2014; 21 females, 16 males)	DSM-IV-TR	↔	↓	↔	↔	↔	↔									
Ransing et al.18 (The year 2020; 68 females, 30 males)	DSM-5	↑	↓	↑	↔	↑		↑	↓	↔	↔					
Kokacya et al.15 (Year 2015; 32 females, 29 males)	DSM-IV-TR		↑		↔	↔			↔							

↑: Significant increase compared to the control group; ↓: Significant decrease compared to the control group; ↔: No significant difference compared to the control

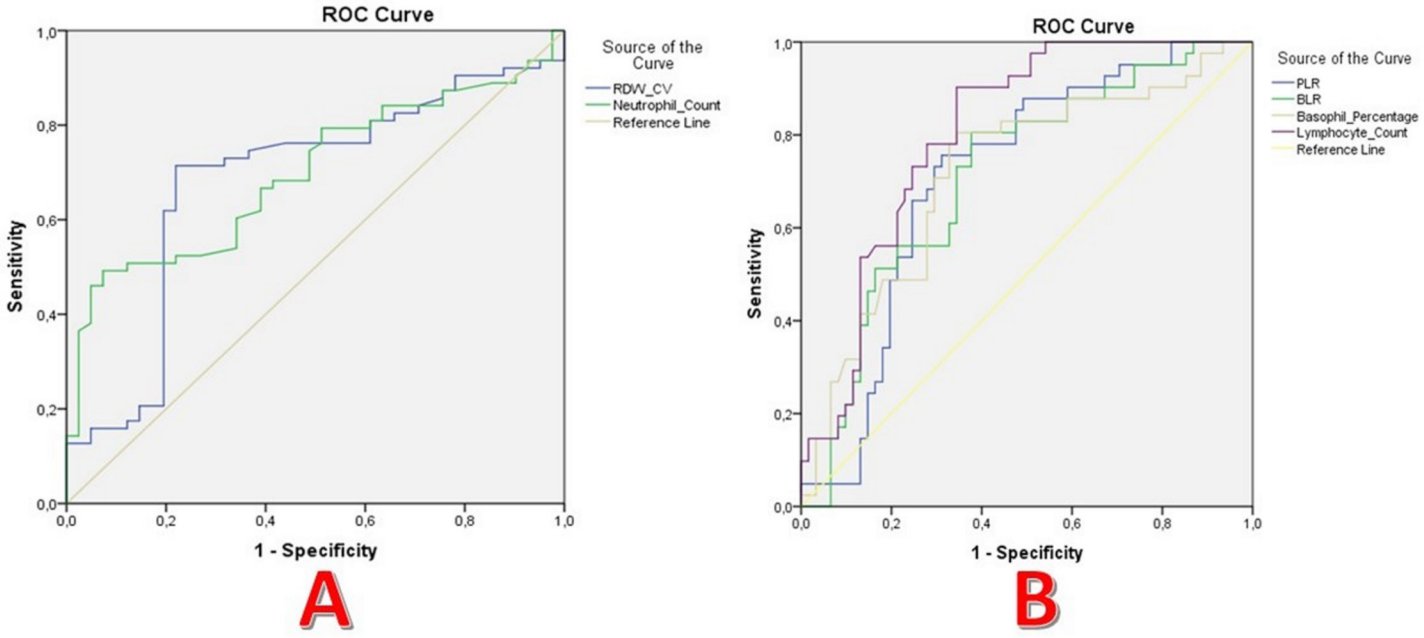


Figure 1. ROC Analysis Findings of PA and PD Groups in Terms of Some CBC Parameters A: PD and Healthy Control; B: PA and Healthy Control

Discussion

Our study suggests that the CBC parameters of PA and PD are demonstrated differently. PA is somewhere between PD and control in terms of RDW_CV, MCH, MCV, MCHC, and PDW values. Significant lowness of MLR, PLR, BLR in PA is associated with LYM increase. A remarkable low basophil was detected in PA. PD was characterized by the neutrophil increase. The reflection of the change in the count of immune cells to the percentages is different and should be taken into consideration when interpreting. Lymphocyte-related ratios were lower in the PA group compared to other groups due to increased LYM. Neutrophil was thought to be an important marker of specificity for the PD group. Lymphocyte parameters and lymphocyte-related ratios were also found to be highly specific for the PA group. Especially the relationship between lymphocyte count and the PA group and neutrophil count and PD group was evident (Figure 1).

The significance levels of the groups' NEU and BASO values and the ordering of the groups' NEU and BASO values were different than the significance level and order of the percentages of the same cells. This condition demonstrated the importance of investigating the immune cell percentage as well as the immune cell count in CBC studies. Gunduz et al. [19] reported that NLR and PLR were similar between PD and control groups. However, in our study, NLR was found to be significantly higher in the PD group than the control group, and the PLR value was similar among the groups.

Table 4 reveals the studies investigating the CBC parameters in PD. RDW_CV has been frequently investigated in PD and has been reported to be mostly elevated. Two studies reported that RDW_CV did not differ significantly between PD and control groups [14,19]. In our study, RDW_CV was found to be elevated in the PD group compared to both PA and control groups. Again, there was no significant difference between PA and control groups in terms of RDW_CV values. This finding suggested that the change in RDW_CV may be more related to the chronicity, not the acute condition. NEU and LYM have only been studied in two types of research [12,19], and their findings were inconsistent (Table 4). In our study, LYM and LYM% increase was associated with PA, and NEU and NEU% increase was associated with PD. While the NEU of PD and PA were similar, the control group's NEU was significantly lower than the patient groups. On the other hand, NEU% of PA and control groups were similar, while NEU% of PD was significantly higher than the PA and control groups. The RDW_CV and LYM findings of Gunduz et al. [19] suggested that the included patient blood results may be from any attack or immediately thereafter. Again, Gunduz et al. [19]'s study reported that NEU did not change significantly in PD. In our study, NEU was high in PD. In PA, NEU% was similar to the control group. This strengthened the possibility that patients included in the study of Gunduz et al. [19] may be PD patients during an acute attack. It is difficult to interpret since Gunduz et al. [19] does not provide information about the period during which the blood samples were taken. Gogcegoz et al. [14] reported that RDW_CV did not reveal a significant difference, while MPV decreased significantly. In our study, MPV was not significant but was lower in PA than PD and control groups (Table 1). These findings suggested the possibility that the blood results included in the study belong to the attack period.

It has been reported that CBC is associated with attack characteristics in psychiatric disorders. It is known that acute or chronic conditions affect CBC differently. Kalelioglu et al. [5] reported that manic and euthymic patients with bipolar disorder showed an increase in NLR and PLR compared to controls. Yildiz et al. [6] reported that NLR is higher in manic and euthymic patients, while depressive patients did not differ from controls in terms of NLR. Giynas-Ayhan et al. [3] stated that NLR was found to be significantly higher in manic, euthymic, and depressed patients with bipolar disorder compared to the control group. Ozdin and Boke [4] reported that NLR, PLR, and MLR values were significantly increased in the relapse period when compared with the remission period of the same patients with schizophrenia. It is suggested that the findings of their study [4] support the inflammation hypothesis of schizophrenia and there is a decrease in the inflammatory response in schizophrenia following treatment.

PA is an important component of PD, but it has an acute feature [2]. Considering that the effects of acute and chronic conditions on CBC can be different, the importance of comparing the CBC values of PD and PA becomes more important. Previous studies have compared CBC parameters between PD patients and control groups [12-19]. Our study is the first of its kind in the literature to compare the CBC values of PA and PD. Also, in our study, the immune cell percentages, MLR, ELR, and BLR of PD were compared for the first time with PA and the control group. The findings of our study support our hypothesis. Table 4 presents all the studies examining the relationship between PD and CBC in a single table. Through this table, it was aimed to compare all the studies in the literature, including the findings of our study.

Despite our significant findings, we have several limitations. The study's retrospective nature was an important limitation. There is a need for studies in which sociodemographic data, psychometric scales, and various inflammatory markers are handled together. Also, it is necessary to compare both attack and non-attack periods of PD in terms of CBC.

As a result, lymphocyte parameters were significantly higher in the PA group. Accordingly, lymphocyte-related ratios were found to be low in PA. Low basophil parameter was suggested to be significantly associated with PA, while neutrophil-related parameters were significantly elevated in PD. The numbers and percentages of the same cells were found to vary between the groups. Further studies can address PD longitudinally and elucidate CBC findings of PA and non-PA. This may also show us the difference between PA in PD and PA without PD.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
All authors declare no financial support.

Ethical approval
Local ethics committee approval was obtained, and all study participants provided written informed consent (2020/3-23).

References

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). Arlington, VA:2013.

2. De Jonge P, Roest AM, Lim CCW, et al. Cross-national epidemiology of panic disorder and panic attacks in the World Mental Health Surveys. Depress Anx. 2016;33:1155-77.

3. Giynas-Ayhan M, Çiçek IE, Inanlı I, et al. Neutrophil/lymphocyte and platelet/lymphocyte ratios in all mood states of bipolar disorder. Psychiat Clin Psych. 2017;27:278-82.

4. Ozdin S, Boke O. Neutrophil/lymphocyte, platelet/lymphocyte, and monocyte/lymphocyte ratios in different stages of schizophrenia. Psychiatry Res. 2019;271:131-5.

5. Kalelioglu T, Akkus M, Karamustafalioglu N, et al. Neutrophil-lymphocyte and platelet-lymphocyte ratios as inflammation markers for bipolar disorder. Psychiatry Res. 2015;228:925-7.

6. Yildiz M, Batmaz S, Songur E, et al. Simple markers for subclinical inflammation in the different phases of bipolar affective disorder. Arch Clin Psy. 2016;43:143-6.

7. Örüm MH. Basophil count, percentage of basophil, and basophil lymphocyte ratio in psychiatry practice: Current approaches and future directions. J Contemp Med. 2020;10:417-8.

8. Orum MH, Kara MZ, Egilmez OB, Kalenderoglu A. Are complete blood count alterations due to the opioid use: what about the lymphocyte-related ratios, especially in monocyte to lymphocyte ratio and platelet to lymphocyte ratio? J Immunoassay Immunochem. 2018;39:365-76.

9. Kara MZ, Orum MH, Egilmez OB. Relationship between immune cells and violent/nonviolent suicide attempts and controls: What about the lymphocyte-related ratios and neutrophil-related parameters? Kaohsiung J Med Sci. 2019;35:315-6.

10. Kara MZ, Örüm MH, Sekmen E. Is there a relationship between basophil, platelet-related parameters, and developmental stuttering? Anadolu Psikiyatri Derg. 2020;21:187-94.

11. Orum MH, Kara MZ. Platelet to lymphocyte ratio (PLR) in alcohol use disorder. J Immunoassay Immunochem. 2020;41:184-94.

12. Gurok MG, Yılmaz S, Temizkan A, et al. Levels of basophils and eosinophils are elevated while lymphocytes are reduced in patients with panic disorder compared to controls: a preliminary study. Psychiat Clin Psych. 2019;29:315-9.

13. Ransing RS, Patil B, Grigo O. Mean platelet volüme and platelet distribution width level in patients with panic disorder. J Neurosci Rural Pract. 2017;8:174-8.

14. Gögçegöz Gül I, Eryilmaz G, Ozten E, et al. Decreased mean platelet volume in panic disorder. Neuropsychiatr Dis Treat. 2014;10:1665-9.

15. Kokacya MH, Copoglu US, Kivrak Y, et al. Increased mean platelet volume in patients with panic disorder. Neuropsychiatr Dis Treat. 2015;11:2629-33.

16. Asoglu M, Aslan M, Imre O, et al. Mean platelet volume and red cell distribution width levels in initial evaluation of panic disorder. Neuropsychiatr Dis Treat. 2016;12:2435-8.

17. Hamzekolaei MG, Jafarisani M, Farajzadeh A, et al. Changes in mean platelet volume and hematologic indices in patients with panic disorder due to oxidative stress. Brain Behav. 2020;10:01569.

18. Ransing RS, Gupta N, Agrawal G, et al. Platelet and red blood cell indices in patients with panic disorder: A receiver operating characteristic analysis. J Neurosci Rural Pract. 2020;11:261-6.

19. Gunduz N, Timur O, Erzincan E, et al. The mean platelet volume, neutrophil lymphocyte ratio, platelet lymphocyte ratio and red cell distribution width in panic disorder. Anadolu Psikiyatri Derg. 2018;19:5-12.

Available online at www.medicinescience.org

ORIGINAL ARTICLE

Medicine Science International Medical Journal

Medicine Science 2021;10:132-5

Urinary bladder herniation in the differential diagnosis of inguinal hernia

Tayfun Kaya, Semra Demirli Atici

University of Health Sciences Tepecik Training and Research Hospital, Department of General Surgery, Izmir, Turkey

Received 17 August 2020; Accepted 13 October 2020
Available online 20.01.2021 with doi: 10.5455/medscience.2020.08.167

Abstract

Urinary bladder hernia is a clinical condition that mimics symptoms of inguinal hernia. It is vital to predict and prevent the iatrogenic bladder injury that may develop secondary to inguinal bladder herniation during inguinal hernia surgery, which is frequently performed, and to be able to determine our preoperative and perioperative surgical approaches. Patients with a diagnosis of inguinal hernia who underwent elective and emergency surgery between 2018 and 2020 were reviewed retrospectively. Age, gender, body mass indexes, imaging modalities, operation techniques, duration of hospital stay, perioperative and postoperative morbidity and mortality of the patients were recorded. Bladder herniation was found in seven patients, five of whom underwent elective surgery and two of whom underwent emergency surgery. The median age of the patients was 84 (min.52-max 89). Perioperative bladder injury was observed in two of the 6 patients who underwent computed tomography in the past year. Two patients, who had a bladder injury, underwent primary repair and were followed up with a foley catheter. Postoperative duration of hospitalization was 3.28 (2-7) days on average and the duration of hospitalization was prolonged up to an average of 6 (5-7) days in two patients with bladder injury. No postoperative mortality and morbidity were observed. It should be taken into consideration that there may be urinary bladder herniation in the differential diagnosis of inguinal swelling in patients presenting with symptoms of inguinal hernia at an advanced age. There is a need for methods that may reduce the morbidity and mortality secondary to bladder herniation.

Keywords: Inguinal hernia, bladder herniation, urinary leakage, bladder catheterization, surgery

Introduction

Inguinal hernia is one of the common diseases in general surgery practice and more than 20 million patients undergo inguinal hernia repair each year [1]. Almost any pelvic organ such as appendix, Meckel's diverticulum, omentum small intestine, colon, ovary, stomach and gallbladder can be located in the hernia sac [2]. Urinary bladder hernia (UBH) is a clinical condition involving less than 5% of all inguinal hernias [3]. The incidence of UBH, which is a rare condition, may be as high as 10% among obese men aged over 50 years [4,5]. UBH, which is often asymptomatic and where multiple factors are considered to be responsible for its etiology, is discovered incidentally during surgery or imaging studies performed [3,4].

The perioperative surprising encounter of the surgeons with this condition during inguinal hernia surgery performed very commonly may often lead to an increased rate of complications [3-5].

In this study, we planned to present the clinical demographic characteristics, perioperative and postoperative complications, and treatment modalities of the patients, who had surgery for an elective and emergency inguinal hernia and in whom bladder herniation was found, with the literature.

Materials and Methods

Patients with a diagnosis of inguinal hernia who underwent elective and emergency surgery at the tertiary Department of General Surgery between January 2018 and January 2020 were reviewed retrospectively via the Probel system. Bladder herniation was observed in seven patients among 978 patients. Seven patients were included in the study. Age, gender, body mass indexes, preoperative imaging modalities, operation techniques, mesh usage status, duration of hospital stay, perioperative and postoperative morbidity and mortality rates of the patients were recorded. A retrospective observational study was performed. Approval from University of Health Sciences Tepecik Training and Research Hospital institutional research ethics board was obtained (decision number 2020/12-1).

***Coresponding Author:** Tayfun Kaya, Department of Biomedical Engineering, Faculty of Technology, Selcuk University, Konya, Turkey
E-mail: kayatayfun@yahoo.com

Results

In this retrospective study of 978 inguinal hernia patients who underwent elective or emergency surgery, bladder herniation was observed in seven operated patients (0.71%). All patients were male with a median age of 84 (min 52- max89) years. Five patients (71.43%) had unilateral and two patients had bilateral (28.57%) inguinal hernias. Left inguinal bladder hernia was found in two patients (28.57%), right inguinal bladder hernia in five patients (71.43%) by imaging and perioperative surgery findings. No perioperative bladder necrosis was observed in any patient and no bladder resection was performed. It was observed that patients, who had elective surgery, had previous urology outpatient clinic admissions and therefore, non-contrast abdominal computed tomography (CT) performed in the last year revealed bladder herniation (Figure 1, Figure 2). Perioperative bladder herniation into the inguinal canal was seen in 6 patients and bladder herniation into the femoral canal in one patient. All patients were using medication due to benign prostatic hyperplasia (BPH). Perioperative bladder injury was observed in two elective patients who underwent non-contrast CT during the admission for their urinary complaints, primary repair of the bladder was performed in these patients and they were followed-up with Foley catheter along with the antibiotherapy support during service follow-up.

The mean body mass index (BMI) of the patients was found to be 21.74 kg/m^2 (19.6-28.8kg/m^2). The mean body mass index of the patients included in our study was observed to be lower compared to the literature. Except for one patient with high BMI, other patients had a normal BMI. We think that this is due to the small patient group and especially when the age distribution is analyzed, due to non-homogeneous distribution secondary to having a patient group, most of which are aged 80 years or older. Although BH is most commonly observed in the 5th-7th decades, all patients in our study were over 80 years old, except for two patients. The American Society of Anesthesiologists (ASA) score of one patient who had elective surgery was 2 and the ASA score of the other four patients was 3. The ASA score of two patients who had emergency surgery due to incarcerated hernia was 3E.

The hernia of one patient who had emergency surgery was repaired primarily and mesh reinforcement was used in the other 6 patients. Except for one patient, concomitant comorbidities and high ASA scores of the patients caused them to be followed up in the intensive care on the first postoperative day. We believe that this had an impact on the total duration of hospitalization and is an effective factor in prolonging the mean duration of hospitalization. In addition, the duration of hospitalization was observed to be prolonged up to 7 days due to perioperative bladder injury in 2 patients. After confirming that there was no urinary leakage following postoperative cystograms, two patients with bladder injury were discharged on appropriate antibiotherapy after their foley catheters were removed. No urinary tract infection or recurrence was seen during the postoperative follow-up of the patients. Perioperative bladder injury was observed in two patients and no postoperative mortality and morbidity were seen.

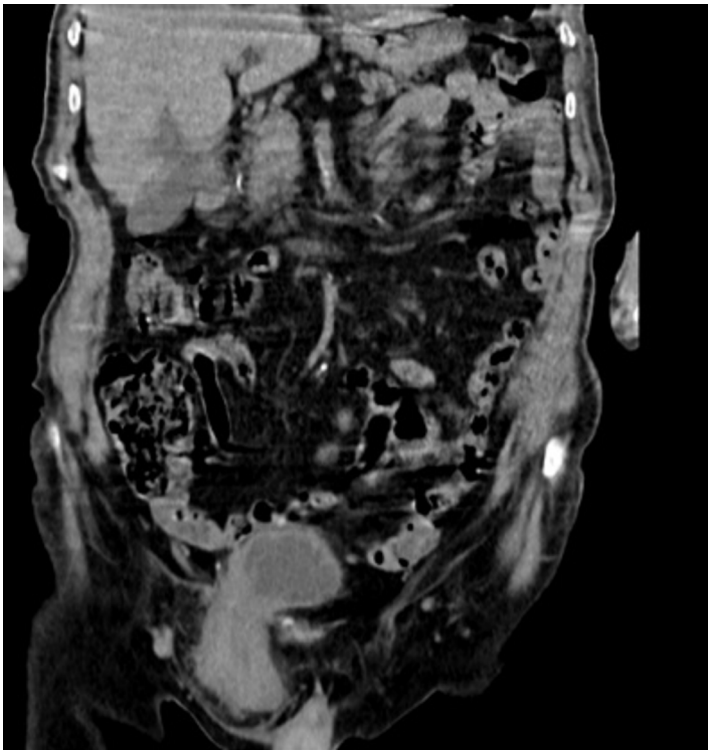


Figure 1. The coronal view of a bladder herniated into the right inguinal canal on CT scan

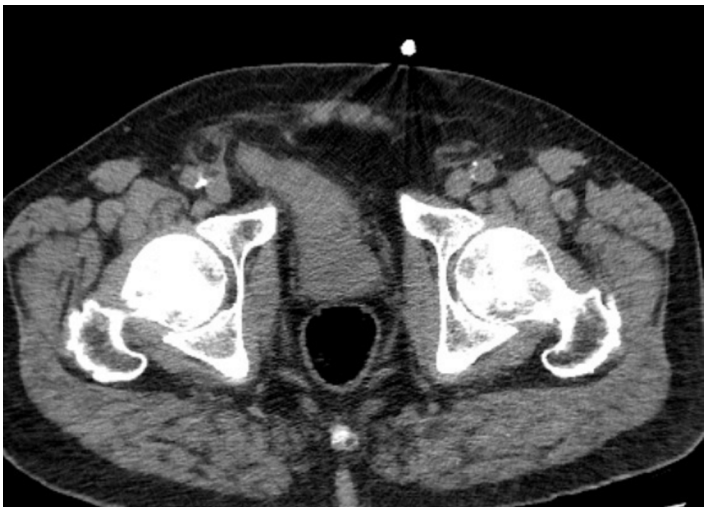


Figure 2. The axial view of a bladder herniated into the right inguinal canal on CT scan

Discussion

Inguinal UBH accounts for 1-4% of all inguinal hernias [3,4]. UBH is divided into three subgroups depending on its relation to the peritoneum: extraperitoneal, paraperitoneal, and intraperitoneal [5]. Paraperitoneal hernia is the most common type [5,6]. The herniation may involve a small area from any portion of the bladder or may include the whole bladder [3,5]. Although herniation is frequently observed in the inguinal (75%) and the femoral canal (23%), UBH can also happen across the obturator, ischiorectal and abdominal peritoneal openings by 2% [5-7].

The incidence of UBH in case series and review studies in the literature has a male dominance [6. Branchu et al [3] reported

an incidence of 95.3% in men, similar to our study. Although the inguinal hernia side was not reported in this study, Kraft et al and Lee et al have reported that the bladder herniation was predominantly in the right inguinal region in their case series, similar to our study [4,6].

Multiple factors such as male gender, advanced age, obesity, BPH, weakness of the pelvic floor muscles, adhesion of the bladder wall to perivesical adipose tissue, decreased bladder tone, bladder diverticulum, tumoral mass leading to urinary obstruction, bladder stone play a role in UBH etiopathogenesis [3-6]. All patients in our study had male sex and BPH as risk factors. No bladder diverticulum, stone, or tumoral mass was seen in the patients. In the study conducted by Lee et al [6], the mean age was reported to be 71 years and the advanced age was emphasized to be a risk factor. The mean age of the patients included in our study was 84 (min 52- max 89) years and the patients in our study had a higher mean age compared to the study conducted by Lee et al [6].

12.7% of patients with UBH are asymptomatic [3-5]. Symptoms, including pain and swelling in the inguinal area, size reduction of inguinal mass after voiding (Mery's sign), dysuria, hematuria, increased urination by pressing on the swelling area, nocturia, urinary urgency, urinary retention, increased frequency of voiding are the most common presenting complaints [3,4]. In addition, UBH may also have severe clinical manifestations such as acute renal failure, and vesicocutaneous fistula. All patients in our study had complaints of swelling in the inguinal region (100%) and pain in the inguinal region (100%). In a systematic review study conducted by Branchu et al.3, it was observed that 60.3% of the patients had inguinal swelling and 39.7% of the patients had inguinal pain, these complaints were similar to common presenting complaints observed in patients with typical inguinal hernia [3.

Less than 7% of UBH can be diagnosed preoperatively, while 16% can be diagnosed postoperatively due to complications such as iatrogenic bladder injury and urinary leakage [6. In our study, two patients who developed bladder injury were detected perioperatively and surgical primary repair was performed. If the bladder herniation is missed out, it may result in serious complications such as vesicoureteral reflux, vesicocutaneous fistula, bladder rupture, hydronephrosis, necrosis secondary to strangulation, and even death [3,6].

Among the preoperative imaging modalities, especially cystography and CT are outstanding imaging modalities. Although many studies advocate cystography as the gold standard, compared to CT, both imaging modalities have some advantages over each other [7-11]. Compared to cystography, CT has a higher rate of predicting structures within the hernia sac and excluding other non-hernia causes [8,9]. There are studies reporting that performing CT especially in the prone position in these patients may provide an advantage in diagnosis. These studies stated that diagnostic accuracy would be higher because it is easier for the contrast agent to pass to the herniated bladder region on images taken in prone position [10,11]. USG, on the other hand, has a lower sensitivity and specificity for the diagnosis compared to cystography and CT [8-11]. In our study, 7 patients who underwent surgery had preoperative superficial tissue USG, and bladder herniation was observed in none of them. On the contrary, superficial tissue ultrasonography stated that there was a herniated bowel loop view. Although performing preoperative CT does not eliminate the risk of urinary injury, it is obvious that CT is superior in diagnosing and revealing the contents of the hernia sac compared to USG [8-10]. In our study, bladder injury was observed in two of six patients who had undergone CT in the past year for previous urological complaints. Although it is possible to have detailed information about the contents of hernia sac with computed tomography that can be performed routinely in all patients in the risk group, this is a costly condition and cannot be expected to be a highly feasible method in routine clinical practice. Also, routine CT may not reduce the risk of developing bladder injury, as in our study.

There is no standardization and there are different opinions for the treatment of bladder herniation due to cases reported frequently on a case-by-case basis and few studies in the literature. Although conventional surgery (80.7%) methods have been often used, it has been reported that laparoscopic (6.5%) and robotic surgery (2.2%) were also used [3,6]. The most commonly used technique in conventional surgery is Lichtenstein with a rate of 32.7%, followed by Bassini, Mac Way, Shouldice methods, respectively. The mesh was reported to be used in the hernia repair by 34.8%. In our study, Lichtenstein (85.7%) was preferred as the most common method and Mac Way (14.2%) method was used in one patient.

Foley catheters were not inserted in any patient who was included in our study, had UBH, and had elective surgery, and bladder injury was observed in 2 (40%) of 5 patients who had elective surgery compared to all operated patients (28.5%). As the preoperative foley catheterization was performed in both patients, who had emergency surgery, we believe that palpation of the balloon of the foley catheter in the area considered to be a hernia sac guides us and reduces the risk of bladder injury. Foley catheterization, which is a simple, inexpensive, and easily applicable method, can be considered as a factor that may reduce the rate of perioperative bladder injury. In our study, we think that prophylactic antibiotherapy given preoperatively and early foley catheter removal in patients without bladder injury may have a role in the absence of the urinary system infection secondary to bladder catheterization in any patient.

Although the number of patients included in our study is limited, performing lower abdominal CT, a preoperative non-invasive method, and bladder foley catheterization, an invasive method, are methods that reduce the risk of perioperative bladder injury and may decrease the mortality that may develop in patients with comorbidities in this advanced age group secondary to postoperative urinary leakage [8,9]. When evaluated on the cost basis, we believe that bladder foley catheterization may be an easily accessible and applicable method.

Conclusion

In conclusion, it should be kept in mind that inguinal bladder herniation may be found in the differential diagnosis of inguinal swelling, especially in patients with advanced age who had inguinal hernia symptoms as well as urinary symptoms. Although not compatible with the literature, BMI was lower in the patient group included in our study, and the mean age of occurrence was found to be higher compared to the literature. Having a bladder injury in two patients who underwent preoperative CT suggests that imaging may not eliminate the risk of perioperative complications

but may decrease it. Prospective studies with a large number of cases on this subject are warranted.

Acknowledgements
I would like to express my gratitude to Professor Cengiz Aydın and Associate Professor Mustafa Emiroğlu for advices drafting the study. We thank our colleagues from University of Health Sciences Tepecik Training and Research Hospital, Department of General Surgery who provided insight and expertise that greatly assisted the research. Thanks to all the peer reviewers and editors for their opinions and suggestions.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
All authors declare no financial support.

Ethical approval
Approval from University of Health Sciences Tepecik Training and Research Hospital institutional research ethics board was obtained (decision number 2020/12-1).

References

1. HerniaSurge Group. International guidelines for groin hernia management. Hernia. 2018;22:1-165.
2. Linder S, Linder G, Månsson C. Treatment of de Garengeot's hernia: a meta-analysis. Hernia. 2019;23:131-41.
3. Branchu B, Renard Y, Larre S, et al. Diagnosis and treatment of inguinal hernia of the bladder: a systematic review of the past 10 years, Turk J Urol. 2018;44:384-8
4. Kraft KH, Sweeney S, Fink AS, et al. Inguinoscrotal bladder hernias: report of a series and review of the literature. Can Urol Assoc J. 2008;2:619–23.
5. Moufid K, Touiti D, Mohamed L. Inguinal bladder hernia: four case analyses. Rev Urol. 2013;15:32–36.
6. Lee TH, Huang CN, Huang SP, et al. Inguinoscrotal herniation of bladder: Case series and literature review, Eur Surg 2014;46:74–8.
7. Bisharat M, O'Donnell ME, Thompson T, et al. Complications of inguinoscrotal bladder hernias: a case series. Hernia. 2009;13:81–4.
8. Bjurlin MA, Delaurentis DA, Jordan MD, et al. Clinical and radiographic findings of a sliding inguinoscrotal hernia containing the urinary bladder. Hernia. 2010;14:635–8.
9. Gadodia A, Parshad R, Sharma R. Bladder hernia: Multidetector computed tomography findings. Indian J Urol. 2011;27:413.
10. Bacigalupo LE, Bertolotto M, Barbiera F, et al. Imaging of urinary bladder hernias, Am J Roentgenol. 2005 184:2.546-51.
11. Cavallaro G, Cittadini G, Loria G, et al. Su un caso di ernia vescicale associata a mixoma ovarico. Radiol Med (Torino). 1993;85:293 –4.

Available online at www.medicinescience.org

ORIGINAL ARTICLE

Medicine Science International Medical Journal

Medicine Science 2021;10(1):136-40

Dieulafoy's lesion as a rare cause of gastrointestinal bleeding: a single-center experience

Ferit Celik, Ali Senkaya, Nalan Gulsen Unal, Seymur Aslanov, Abdullah Murat Buyruk, Fatih Tekin, Ahmet Omer Ozutemiz

Ege University, Faculty of Medicine Department of Gastroenterology, Izmir, Turkey

Received 24 August 2020; Accepted 02 October 2020
Available online 20.01.2021 with doi: 10.5455/medscience.2020.08.173

Abstract

To define the clinical characteristics of Dieulafoy's lesion (DL),determine the localization features, and investigate endoscopic treatments and their results. This retrospective study included 20 patients who presented to the Department of Gastroenterology due to gastrointestinal (GI) bleeding between January 2015 and December 2019 and were diagnosed with DL. Age, gender, comorbidities, medications used, presentation findings, hemoglobin and hematocrit values at the time of presentation, number and type of transfusions if applied, length of hospitalization in days, mortality/survival, and endoscopic procedure parameters, including the number of procedures, localization of DL, type of bleeding stigmata, and the applied technique were recorded for all patients. Ten (50%) of the patients were women, and the mean age of all patients were 66.8±17.8 years. One or more comorbidities were present in 90% of the patients. The use of acetyl salicylic acid (ASA) was present in five (25%) patients, ASA+ clopidogrel in five (25%), warfarin in two (10%), and non-steroidal anti-inflammatory drugs in two (10%). The most common complaint was observed to be hematemesis and/or melena in 16 patients (80%). DL was most frequently seen in the stomach (n=10; 50%) where it was most commonly located in the proximal corpus (n=6; 60%). The most prevalent bleeding stigma was active bleeding, which was seen in nine (45%) patients during endoscopy. Eight (40%) patients received endoscopic treatment combined with a mechanical method, and nine (45%) patients only received a mechanical treatment (endoscopic band ligation or hemoclip). The median number of hospitalizations was five days (2-22). Transfusion was required by 13 patients (65%). The mortality rate was determined as 5%. DL should be considered especially in older patients with chronic diseases who present with recurrent GI bleeding. An endoscopic examination is the first method to be applied in the diagnosis and treatment of DL. Mechanical methods should be prioritized in endoscopic treatment.

Keywords: Gastrointestinal system, bleeding, Dieulafoy's lesion, endoscopic treatment

Introduction

Although advances in the treatment of causes leading to acute gastrointestinal (GI) bleeding have significantly reduced the number of bleeding cases, it is still a major cause of morbidity and mortality. The annual incidence of GI bleeding ranges from 50 to 150 per 100,000 [1], and related mortality is around 5-10% [2]. The most common cause of GI bleeding is peptic ulcer, and one of the rare causes is Dieulafoy's lesion (DL). DL is a submucosal arterial formation that protrudes from a small mucosal defect anywhere in the GI tract and leads to massive GI bleeding, especially in the elderly[3]. Also known as a 'caliber persistent artery', DL has an incidence of0.3% to 6.7% [1,4,5].

DL was first described as an aneurysm in the stomach by Gallard in 1884, but the actual clinician that named this lesion and demonstrated its clinical characteristics was Paul Georges Dieulafoy[6]. The majority of DLs occur in the proximal stomach, but they can also be localized in the esophagus, small intestine, and large intestine [7,8].

The first step in the diagnosis of DL is GI endoscopy. However, even experienced endoscopists can overlook the diagnosis of DL. In cases where no focus is detected on endoscopy, angiography and/or endoscopic ultrasonography can be used [5]. The treatment options include band ligation, thermoregulation, bipolar electrocoagulation, sclerotherapy and endoscopic hemoclip. The success rate with endoscopic treatment methods is 75-100% [9]. In cases where treatment cannot be successfully provided by endoscopic techniques, surgical treatment options should be considered [10,11].

***Coresponding Author:** Ferit Celik, Ege University, Faculty of Medicine Department of Gastroenterology, Izmir, Turkey
E-mail: drferitcelik35@yahoo.com.tr

The purpose of this retrospective study was to define the clinical characteristics of DL, determine the localization of this lesions, and investigate the endoscopic treatments applied and their results.

Materials and Methods

This retrospective single-center study included patients that underwent endoscopy due to GI bleeding and were diagnosed with DL at the Department of Gastroenterology between January 2015 and December 2019. Patients were screened by searching the term 'Dieulafoy' lesion' in the Endocam system, and their endoscopy reports were obtained. Using the esophagogastroduodenoscopy and ileocolonoscopy reports of the patients, the data concerning the location of DL, bleeding stigma type, localization in the stomach, endoscopic treatment methodapplied, number of hemoclipsused, and number of endoscopic procedures required were recorded. In addition, age, gender, comorbidities, medications used, presentation findings, hemoglobin, hematocrit, platelet and international normalized ratio values, number and type of transfusions if applied, length of hospital stay in days, and mortality/survival status were obtained from the hospital electronic database and recorded in the case report forms.

Endoscopic examinations were performed using Olympus GIF-HQ190 esophagogastroduodenoscopy and Olympus CFH-170L-CFQ-150 Lileocolonoscopy devices by a gastroenterology specialist or a sub-branch specialist under the supervision of a gastroenterology specialist, accompanied by an endoscopy nurse. DL, usually diagnosed by endoscopic examination, is defined as a pigmented protuberance from the vessel stump with minimal surrounding erosion and no ulceration but sometimes caused actively bleeding or oozing [12] (Figure 1). The treatments were classified as endoscopicsclerotherapy, endoscopic band ligation (EBL), and endohemoclip application. Endoscopic sclera therapy was performed using adrenaline diluted with saline to 1/10,000 and/or 1% Aethoxysklerol, EBL using a Speedband Superview Super 7 ™ Boston multiple band ligament set, and the endoscopic hemoclip was Quick Clip 2™ Olympus hemoclip. EBL and endoscopic hemoclip application were accepted as mechanical methods. Endoscopic treatment combined with a mechanical method was defined as adrenaline + hemoclip, adrenaline + Aethoxysklerol+ hemoclip, adrenaline + Aethoxysklerol+ EBL,oradrenaline + EBL.

For the statistical analyses, SPSS Statistics ver. 22.0 (SPSS Inc. Chicago, IL. USA) was used. The conformance of variables to normal distribution was examined by visual (histogram) and analytical methods (Shapiro-Wilk test). Numerical data were expressed as median, standard deviation, maximum and minimum values and categorical data were given as descriptive statistics, such as rate and percentages. Student's t-test was conducted to determine whether there was a statistical difference in the mean values of the numerical variables of age and hemoglobin according to gender. Values with a p value below 0.05 were considered statistically significant.

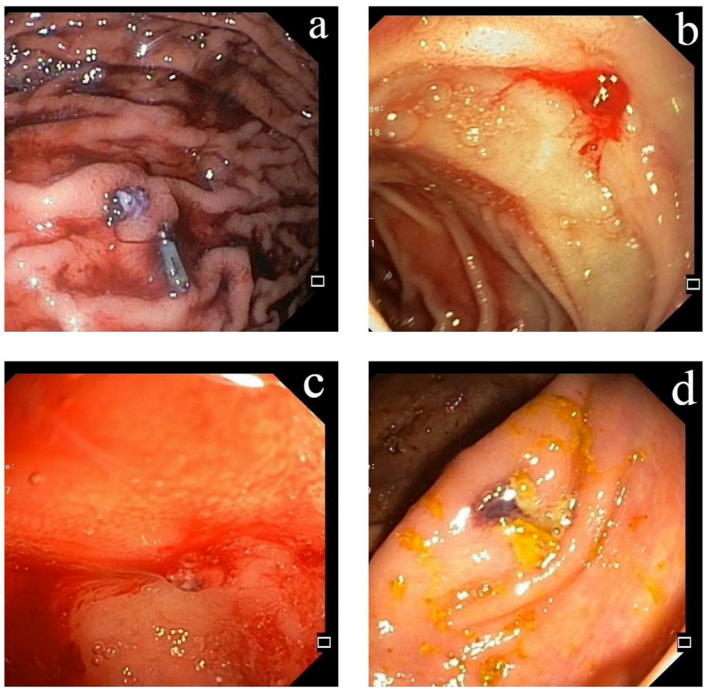


Figure 1. Location of Dieulafoy's lesions in gastrointestinal system. a-stomach, b- duodenum, c-ileum, d-colon (Achieved from the archive of the Ege University Gastroenterology Department Endoscopy Unit)

Results

Of the 20 patients diagnosed with DL, 10 (50%) were female and 10 (50%) were male, with a mean age of 66.8 ± 17.8 years. The mean age of women was 68.4 ± 23.4 years, and that of men was 65.2 ± 10.8 years. One or more comorbidities were present in 90% of the patients. The presentation findings were hematemesis in eight patients (40%), hematochezia in four (20%), hematemesis and melena in three (15%), melena alone in three (15%), and hematemesis and hematochezia in two (10%).At the time of presentation, the median values of hemoglobin and hematocrit were measured as 8.10g/d Land 24.8%, respectively. Table 1 presents the demographic, clinical and laboratory features of the patients.

When the distribution of DLs in the GI system was examined, it was most frequently seen in the stomach (n = 10; 50%). The localization of DL was determined as the second segment of the duodenum in three (20%) patients, colon in three (15%) patients, bulbus in two (10%) patients, terminal ileum in one (5%) patient, and esophagus in one (5%) patient. Within the stomach, the most common localization of DL was the proximal corpus (n = 6; 60%), followed by the fundus (n = 2; 20%), antrum (n =1; 10%), and cardia (n = 1; 10%). During endoscopy, active bleeding was present in nine (45%) patients, protuberance from the vessel stump in eight (40%), and vessels with clots in three (15%). The endoscopic data of the patients are shown in Table 2.

When the endoscopic treatments were examined, combination therapy with a mechanical method was applied in eight (40%) patients, hemoclipalone in seven (35%), EBL alone in two (10%), sclerotherapy with 1/10,000 adrenaline alone in two (10%), and

sclerotherapy with 1/10,000 adrenaline+1% Aethoxysklerol in two (10%). The number of median hemoclip was three [1-5] in patients who underwent this procedure. There was no statistically significant difference in the comparison of the EBL andhemoclip method. The median number of hospitalization days was five [2-22]. Thirteen (65%) patients required a transfusion, for which only erythrocyte suspension (ES) was used in 11 (55%) patients, ES + apheresis platelet suspension in one patient (5%), and ES + fresh frozen plasma replacement in another patient (5%). For those requiring a transfusion, the median (min-max) unit of ES given was three [1-8]. The mortality rate amongthe patients hospitalized due to DL was 5%. Table 3 presents the treatment and clinical follow-up data of the patients.

Table 1. Demographic, clinical and laboratory characteristics of the patients

	n (%)
Age (mean± SD)	66.80±17.86
Gender (n=20)	
Female	10 (50)
Male	10 (50)
Comorbidities	
Coronary artery disease	10 (50)
Hypertension	9 (45)
Diabetes mellitus	5 (25)
Medications used (n=20)	
Acetylsalicylicacid (ASA)	5 (25)
ASA+Clopidogrel	5 (25)
Warfarin	2 (10)
NSAID	2 (10)
Unknown	6 (30)
Presentation complaint (n=20)	
Hematemesis	8 (40)
Hematochezia	4 (20)
Melena	3 (15)
Hematemesis and melena	3 (15)
Hematemesis and hematochezia	2 (10)
Laboratory parameters	**Median (min-max)**
Hemoglobin (g/dl)	8.1 (3.6-12.9)
Hematocrit(%)	24.75 (11.7-39.2)
Platelet (10^3/µL)	241.5 (93-371)
INR	1 (0.9-3.1)

INR: International normalized ratio, NSAID: Non-steroidal anti-inflamatory drug.

Table 2. Endoscopic data of the patients

Parameters	n (%)
Locationof lesion (n=20)	
Stomach	10 (50)
Duodenum second segment	3 (15)
Colon	3 (15)
Bulbus	2 (10)
Esophagus	1 (5)
Terminal ileum	1 (5)
Localization of lesions within the stomach (n=10)	
Proximal corpus	
Greater curvature	3 (30)
Lesser curvature	3 (30)
Cardia	1 (10)
Fundus	2 (20)
Antrum	1 (10)
Endoscopic findings (n=20)	
Active bleeding	9 (45)
Pigmented protuberance from the vessel stump	8 (40)
Vessels with clots	3 (15)

Table 3. Treatment and clinical follow-up data of the patients

Treatments applied (n=20)	**n(%)**
Combination with a mechanical method	8 (40)
Adrenalin+hemoclip	3 (15)
Adrenalin+Aethoxysklerol+hemoclip	3 (15)
Adrenalin+Aethoxysklerol+EBL	1 (5)
Adrenalin+EBL	1 (5)
Hemoclip	7 (35)
EBL	2 (10)
Adrenalin+Aethoxysklerol	2 (10)
Adrenalin	1 (5)
Outcome (n=20)	
Mortality	1 (5)
Surviving	19 (95)
Transfusion requirement (n=20)	
Present	13 (65)
ES	11 (55)
ES+platelet suspension	1 (5)
ES+FFP	1 (5)
Absent	7 (35)
	Median (min-max)
Number of ES units	3 (1-8)
Number of hemoclip used	3 (1-5)
Number of endoscopic procedures applied	1 (1-2)
Number of hospitalized days	5 (2-22)

EBL: endoscopic band ligation, ES: erythrocyte suspension, FFP: fresh frozen plasma

Discussion

DL is a rare emergency gastroenterological condition that leads to massive bleeding, sometimes overlooked on endoscopy. It is more common in older men and often accompanied by comorbidities.

Mortality in DL has been reduced with the widespread use of endoscopy and is around 5-10% in the literature [2,13]. In studies conducted in Turkey, DL-related mortality has been reported to range from 3.7 to 38.9% [14,15]. In a study conducted in our center in 1998, the mortality rate was determined to be 8% in patients with DL localized in the stomach [16]. In our study, we calculated the mortality rate as 5%. Only one of our patients died, and the cause of mortality in this patient was not bleeding; it was hospital-acquired pneumonia. The reasons for the lower mortality rate in our study compared to the literature may be thatour hospital isa tertiary reference center, endoscopyis performed early in cases of active GI bleeding, and an advanced endoscopy specialist and academician is oncall when needed for the endoscopy procedure.

In the literature, it has been reported that DL is more common in men (55.6%-66.6%) [3,14-16]. In our study, this rate, unlike the literature, was equal in males and females, which was probably due to the limited number of our patients. Advanced age has been determined as a risk factor for DL [17]. In studies conducted, the mean age has been reported to be 73-79 years [3,14]. In our study, the mean age of the patients was calculated as 66.8 years, similar to the literature. The possible reasons for this finding may be the elongation of the submucosal artery, development of mucosal atrophy in the stomach, and the increased use of non-steroidal anti-inflammatory drugs and ASA that can cause ischemic damage in the stomach, with age [12].

Comorbidities have been reported in approximately 70.8% of patients with DL, most commonly in the form of diabetes mellitus, hypertension, chronic kidney failure, and coronary artery disease. In addition, the most frequently used drugs among these patients have been determined as NSAIs, ASA, and warfarin [1,9,15]. Similarly, in our study, 90% of patients had one or more comorbidities, with the most common being coronary artery disease, hypertension, and diabetes mellitus. The information on the medications used by the patients was obtained for 70% of the cases, and the types of drugs used were, in order of frequency, ASA, ASA + clopidogrel, warfarin, and NSAI, which is in agreement with the literature.

Most of the DL cases present with melena and/or hematemesis. In many studies, melena (75-33%) has been evaluated as the most common reason for presentation to hospital in this patient group [1,9,14,15]. In one study, hematemesis (60%) was the most common presentation finding [3]. In our study, consistent with the literature, the most common patient presentation was hematemesis and/or melena (70%), which is probably because in the majority of our cases, DLs originated from the upper GI.

In previous studies, the average requirement of transfusion has been reported as 2-3 units of ES [3,15], which is similar to the value we obtained in our study (2.5 units of ES). The possible reason for this transfusion requirement is massive bleeding.

The most common location of DL in the GI system is the stomach [18]. Within the stomach, 46.6-66.6% of DLs are reported to be localized in the corpus and 59.2% in the fundus [3,14,15]. However, approximately one-third of the lesions are extragastric, which are most often located in the duodenum, followed by the colon [1,7,8]. In addition, there are cases in the literature defined in the bronchi other than the GI system[13].In our study, the most common location of DLs in the GI system was the stomach (50%). Within the stomach, DLs were most frequently seen in the proximal corpus at 60%, and as extragastric locations, the duodenum and colon were most observed. One of the possible reasons for the frequent occurrence of DLs in the stomach may be that vibrations in a large submucosal vein in this area lead to the disruption of the upper epithelium, while another reason may be considered as gastric abrasion and wear increasing thrombosis within the artery and subsequently leading to necrosis [18,19]. In the colon and rectum, solid content can lead to mucosal stercoral ulcers, resulting in rupture and hemorrhage [1].

There is no consensus on the treatment of DL. The location of the lesion depends on the presence of active bleeding and the technical competence and experience of the specialist. With the development of endoscopic methods, the need for surgery in DL has significantlydecreased. In endoscopic treatment, there are thermal (electrocoagulation and argon plasma coagulation), local injection (epinephrine and Aethoxysklerol) and mechanical (EBL and hemoclip) methods [20]. Using endoscopic treatment methods, the success rate has been shown to vary between 75 and 100% [21,22]. In the literature, it has been reported that the rates of recurrent bleeding and hemostasis failure were higher in patients who underwent epinephrine injection or heater probe coagulation alone compared to those also receiving mechanical treatments. This has brought endoscopic mechanical methods to the fore in DL treatment [10,23,24]. The success rates of DL with hemoclip treatment have been observed to range from 94 to 95.2% [25-27]. In our study, similar to the literature, there is no significant difference between EBL and hemoclip in terms of efficacy or safety [9,21]. Today, most endoscopists prefer the combined treatment of hemoclip and injections as the primary treatment [21,28,29]. Similarly, in our study, the most preferred treatment methods were mechanical and/or combination therapy, and our success rate was 95%.

In the literature, the median duration of hospitalization has been reported as 10.5 (1-28) days, and the mean duration ass even days (3,14). In our study, the median and mean lengths of hospital stay were five (2-22) days and 7.6 days, respectively, which is similar to the literature.

Since our center is more experienced in mechanical methods, thermal coagulation is not used sufficiently. One of the limitations of our study is that we do not have data on thermal coagulation method, so mechanical methods cannot be compared with thermal coagulation methods. Other limitations of our study can be considered as retrospective design and small sample size.

DL is a rare cause of GI bleeding, which had high morbidity and mortality before the widespread use of endoscopy. The pathogenesis of DL has not yet been fully elucidated. DL should be considered in patients with chronic diseases presenting with GI bleeding for whom an etiological cause cannot be identified on the first endoscopy, as well as in those presenting with recurrent bleeding. An endoscopic examination is the first method to be

preferred in the diagnosis and treatment of these patients since it is effective, inexpensive, and reliable. Mechanical methods should be prioritized in endoscopic treatment. Further studies are needed to raise clinicians' awareness of these rare lesions.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
All authors declare no financial support.

Ethical approval
The local ethics committee approved the study. 20-5T/7.

References

1. Baxter M, Aly EH. Dieulafoy's lesion: current trends in diagnosis and management. Ann R Coll Surg Engl. 2010;92:548-54.
2. Sostres C, Lanas A. Epidemiology and demographics of upper gastrointestinal bleeding: prevalence, incidence, and mortality. Gastrointest Endosc Clin N Am. 2011;21:567-81.
3. Nagri S, Anand S, Arya Y. Clinical presentation and endoscopic management of Dieulafoy's lesions in an urban community hospital. World J Gastroenterol. 2007;13:4333.
4. Morowitz M, Markowitz R, Kamath B, et al. Dieulafoy's lesion segmental dilatation of the small bowel: an uncommon cause of gastrointestinal bleeding. J Paediatr Surg. 2004;39:1726–8.
5. British Society of Gastroenterology Endoscopy Committee. Non-variceal upper gastrointestinal haemorrhage: guidelines. Gut. 2002;51:1-6.
6. Peumery JJ. Georges Dieulafoy (1839-1911) and the teaching of medicine in Paris at the hinge of the Second Empire and the Third Republic Vesalius. 2004;10:74- 7.
7. Romãozinho JM, Pontes JM, Lérias C, et al. Dieulafoy's lesion: management and long-term outcome. Endoscopy. 2004;36:416–20.
8. Blecker D, Bansal M, Zimmerman RL, et al. Dieulafoy's lesion of the small bowel causing massive gastrointestinal bleeding: two case reports and literature review. Am J Gastroenterol. 2001;96:902–5.
9. Ji JS, Kim HK, Kim SS, et al. Clinical outcome of endoscopic management of duodenal Dieulafoy's lesions: endoscopic band ligation versus endoscopic hemoclip placement. Surg Endosc. 2016;30:3526-31.
10. Alis H, Oner OZ, Kalayci MU, et al. Is endoscopic band ligation superior to injection therapy for Dieulafoy lesion? Surg Endosc.2009;23:1465-9.
11. Marek TA. Gastrointestinal bleeding. Endoscopy.2007;39:998-1004.
12. Nojkov B, Cappell MS. Gastrointestinal bleeding from Dieulafoy's lesion: clinical presentation, endoscopic findings, and endoscopic therapy. World J Gastrointest Endosc. 2015;7:295–307.
13. Alshumrani G, Almuaikeel M. Angiographic findings and endovascular embolization in Dieulafoy disease: a case report and literature review. Diagn Intervent Radiol. 2006;12:151–4.
14. Akpınar MY, Öztaş E, Derya A et al. Dieulafoylezyonunda endoskopik tedavi. Akademik Gastroenteroloji Dergisi. 2016;15:102-5.
15. Beyazit, Y, Dişibeyaz S, Suvak, B, et al. Dieulafoylezyonuna bağlı akut gastrointestinal system kanaması nedeniyle acil servise başvuran olguların tedavi sonuçlarının değerlendirilmesi. Ulus Travma Acil Cerrahi Derg. 2013;19:133-9.
16. Yılmaz M, Özütemiz Ö, Ersöz G, et al. Seyrek gorülen bir üst gastrointestinal system kanama nedeni: Dieulafoylezyonu. Turk J Gastroenterol. 1998;2:149.
17. Marchese M, De Cristofaro R, Federici AB, et al. Duodenal and gastric Dieulafoy's lesions in a patient with type 2A von Willebrand's disease. Gastrointest Endosc. 2005;61:322-5.
18. Chaer R, Helton WS. Dieulafoy's disease. Am Coll Surg. 2003;196:290-6.
19. Scudiere JR, Cimbaluk D, Jakate S. A 74 year-old man with fatal gastrointestinal bleeding. Arch Pathol Lab Med. 2006;130:223–4.
20. Yoshikumi Y, Mashima H, Suzuki J, et al. A case of rectal Dieulafoy's ulcer and successful endoscopic band ligation. J Gastroenterol. 2006;20:287–90.
21. Park CH, Joo YE, Kim HS, et al. A prospective, randomized trial of endoscopic band ligation versus endoscopic hemoclip placement for bleeding gastric Dieulafoy's lesions. Endoscopy. 2004;36:677- 81.
22. Valera JM, Pino RQ, Poniachik J, et al. Endoscopic band ligation of bleeding Dieulafoy lesions: the best therapeutic strategy. Endoscopy. 2006;38:193-4.
23. Chung IK, Kim EJ, Lee MS, et al. Bleeding Dieulafoy's lesions and the choice of endoscopic method: comparing the hemostatic efficacy of mechanical and injection methods. Gastrointest Endosc. 2000;52:721-4.
24. Baettig B, Haecki W, Lammer F, et al. Dieulafoy's disease: endoscopic treatment and follow up. Gut. 1993;34:1418-21.
25. Yamaguchi Y, Yamato T, Katsumi N, et al. Short-term and longterm benefits of endoscopic hemoclip application for Dieulafoy's lesion in the upper GI tract. Gastrointest Endosc. 2003;57:653-6.
26. Ljubicic N. Efficacy of endoscopic clipping and long-term follow-up of bleeding Dieulafoy's lesions in the upper gastrointestinal tract. Hepatogastroenterology. 2006;53:224–7.
27. Katsinelos P, Paroutoglou G, Mimidis K, et al. Endoscopic treatment and follow-up of gastrointestinal Dieulafoy's lesions. World J Gastroenterol. 2005;11:6022–6.
28. Brown GR, Harford WV, Jones WF. Endoscopic band ligation of an actively bleeding Dieulafoy lesion. Gastrointest Endosc.1994;40:501-3.
29. Lara LF, Sreenarasimhaiah J, Tang SJ, et al. Dieulafoy lesions of the GI tract: localization and therapeutic outcomes. Dig Dis Sci. 2010;55:3436-41.

Available online at www.medicinescience.org

ORIGINAL ARTICLE

Medicine Science International Medical Journal

Medicine Science 2021;10(1):141-6

Characterization of the suicide cases admitted to an emergency service in Turkey

Meltem Songur Kodik[1], Merve Akin Ozdemir[2]

[1]Ege University, School of Medicine, Department of Emergency Medicine, Izmir, Turkey
[2]Ercis Sehit Ridvan Cevik Hospital, Department of Emergency Service, Van, Turkey

Received 22 September 2020; Accepted 02 November 2020
Available online 20.01.2021 with doi: 10.5455/medscience.2020.09.197

Abstract

Suicide attempts are multifaceted actions originating from a wide variety of socio-demographic and clinical factors. This study aimed to characterize suicide cases presented to the emergency service of a University Hospital in Turkey. This retrospective cross-sectional study was conducted by evaluating patients admitted to the emergency service. Descriptive statistics, Chi-square, and the Student's t-test were used to compare groups. A total of 507 patients were admitted to the emergency department with a suicide attempt. Among the applicants, 383 (75.5%) were due to drug poisoning, 79 (15.6%) due to self-laceration, and 45 (8.9%) due to other reasons. Among the patients with drug self-poisoning, the most frequent intoxication was with multiple medications. Most of the patients were females, aged 26-44 years, single, unemployed, living with their family, attempted at home in weekdays, and accompanied by a family member in the emergency unit. Of the patients, 74 (14.6%) had a history of at least one previous suicide attempt. The total number of discharged patients was 438 (86.3%), while the remaining 69 (13.7%) were hospitalized, of whom 39 (56.5%) were males (p=0.004). The majority of hospitalized patients were in the 17-44-age interval. There was a significant difference between hospitalized and discharged patients concerning age groups (p=0.007). Also, a positive family history of a psychiatric disease was associated with the proportions of hospitalization (positive history: 14 (28.0%) hospitalizations vs. negative history: 55 (12.0%) hospitalizations) (p=0.002). Logistic regression analysis demonstrated that suicide attempts with drugs was significantly associated with gender and accompanying alcohol use (p<0.05). In conclusion, close follow-up of the first attempters by their family physicians, psychologists, and psychiatrists, as well as the education of families or inmates could be of benefit to prevent suicide attempts. Further research is recommended to enlighten social behaviors and ideations, leading to suicide attempts.

Keywords: Suicide, attempted; emergencies; emergency outpatient unit; self-injurious behavior; observational study

Introduction

Each year, 800 000 patients die from suicide worldwide. Although it is reported that 79% of the suicides occur in underdeveloped or developing countries, this health problem affects all populations and age groups. It is the second most common cause of death between the ages of 15-29 [1]. On the other hand, approximately 70% of the cases are unsuccessful attempts, not leading to death [8, 9]. Suicides beginning in the adolescent period continue to increase during early maturity [2]. Although the attempt rate is higher in women, successful suicide is more common among men [3].

***Coresponding Author:** Meltem Songur Kodik, Ege University, School of Medicine, Department of Emergency Medicine, Izmir, Turkey.
E-mail: songurm@yahoo.com

Research shows that the most frequently applied suicide mechanism is intoxication, followed by self-injuries, such as cutting or stabbing [4,5]. The first contact with the health system in almost all suicide attempts is the emergency service [6]. The initial evaluation and treatment of these patients are done by emergency doctors. Emergency doctors provide management of the acute stage, and they also coordinate proper psychiatric care. After the first evaluation, the health team assesses the risk to finalize suicide, and accordingly, may decide to discharge the patient [7].

The most fundamental risk factor for a suicide attempt is a previous try. Thus, when the behavioral aspect of suicidal interventions is evaluated from the public health perspective, determining the triggering factors becomes crucial for emergency medicine. For this reason, it is essential to record any suicide ideas and administer assistance for prevention. Although there are worldwide geographical and cultural differences in the death ratios due to suicide, local figures describing the condition in the Aegean area are scarce [8]. Therefore, we decided to study the characteristics

of the patients admitted to a local training hospital in Izmir, with the objective of foreseeing the factors that can prevent secondary attempts. The main study question of the research was to compare admitted and discharged patients concerning suicide mechanisms.

Materials and Methods

This cross-sectional study was reported according to the Strobe Guidelines [9]. The local ethics committee at Izmir University Medical Faculty approved the research protocol (Approval number: 20-13T/4 Date: March 4, 2020).

Setting

This study was conducted between April and September 2020 in the Emergency Department (ED) of the Ege University Medical Faculty, a single-center tertiary-level referral hospital in Izmir, Turkey, having nearly annually 190 000 ED visits.

Data Collection

Using the hospital automation system, the electronic medical records of patients over 17 years old (17 exclusive), admitted to the emergency department due to suicide attempts between January 1, 2017, and December 31, 2019, and examined by emergency physicians were reviewed retrospectively. Accidental poisonings (n=22) and suicide attempts without any harmful consequences (n=14) were discarded (Figure 1).

The sample size calculation was based on the primary outcome variable 'suicide mechanism. Using the GPower 3.1 software (Heinrich Heine University, Düsseldorf, Germany), it was calculated that a sample size of 507 patients provides a power of 99% to compare admitted and discharged patients concerning the suicide mechanism (with drugs/other) with an effect size of 0.2 (small-medium).

The archive search was conducted by an experienced data analyst from the hospital's IT department using the relevant ICD codes (International Statistical Classification of Diseases and Related Health Problems) [10], which revealed a total of 507 patients.

A standard case report form was used to collect demographic and clinical information of the patients. Data were retrieved on socio-demographic characteristics (age, sex, marital status, living partners, and employment status), details of the suicide (mechanism, venue, weekday/weekend), clinical specifications (history of psychiatric illness, history of psychiatric disease in the family, previous suicide attempts, alcohol or drug use during suicide), and the accompanying person.

Also, the patients' duration of stay in the emergency service, transfer to other clinics, discharge status, transfer to the intensive care unit, and leaving without doctors consent was noted. During the analysis, two categories (admitted/discharged) were formed by merging those leaving without doctors' consent and treatment refusal under the 'discharged' group.

Age was analyzed in three groups (17-25 years, 26-44 years, and ≥45 years). Job-status was grouped as 'student', 'employed', and 'unemployed'. Retired patients were included in the unemployed group. The marital status was described as 'single' and 'married'. Divorced and widowed patients were regarded as singles.

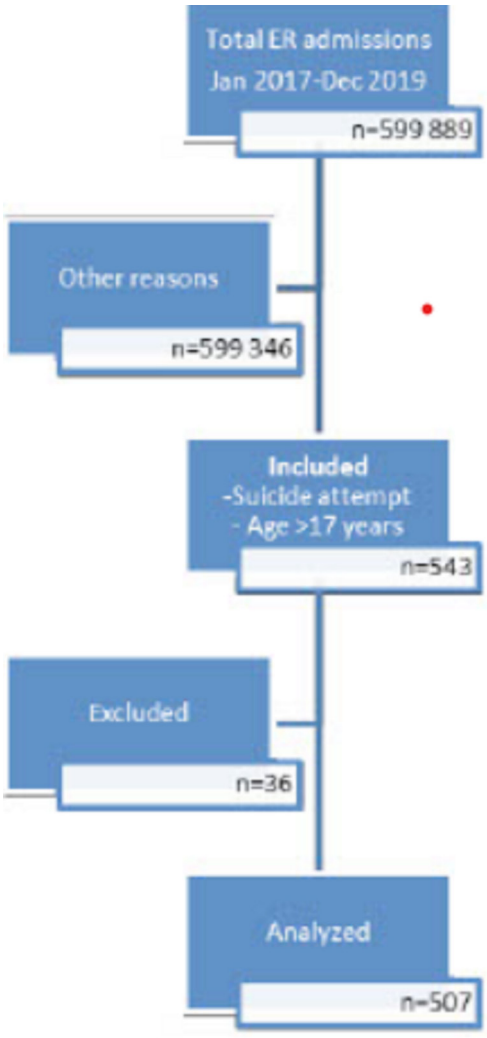


Figure 1. Participant flow diagram

Statistical Analysis

Data were recorded and analyzed using the SPSS (Statistical Package for Social Sciences, IBM inc. Armonk, New York, USA) software version 25.0 for Windows. Continuous and categorical variables were presented by mean±standard deviation (SD) and frequency/percentage, respectively. Patient characteristics and the studied variables were compared using the Pearson's Chi-square/Fisher's exact and Student's t-tests. The logistic regression analysis was used as a multivariate test to examine the effect on the categorical dependent variable suicide mechanism (suicide with drugs/other suicide mechanisms). The impact of the following variables on the dependent variable were analyzed: sex, marital status, occupation, venue of attempt, concomitant alcohol and/or drug use, previous suicide attempt, family history of suicide, known psychiatric illness, and family history of psychiatric disease. The regression analysis results were presented as odds ratios (OR) and corresponding 95% confidence intervals. The tests were regarded as significant, given that the p-value was <0.05.

Results

The total number of post-suicide admissions is 507, which is 0.08% of the total admissions. The mean age was 31.29 ± 11.64 years.

The majority of the patients were female (59.4%), between 26-44 years old (44.8%), single (71.8%), and unemployed (62.3%). Also, 75.5% of the patients attempted suicide with an overdose of drugs. During the attempts, 98 (19.3%) of the patients used alcohol, and 19 (3.7%) used narcotic drugs (Table 1).

Psychiatric consultation was performed on 488 (96.3%) patients, and 343 (67.7%) of the cases were discharged with medical advice and outpatient follow up. Three patients (0.6%) died in the emergency service, and 13 (2.6%) were transferred to the intensive care unit for further treatment. Thirty patients were hospitalized in the psychiatry department (Table 1).

Of the self-poisonings with medications, 39.2% (150 patients) were with multiple drugs, of which 66 (44.0%) used analgesic-based medicines, and 34 (22.7%) used psychiatric drugs. Among the patients with single-drug poisonings (n=233), psychiatric drugs were most frequently used (39.9%, n=93), followed by analgesic medications (24.0%, n=56). The total number of self-injury attempts was 79 (15.6%), while the remaining 45 (8.9%) was classified as others (hanging, fall from a height, fire gun injury, combined drug, and self-injury, and liquefied petroleum gas inhalation). Of the 3 patients who died, one had carotid artery trauma, one jumped from height, and one hung himself. Of the patients, 74 (14.6%) had a history of at least one suicide attempt (Table 1).

As seen in Table 2, 271 (90.0%) of the females and 167 (81.1%) of the males were discharged (p=0.004). The highest discharge rate was seen between 17and 44 (n=375, 73.9%, p=0.007). Of the drug self-poisoned patients, 353 (92.2%) were discharged (p<0.001). Fourteen (28%) of the patients having a history of psychiatric disorder in the family in contrast to 55 (12%) of those without a family history were hospitalized (p=0.002). The median (min.-max.) duration of stay in the emergency service was 6 (1-120) hours.

Of the drug self-poisoned cases, 154 (40.2%) were aged between 17-25, 169 (44.1%) between 26-44, and 60 (15.7%) were ≥45. Most of the patients attempted suicide with multiple medications (48.0%, n=184), and among the group using single drugs, psychiatric remedies were most frequently used (18.3%). The number of drug self-poisoning cases was 259 (67.6%) for females and 124 (32.4%) for males. In comparison, the number of self-harm with cutting and stabbing was 21 (26.6%) for females and 58 (73.4%) for males. On the other hand, of the self-intoxications with other modalities, 21 (46.7%) were females, while 24 (53.3%) were males.

In the multivariate logistic regression analysis, gender and concomitant alcohol abuse were the only independent significant variables affecting suicide attempts with medications (Table 3). Accordingly, women are 3.45 times more likely to commit suicide with drugs than men. The 95% confidence interval of the risk of suicide with medications for women compared to men varies between 2.18 times and 5.45 times. Also, the risk of suicide with drugs is 2.113 times for those who do not have a history of concomitant alcohol use than those who have. The 95% confidence interval of the risk of suicide with drugs varies between 1.273 times and 3.508 times compared to those who used alcohol (Table 3).

Table 1. Demographic and clinical characteristics of the participants (n=507)

Variables		n	%
Age group	17-25	205	40.4
	26-44	227	44.8
	≥44	75	14.8
Sex	Female	301	59.4
	Male	206	40.6
Marital status	Single	364	71.8
	Married	143	28.2
Residential status	Single	305	60.2
	Married	36	7.1
	Family	27	5.3
	Alone	139	27.4
Occupation	Employed	133	26.2
	Unemployed	316	62.3
	Student	58	11.4
Mechanism of attempt	Self-poisoning with drugs	383	75.5
	Self-laceration	79	15.6
	Other	45	8.9
Venue of attempt	Home	453	89.3
	Other	54	10.7
Day of attempt	Weekday	352	69.4
	Weekend	155	30.6
Season of attempt	Spring	129	25.4
	Summer	139	27.4
	Winter	135	26.6
	Autumn	104	20.5
Concomitant alcohol use	Yes	98	19.3
	No	409	81.7
Concomitant drug use	Yes	19	3.7
	No	488	96.3
Previous attempt	At least one previous attempt	74	14.6
	More than one attempt	38	7.5
Family history of suicide	Yes	18	3.6
	No	489	96.4
ED attendant of the patient	Family member	226	44.6
	Friend	35	6.9
	None	35	6.9
	Other/unknown	211	41.6
Known psychiatric illness		236	46.5
		271	53.5
Family history of psychiatric illness	Yes	50	9.9
	No	457	90.1
Patient Outcome	Discharged	343	67.7
	Transferred to the intensive care unit	13	2.6
	Transferred to the psychiatric ward	30	5.9
	Left the ED without doctor consent	52	10.3
	Exitus	3	0.6
	Treatment refusal	36	7.1
	Other	30	5.8

Table 2. Comparison of the assessed variables between discharged and admitted patients

Variables		Discharged n=438		Admitted n=69		p-value
		n	%	n	%	
Sex	Female	271	90.0	30	10.0	0.004
	Male	167	81.1	39	18.9	
Age group	17-25	189	92.2	16	7.8	0.007
	26-44	186	81.9	41	18.1	
	≥45	63	84.0	12	16.0	
Marital Status	Single	321	88.2	43	11.8	0.060
	Married	117	81.8	26	18.2	
Employment status	Employed	112	84.2	21	15.8	0.676
	Unemployed	276	87.3	40	12.7	
	Student	50	86.2	8	13.8	
Residential status	Single	30	83.3	6	16.7	0.130
	Family	256	83.9	49	16.1	
	Friend	25	92.6	2	7.4	
	Other	127	91.4	12	8.6	
Mechanism of attempt	Self-poisoning with drugs	353	92.2	30	7.8	<0.001
	Self-laceration	55	69.6	24	30.4	
	Other	30	66.7	15	33.3	
Venue of attempt	Home	391	86.3	62	13.7	0.883
	Other	47	87.0	7	13.0	
Day of attempt	Weekday	307	87.2	45	12.8	0.414
	Weekend	131	84.5	24	15.5	
Season of attempt	Spring	114	88.4	15	11.6	0.430
	Summer	122	87.8	17	12.2	
	Autumn	91	87.5	13	12.5	
	Winter	111	82.2	24	17.8	
Concomitant alcohol use	Yes	85	86.7	13	13.3	0.912
	No	353	86.3	56	13.7	
Concomitant drug use	Yes	17	89.5	2	10.5	1.000*
	No	421	86.3	67	13.7	
Previous attempt	At least one previous attempt	59	79.7	15	20.3	0.104
	More than one attempt	31	81.6	7	18.4	
Family history of suicide	Yes	12	66.7	6	33.3	0.025
	No	426	87.1	63	12.9	
Family history of psychiatric disorders	Yes	36	72.0	14	28.0	0.002
	No	402	88.0	55	12.0	
ED attendant of the patient	Family member	185	81.9	41	18.1	0.024*
	Friend	34	97.1	1	2.9	
	None	30	85.7	5	14.3	
	Other/unknown	189	89.6	22	10.4	
Known psychiatric illness	Yes	197	83.5	39	16.5	0.074
	No	241	88.9	30	11.1	

ED: Emergency department, *Fisher's Exact test.

Table 3. Multivariable logistic regression analysis showing factors associated with self-poisoning using drugs

Parameters		OR (95% CI)	p-value
Sex	Male	1	<0.001
	Female	3.45 (2.18-5.45)	
Marital status	Married	1	0.693
	Single	0.899 (0.531-1.52)	
Occupation	Student	1	0.667
	Unemployed	0.705 (0.315-1.57)	
	Employed	0.980 (0.283-1.63)	
Venue of attempt	Other	1	0.412
	Home	1.32 (0.678-2.583)	
Concomitant alcohol abuse	Yes	1	0.004
	No	2.113 (1.273-3.508)	
Concomitant drug abuse	No	1	0.060
	Yes	0.369 (0.131-1.03)	
Previous attempt	None	1	0.235
	At least one previous attempt	0.818 (0.444- 1.506)	
	More than one	0.511 (0.233 - 1.122)	
Family history of suicide	No	1	0.957
	Yes	1.03 (0.302 - 3.54)	
Known psychiatric illness	No	1	0.610
	Yes	0.885 (0.554-1.41)	
Family history of psychiatric	No	1	0.226
	Yes	0.608 (0.271-1.36)	

Discussion

One of the most common reasons for ED admissions is suicide attempts. These attempts can originate from various socio-demographic or clinical factors. It is vital to describe the profile of these attempted patients, and determine the triggering factors. Key findings of this study can be summarised as follows: women attempted more suicides compared to men, the most common suicide mechanism was with medications, and being a woman and having no associated alcohol use were the two independent factors associated with suicide attempts using drugs.

Based on our findings, self-intoxication with medications is the primary mechanism of suicide. The majority of the patients were female (male to female admission ratio is 1:1.46), generally aged 17-44 years, single, unemployed, living with their family, and attempted suicide during a weekday and at home. All these findings are coherent with the related literature [10–12]. Suicide attempts are more common in women. However, men usually complete their attempts [13]. A suicide attempt with intoxication is the most frequent mechanism in all age categories [6]. On the other hand, the most frequent intoxication mechanism is intoxications with drugs [14]. Tink et al. [15] stated in their work that undetermined and unsubscribed drug use is one of the most frequently utilized methods. Multiple drug use is an increasing concern with time [16]. In our study, the most common mechanism was self-poisoning with drugs, where the majority of cases utilized multiple medications.

Our analysis also showed that single persons had a more tendency for suicide attempts. However, the literature has conflicting results in this regard. In some work, the number of married and unmarried cases were equal [11], while in some others, married [17] or unmarried [12,18] were more prominent. Parallel to our work, another study from Turkey demonstrated a higher tendency of attempts by unmarried people [12]. Our work confirms that unemployed suicide attempts are much higher. Increased unemployment rates lead to the short-term rise of the working-age female as well as male suicides [19]. Unemployment also increases other risk factors such as lack of economic support, less socialization, and difficulty maintaining life [20]. Eighteen of our patients (3.6%) had a family history of suicide. It has been reported that the risk of suicide increases in those with a positive family history [21]. The psychiatric disease rate in this study is 46.5%, and it is known that this contributes to increased risk [22]. Among the suicide patients admitted to our emergency service, 69.4% attempted during weekdays and 30.6% during the weekends. Our results are parallel with the literature data and show the tendency for in-week casualties [23]. When we observe the emergency service application complaints, 8% of adult patients recently had the idea of suicidal tendencies, which is in accordance with the literature [24]. In our research, 22.1% of the patients had a history of a suicide attempt. Previous works suggest that suicide is seen more frequently in patients with suicide history [25].

Compared to men, being women constituted 3.5 times more risk for suicide attempts using medications. According to previous research, while females prefer self-poisoning as an attempt, males rather use more violent and deadly alternatives [26], which is confirmed by our study. Also, our analysis revealed that males tend to complete the attempt more than females. Some patients had concomitant alcohol use during the attempt. Yet, drug self-poisoning was more common in patients without concomitant alcohol use.

Furthermore, living alone is often a risk factor for suicide attempts [27]. Additionally, previous work by Duberstein et al. [28] shows that social support and protective effects of living with family members reduces the risk of suicides. This was found contradictory in our study; most of our patients (60.2%) were living with their families.

There are many ways suggested to avoid suicide. Direct conversations, detecting the possible risks, avoiding deadly tools, social support, and interference are some common approaches. People who have the opportunity to reach convenient mental health care and build healthy personal relationships are capable of overcoming problems deterring suicide [29]. Various unique strategies were presented by the 2012 National Strategy for Suicide Prevention that target to avoid suicide attempts. Reducing the doses offered in over-the-counter medications and preventing access to suicidal tools, such as toxic substances, poisons, and handguns, are among these strategies [30].

Although a prior suicide attempt, family history of suicide, and a family history of a mental disorder or substance abuse are among the known risk factors, it is possible to take effective preventative measures. As suggested by Swiss researchers, these measures

can be regular meetings arranged by professionals to talk with the suicidal person [31]. These conversations could be about the depression, as well as the plan and means of the possible attempt.

This study should be interpreted in light of some limitations. The primary limitation of our study is that it is retrospective, cross-sectional, and is conducted in a single emergency service. On the other hand, the research covered a timespan of three years, which provided a sufficient sample size. Secondly, the inclusion of the educational status could yield valuable information concerning the relationship between education and suicide. Third, patients who die at the suicide venue are not registered in the hospital electronic medical records database. Thus, this study lacks any information on these cases.

Conclusions

Carried out in a third-level health institution, this study contributes to the available scientific data on suicide attempts in Turkey by analyzing the patients admitted to the emergency service. The principal analysis was based on the patients' suicide mechanisms, demographic characteristics, psychiatric events, discharge, and hospitalizations to other departments in the hospital. On behalf of the findings in this study, we suggest that the health team caring for suicide patients should collaborate to prevent of future attempts, which carry a higher risk of success. Close follow-up of the first attempters by their family physicians, psychologist, and psychiatrists, as well as education of the families or other inmates, could be of benefit too. Future studies should aim to uncover and prevent the underlying psychosocial reasons in patients admitting suicide.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
All authors declare no financial support.

Ethical approval
The local ethics committee at Ege University Medical Faculty approved the research protocol (Approval number: 20-13T/4 Date: March 4, 2020).

References

1. Organization WH. Meeting report: WHO technical consultation: nutrition-related health products and the World Health Organization model list of essential medicines–practical considerations and feasibility: Geneva, Switzerland, 20–21 September 2018. WHO. 2019.
2. Hawton K, Saunders KEA, O'Connor RC. Self-harm and suicide in adolescents. Lancet. 2012;379:2373–82.
3. Nock MK, Borges G, Bromet EJ, et al. Cross-national prevalence and risk factors for suicidal ideation, plans and attempts. Br J Psychiatry. 2008;192:98–105.
4. Spittal MJ, Pirkis J, Miller M, Studdert DM. Declines in the lethality of suicide attempts explain the decline in suicide deaths in Australia. PLoS One. 2012;7:e44565.
5. Canner JK, Giuliano K, Selvarajah S, Hammond ER, Schneider EB. Emergency department visits for attempted suicide and self harm in the USA: 2006–2013. Epidemiol Psychiatr Sci. 2018;27:94–102.
6. Lee CA, Choi SC, Jung KY, et al. Characteristics of patients who visit the emergency department with self-inflicted injury. J Korean Med Sci. 2012;27:307–12.
7. Baraff LJ, Janowicz N, Asarnow JR. Survey of California emergency departments about practices for management of suicidal patients and resources available for their care. Ann Emerg Med. 2006;48:452–8.
8. Keskin Gokcelli D, Tosun Tasar P, Akcam NO, et al. Evaluation of attempted older adults suicides admitted to a University Hospital Emergency Department: Izmir study. Asian J Psychiatr. 2017;30:196-9.
9. Von Elm E, Altman DG, Egger M, et al. The Strengthening the reporting of observational studies in epidemiology (STROBE) Statement: guidelines for reporting observational studies. Int J Surg. 2014;12:1495–9.
10. El Majzoub I, El Khuri C, Hajjar K, et al. Characteristics of patients presenting post-suicide attempt to an Academic Medical Center Emergency Department in Lebanon. Ann Gen Psychiatry. 2018;17:21.
11. Filippatos G, Karasi E. Characteristics of attempted suicide patients presenting to a greek emergency department. Heal Sci J. 2017;11:1.
12. Turhan E, Inandi T, Aslan M, et al. Epidemiology of attempted suicide in Hatay, Turkey. Neurosci. 2011;16:347-52.
13. Vos T, Abajobir AA, Abbafati C, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: A systematic analysis for the Global Burden of Disease Study 2016. Lancet. 2017.
14. Kvaran RB, Gunnarsdottir OS, Kristbjornsdottir A, et al. Number of visits to the emergency department and risk of suicide: a population-based case–control study. BMC Public Health. 2015;15:227.
15. Ting SA, Sullivan AF, Boudreaux, et al. Trends in US emergency department visits for attempted suicide and self-inflicted injury, 1993–2008. Gen Hosp Psychiatry. 2012;34:557–65.
16. Mowry JB, Spyker DA, Cantilena Jr LR, et al. 2013 Annual report of the American association of poison control centers' National poison data system (NPDS): 31st annual report. Clin Toxicol. 2014;52:1032–283.
17. Kawashima Y, Yonemoto N, Inagaki M, et al. Prevalence of suicide attempters in emergency departments in Japan: a systematic review and meta-analysis. J Affect Disord. 2014;163:33–9.
18. Ronquillo L, Minassian A, Vilke GM, et al. Literature-based recommendations for suicide assessment in the emergency department: a review. J Emerg Med. 2012;43:836-42.
19. Fairweather-Schmidt AK, Anstey KJ, Salim A, et al. Baseline factors predictive of serious suicidality at follow-up: findings focussing on age and gender from a community-based study. BMC Psychiatry. 2010;10:41
20. Stuckler D, Basu S, Suhrcke M, et al. The public health effect of economic crises and alternative policy responses in Europe: an empirical analysis. Lancet. 2009;374:315-23.
21. Qin P, Agerbo E, Mortensen PB. Suicide risk in relation to family history of completed suicide and psychiatric disorders: a nested case-control study based on longitudinal registers. Lancet. 2002;360:1126–30.
22. Burón P, Jimenez-Trevino L, Saiz PA, et al. Reasons for attempted suicide in Europe: prevalence, associated factors, and risk of repetition. Arch Suicide Res. 2016;20:45–58.
23. Joubert L, Petrakis M, Cementon E. Suicide attempt presentations at the emergency department: outcomes from a pilot study examining precipitating factors in deliberate self-harm and issues in primary care physician management. Soc Work Health Care. 2012;51:66-76.
24. Betz ME, Boudreaux ED. Managing suicidal patients in the emergency department. Ann Emerg Med. 2016;67:276.
25. Larkin C, Di Blasi Z, Arensman E. Risk factors for repetition of self-harm: a systematic review of prospective hospital-based studies. PLoS One. 2014;9:e84282.
26. Callanan VJ, Davis MS. Gender differences in suicide methods. Soc Psychiatry Psychiatr Epidemiol. 2012;47:857-69.
27. Conwell Y, Duberstein PR, Caine ED. Risk factors for suicide in later life. Biol Psychiatry. 2002;52:193–204.
28. Duberstein PR, Conwell Y, Conner KR, et al. Poor social integration and suicide: fact or artifact? A case-control study. Psychol Med. 2004;34:1331.
29. Simon RI. Assessing and managing suicide risk: Guidelines for clinically based risk management. American Psychiatric Pub. 2008.
30. Office of the Surgeon General (US); National action alliance for suicide prevention (us). 2012 national strategy for suicide prevention: goals and objectives for action: A report of the U.S. Surgeon General and of the National Action Alliance for Suicide . Washington (DC), USA: US Department of Health & Human Services (US); 2012.
31. World Health Organization. Preventing suicide: A resource for primary health care workers. Geneva, Switzerland: WHO. 2000.

Available online at www.medicinescience.org

ORIGINAL ARTICLE

Medicine Science International Medical Journal

Medicine Science 2021;10(1):147-52

Retrospective evaluation of patients with non-varicose upper gastrointestinal bleeding

Ece Unal Cetin, Fatih Kamis, Adil Ugur Cetin , Yavuz Beyazit

Canakkale Onsekiz Mart University, School of Medicine, Department of Internal Medicine, Canakkale, Turkey

Received 16 October 2020; Accepted 05 November 2020
Available online 21.01.2021 with doi: 10.5455/medscience.2020.10.220

Abstract

Upper gastrointestinal tract (GIS) bleeding refers to any bleeding originates from the area from upper esophagus to the proximal of the treitz ligament. It has a wide range of clinical manifestations ranging from hypovolemic shock to death. Bleeding from peptic ulcer (PU) is one of the major cause of upper GIS bleeding. Despite improvements in therapeutic endoscopy and angiography, gastrointestinal bleeding is still an important source of morbidity and mortality. Although approximately 80-85% of upper GIS bleeding stops spontaneously, supportive treatment is required. In this study, we aimed to determine the clinical, laboratory and demographic characteristics of patients with upper GIS bleeding and their relationship with major scoring systems. Two hundred thirteen patients over 18 years old that were admitted to Çanakkale Onsekiz Mart University Training and Research Hospital between January 2016 and March 2020 with a diagnosis of non-variceal GIS bleeding were retrospectively enrolled to this study. Age, gender, blood group, comorbid conditions, endoscopic findings, laboratory values and medications were recorded for each patient. Prognostic scorings were calculated for each patient. The mean age of patients was 68.67±14.8 years (Male/Female: 156/57). In overall, 90.7% of patients were discharged and 7.5% of patients were transferred to intensive care unit. The mortality rate was 1.8%. Endoscopic evaluation revealed that 31.9% of patients had duodenal ulcer and 19.2% of patients had gastric ulcer. Medical treatment was applied to 84.8% of patients and 13.4% of patients received endoscopic treatments. Length of stay was significantly correlated with Rockall and Glasgow Blatchford scores. This study revealed that age, comorbid conditions and prior drug history were related to predisposition to GIS bleeding. Early diagnosis and intervention might reduce the mortality in these patients. Despite early endoscopic interventions and the improvements in endoscopic techniques GIS bleeding still associated with increased rates of morbidity and mortality.

Keywords: Upper gastrointestinal bleeding, glasgow-blatchford score, rockall classification, treatment

Introduction

Upper gastrointestinal bleeding (GIB) originates from the upper oesophagus up to the proximal of the Treitz ligament. GIB appears in a wide range of clinical findings ranging from occult blood positivity in the stool to hypovolemic shock [1]. Despite advances in therapeutic endoscopy and angiography, gastrointestinal bleeding is still a major cause of morbidity and mortality. Approximately 80–85% of upper GIB stops spontaneously, in which cases only supportive treatment is required [2,3]. In the remaining 15% of cases, bleeding continues, or recurrent bleeding develops. The patients affected by this kind of bleeding constitute a high-risk group with significantly increased morbidity and mortality [4].

***Coresponding Author:** Ece Unal Cetin, Canakkale Onsekiz Mart University, School of Medicine, Department of Internal Medicine, Canakkale, Turkey
E-mail: eceunalcetin@gmail.com

The causes of upper GIB can be divided into varicose factors and non-varicose factors. Studies have shown that the rate of varicose bleeding increased from 4% in 1994 to 8% in 2007. This increase has been associated with an increase in end-stage liver disease [5]. Peptic Ulcer (PU) is still the most common cause of upper GIB, despite a decrease in its incidence and in its inflicted mortality among patients in the last thirty years [6].

While risk-scoring parameters for GIB are generally based on treatment needs, some parameters are based on mortality risk and recurrent bleeding. Some of the scores used to evaluate GIB are APACHE II, Rockall, Simplified Acute Physiology Score, Baylor, Forrest, and Glasgow-Blatchford [7]. The most widely used GIB scoring today is the Rockall scoring system [8]. For patients with acute upper GIB, endoscopy is helpful both for diagnosing and for potentially gaining control of bleeding. Early endoscopy (within 2–24 hours) has been shown to be safe and effective for all risk groups [9]. In high-risk patients such as those with tachycardia, hypotension, bloody vomiting or bloody nasogastric aspirate,

endoscopy has been shown to decrease mortality if performed within the first 12 hours [10,11]. In this retrospective study, we examined patients at Çanakkale Onsekiz Mart University hospital who had been diagnosed with upper non-varicose GIB in the last four years.

Materials and Methods

This study enrolled 213 patients over 18 years old with upper non-varicose GIB, who were admitted to the emergency department of Çanakkale Onsekiz Mart University hospital between January 2016 and March 2020. This study did not include patients whose endoscopies were not performed by our gastroenterology department, who did not accept endoscopy, patients with defiecent medical data or who were diagnosed with varicose bleeding by endoscopy.

Patients were evaluated according to the Rockall scoring system, which includes age, pulse, systolic blood pressure (SBP), co-morbidity, diagnosis and endoscopic findings. The patients who scored 0–2 were considered low-risk; 3–4, medium-risk; ≥5, high-risk. Simultaneously, using the Glasgow-Blatchford scoring system, which includes SBP, urea, hemoglobin (HGB) and additional risk factors, patients were grouped either as low-risk, scoring 0–5 points, and high risk, scoring ≥6 points.

Statistical analysis was made using the SPSS 22.0 program. Data were expressed as number percentage or mean ± standard deviation. $P < 0.05$ was considered statistically significant. Differences between groups were evaluated using Pearson's chi-square test.

Results

According to the demographic data of the patients included in the study, 156 (73.3%) of the patients were male. The mean age was 68.67 ± 14.8. According to an examination of the complaints in the patients' applications, 130 (61.1%) had melena, 27 (12.6%) had hematemesis, 41 (19.3%) had both hematemesis and melena, 6 (2.8%) had hematochezia, 6 (2.8%) presented with syncope and 3 (1.4%) had other complaints. The mean SBP of the patients at the times of admission was 117.65 ± 18.44 (mm/Hg), their mean diastolic blood pressure was 72.90 ± 12.09 (mm/Hg), and their mean heart rate was 87.61 ± 13.89 (bpm). In the examination of laboratory values at the times of admission, the mean hemoglobin value was 8.68 ± 2.60 (g/dl) and the mean hematocrit (Htc) value was 28.06 ± 7.77 (%). The demographic and laboratory values of the patients included in the study are given in detail in Table 1.

An examination of the patients' accompanying chronic diseases showed that 112 (52.5%) had hypertension, 63 (29.5%) had coronary artery disease, 46 (21.5%) had diabetes mellitus, 32 (15%) had cerebrovascular accident, 27 (12.6%) had chronic kidney disease, 26 (12.2%) had congestive heart failure, 26 (12.2%) had other cardiac diseases and 21 (9.8%) had malignancy. Sixty-nine (32.3%) of the patients had other additional diseases.

According to the endoscopic findings, duodenal ulcer was found to have the highest rate of detection. This was followed by antral ulcer and erosive gastritis. The endoscopic results are given in detail in Table 2.

Table 1. Demographic and laboratory data of the cases included in the study

		N=213
Age (years)		68.67 ± 14.8
Sex	Female, n(%)	57 (26.7)
	Male, n(%)	156 (73.3)
Length of stay (day)		4.60 ± 3.40
Bleeding related symptoms, n(%)	Hematemesis	27 (12.6)
	Melena	130 (61.1)
	Hematochezia	6 (2.8)
	Hematemesis + Melena	41 (19.3)
	Syncope	6 (2.8)
	Other	3 (1.4)
SBP* (mm/Hg)		117.65 ± 18.44
DBP* (mm/Hg)		72.90 ± 12.09
Heart rate (/minute)		87.61 ± 13.89
Initial laboratory data	Haemoglobin (g/dl)	8.68 ± 2.60
	White blood cell (/mm3x103)	10.22 ± 4.28
	Haemotocrit (%)	28.06 ± 7.77
	Platelets (/mm3x103)	244.45 ± 107.32
	Urea (mg/dL)	85.48 ± 49.05
	Creatinine (mg/dL)	1.21 ± 0.80
	INR* (%)	1.74 ± 2.23
	APTT* (sn)	31.06 ± 18.59
	ALT* (IU/L)	17.24 ± 28.41
	AST* (IU/L)	19.94 ± 21.15

(*SBP: Systolic blood pressure; DBP: Diastolic blood pressure; INR: International normalized ratio; APTT: Activated partial thromboplastin time; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase)

Table 2. Endoscopic features of patients with nonvariceal upper gastrointestinal bleeding

	N=213 (%)
Duodenal ulcer	68 (31.9%)
Gastric ulcer	41 (19.2%)
Erosive gastritis	18 (8%)
Esophageal ulcer	13 (6.1%)
Esophagitis	9 (4.2%)
Gastric cancer	4 (1.9%)
Dieulafoy lesion	3 (1.4%)
Other *	57 (26.8%)

Other: Patients with no focus, vascular ectasia, hemobilia, etc

An examination of the patients' treatment methods showed that 179 (84.8%) had received medical treatment and 21 (9.6%) had received endoscopic sclerotherapy. The patients' treatment methods are shown in Table 3.

When the patients' clinical parameters were compared according to the Rockall scoring system, it was observed that erythrocyte transfusion (ET) and intensive care increased significantly as the severity of the disease increased (p: 0.0001 for ET; p: 0.002 for intensive care). Rockall score was significantly associated with the use of acetyl salicylic acid (ASA) (p: 0.015), non-ASA antiplatelet drugs (p: 0.003) and anticoagulants (p: 0.021) (Table 4).

Table 3. Treatment methods of the patients included in the study

	N=213 (%)
Medical therapy	179 (84.8 %)
Endoscopic sclerotherapy	21 (9.6 %)
Endoscopic heater probe	5 (2 %)
Endoscopic hemoclip	4 (1.8 %)
Surgical treatment	4 (1.8 %)

Table 4. Comparison of clinical parameters according to the Rockall Risk scoring system

		Rockall Score			
Length of stay (day)		0-2 (n:31)	3-4 (n:85)	≥5 (n:97)	p
		3.35±1.08	4.11±2.14	5.42±4.44	0.003
Blood requirement n(%)	0	11 (35.5)	25 (29.4)	11 (11.3)	0.001
	1 unit	2 (6.5)	12 (14.1)	5 (5.2)	
	2 unit	7 (22.6)	10 (11.8)	14 (14.4)	
	≥3 unit	11 (35.5)	38 (44.7)	67 (69.1)	
Intensive Care requirement n(%)	+	0 (0)	2 (2.4)	14 (14.4)	0.002
	-	31 (100)	83 (97.6)	83 (85.6)	
Medications n(%)					
ASA	+	2 (6.5)	24 (28.2)	32 (33)	0.015
	-	29 (93.5)	61 (71.8)	65 (67)	
Non-ASA anti-platelet	+	0 (0)	17 (20)	28 (28.9)	0.003
	-	31 (100)	68 (80)	69 (71.1)	
Use of 2 different antiplatelet drugs	+	0 (0)	8 (9.4)	13 (13.4)	0.091
	-	31 (100)	77 (90.6)	84 (86.6)	
Use of anticoagulants	+	1 (3.2)	22 (25.9)	25 (25.8)	0.021
	-	30 (96.8)	63 (74.1)	72 (74.2)	

The clinical parameters of the patients were compared with Glasgow-Blatchford scores (Table 5). While there was a statistically significant difference between the Glasgow-Blatchford score and the need for ET (p: 0.000), there was no significant difference between hospitalization time (p: 0.157) and the need for intensive care (p: 0.606). When the patients' medication use was evaluated, no difference was found in the Glasgow-Blacthford score (Table 5).

The length of stay and the patients' scoring systems were compared using the Spearman correlation analysis. The Rockall and Glasgow-Blatchford scoring systems showed a significant correlation between the length of stay (r = 0.233, p = 0.001 for Rockall; r = 0.231, p = 0.001 for Glasgow-Blatchford).

When the researchers examined the relationship between the blood pressure and pulse values, measured at the times of admission, and the ET, we observed that a high pulse rate and low blood pressure were associated with increased need for ET (Table 6).

The patient follow-up outcomes, which were included in the study, were also examined. 193 patients were discharged with complete remission. Four patients required surgery, 16 patients were referred to intensive care units and 4 patients died.

Table 5. Comparison of clinical parameters according to Glasgow-Blatchford scoring system

		Glasgow-Blatchford Score		
Length of stay (day)		0-5 (n:12)	≥6 (n:201)	p
		3.25±1.05	4.68±3.47	0.157
Blood requirement n(%)	0	11 (91.7)	36 (17.9)	0.000
	1 unit	1 (8.3)	18 (9)	
	2 unit	0 (0)	31 (15.4)	
	≥3 unit	0 (0)	116 (57.7)	
Intensive Care requirement n(%)	+			0.606
	-			
Medications n(%)				
ASA	+	4 (33.3)	54 (26.9)	0.739
	-	8 (66.7)	147 (73.1)	
Non-ASA antiplatelet	+	2 (16.7)	43 (21.4)	0.978
	-	10 (83.3)	158 (78.6)	
Use of 2 different antiplatelet drugs	+	2 (16.7)	19 (9.5)	
	-	10 (83.3)	182 (90.5)	
Use of anticoagulants	+	1 (8.3)	47 (23.4)	0.306
	-	11 (91.7)	154 (76.6)	

Table 6. The relationship of patients' basal vital signs with ET replacement

		0 (n: 47)	1 (n:19)	2 (n:31)	≥3 (n:116)
Blood pressure (mm/Hg),	SBP ≤ 100	2 (4.2)	4 (12.9)	29 (25)	
	100 < SBP <140	34 (72.3)	26 (83.8)	75 (64.6)	
	SBP ≥ 140	11 (23.5)	1 (3.3)	12 (10.4)	
Heart rate (minute), n(%)	< 100	43 (91.4)	27 (87)	86 (74.1)	
	≥ 100	4 (8.6)	4 (13)	30 (25.9)	

Discussion

Acute GIB is a clinical condition that is common worldwide and is associated with significant mortality and morbidity rates [12]. Various risk factors for GIB that is related to morbidity and mortality includes older age, liver cirrhosis, heart failure, use of antiplatelet or anticoagulant agents [13]. It is more common in men and in individuals over the age of 60 [14].

Regarding the study's epidemiological data, 73% of the patients were male, and the mean age of the patients was 68.67 ± 14.8. Studies have shown that GIB is about twice as common in men than in women [15,16]. Stanley et al. [17] found that the mean age of cases was 65 [17]. One of the contributing factors to a higher ratio of upper GIB in men is the higher frequency of accompanying chronic diseases. n addition, it is suggested that another contributing factor is that gastric mucosa endurance and integrity is better in women [18].

When the patients' complaints were examined, it was observed that, in most studies, patients most frequently present with melena [19-21]. In our study, 61% of the patients presented with melena. In some studies, patients most frequently present with hematemesis [22], or the frequency of presentation with melena and hematemesis is similar [23]. The reason for this difference may be that patients with varicose bleeding were not included in this study.

The patients' blood pressure and mean heart rate were compatible with the literature [24,25]. When the laboratory values at the times of admission were examined, the mean HGB was 8.68 ± 2.60 (g/dl), which is similar to that from the study conducted by Min Park et al. [26]. The mean urea levels were found to be higher than in other studies, and it was thought that the reason may be that the chronic kidney disease patients and active bleeding rates in our study were higher than in other studies. The patients' other laboratory results were compatible with the studies in the literature.

When the patients' accompanying chronic diseases were examined, it was observed that hypertension was more common than other diseases. Gölgeli et al. [27] found that hypertension is the most common comorbid disease. Again, Okutur et al. [28] found that hypertension was found in 46.2% of patients; diabetes mellitus, in 22%; and coronary artery disease, in 16.5%.

7.5% of our patients needed intensive care and 1.8% of them died. The mortality rate was 17.3% in the study by Budimir et al. [29] and 4.2% in the study by Robertson et al. [30]. Bozkurt et al. found the need for intensive care to be 30.9% [23]. The reason for the low mortality and intensive care rates in our study, compared to the literature, may be that varicose bleeding was not included in this study.

1.8% of the patients in our study needed surgery, and in the study of 502 patients with upper GIB performed by Günşar et al. [31], between1993-1995, surgical intervention was applied to 6.1% of the patients. The reason this rate was less in our study is thought to be the lower number of patients and the further development of medical and endoscopic treatment methods in recent years.

Medical treatment was applied to 84.8% of the patients in our study. Among the patients who had endoscopic treatment, most were treated with sclerotherapy. Cheng et al. [32] reported that they performed endoscopic treatment at a rate of 24% and Pang et al. [33] reported a rate of 27.3%. Dicu et al. [19], Bozkurt et al. [23] and Okutur et al. [28] observed that sclerotherapy was the most common endoscopic treatment.

Cheng et al. [32] found gastric ulcer in 22% of the cases of GIB, and Dicu et al. found gastric and duodenal ulcers in 41.4% [19]. ln our study, in accordance with the literature, the most common cause of ulcers was PU. Forrest 3 was the most common in patients with PU, which is consistent with the literature [34-36].

When tachycardic and hypotensive patients were evaluated, it was seen that three or more units of ET were given to most of them. This shows the relationship between increased bleeding and impaired hemodynamics and supports the literature.

We found a significant correlation between the Rockall scoring system and the duration of hospitalisation, ET and intensive care requirement. Glasgow-Blatchford scoring found to be related with ET requirement. While a statistically significant difference was found between the uses of ASA, non-ASA antiplatelet and anticoagulants and the Rockall score, no significant difference was found in the use of two different antiplatelet drugs. In other studies, which used the Rockall score, parallel to our results the duration of hospitalisation and the need for ET increased, and the prognosis deteriorated with the increase in the score [37-39].

Again, in recent studies, the Glasgow-Blatchford score was more sensitive than the Rockall score in distinguishing high-risk patients, but its specificity was low [17, 40, 41]. No relationship was found between drug uses and scoring systems, and our finding of a significant relationship between the Rockall scoring system and some drugs increases the value of our study. It has been shown in many human and animal studies that ASA causes gastric erosions by inhibiting thromboxane synthesis [42]. In a study conducted in France, PU was found to be the most common cause (34%) of GIB in patients using low-dose ASA [43]. This explains the significant relationship between the Rockall scoring system and ASA demonstrated in our study. The differences between our study and other studies can be attributed to the difference in patient numbers, ethnic origin, and diversity of endoscopic facilities. Both scoring systems have advantages over the other, and it is appropriate to use all the scores together in patient evaluation.

We recognize some limitations regarding our study. Being retrospective and single center study some of the data could not be reached. It was therefore single-center and had limited possibilities. In addition, as our hospital is a third-level research hospital, some patients might have been referred, or their endoscopy and treatments might have been completed in the emergency department due to an absence of empty beds. Additionally, the homogenous distribution of the patients might be due to the referral of critical patients to Çanakkale Onsekiz Mart University hospital.

In conclusion, this study determined that older age, comorbidity and drugs increase the risk of GIB. Despite early endoscopy, performed with developing endoscopic interventions and scoring systems for determining prognosis, caution should be taken regarding GIB, which is still a common cause of mortality

worldwide. Older patients should be informed about the use of drugs that may cause bleeding, and gastroprotective drugs should be given simultaneously, if necessary, in the presence of multiple risk factors. Patients who require early endoscopy should be determined using the risk scores. Care should be taken with patients with high risks of mortality or re-bleeding, and these patients' hemodynamics should be followed closely. Prospective and multi-centre studies on this subject are needed for clearer and more accurately guiding results.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
All authors declare no financial support.

Ethical approval
Ethical approval obtined from COMU ethical board no:2011-KAEK-27/2020-E.2000029099

References

1. Kurien M, Lobo AJ. Acute upper gastrointestinal bleeding. Clin Med (Lond). 2015;15:481–85.
2. Sarin N, Monga N, Adams PC. Time to endoscopy and outcomes in upper gastrointestinal bleeding. Can J Gastroenterol. 2009;23:489-93.
3. Kivkin K, Lyakhovetskiy A. Treatment of non variceal upper gastrointestinal bleeding. Am J Health-Syst Pharm. 2005;62:1159–70.
4. Kankaria AG, Fleischer DE. The critical care management of non-variceal upper gastrointestinal bleeding. Crit Care Clin. 1995;11:347-68.
5. British Society of Gastroenterology (BGS). UK Comparative audit of upper gastrointestinal bleeding and the use of blood. December 2007.
6. Loperfido S, Baldo V, Piovesana E, et al. Changing trends in acute upper-GI bleeding: a population-based study. Gastrointest Endosc. 2009;70:212-24.
7. Rockall TA, Logan RF, Devlin HB, et al. Incidence of and mortality from acute upper gastrointestinal haemorrhage in the united kingdom. steering committee and members of the national audit of acute upper gastrointestinal haemorrhage. BMJ. 1995;311.
8. Vreeburg EM, Terwee CB, Snel P, et al. Validation of the Rockall risk scoring system in upper gastrointestinal bleeding. Gut. 1999;44:331-35.
9. Spiegel BM, Vakil NB, Ofman JJ. Endoscopy for acute nonvariceal upper gastrointestinal tract hemorrhage: is sooner better? A systematic review. Arch Intern Med. 2001;161:1393-404.
10. Yaka E, Yilmaz S, Dogan NÖ, et al. Comparison of the Glasgow-Blatchford and AIMS65 scoring systems for risk stratification in upper gastrointestinal bleeding in the emergency department. Acad Emerg Med. 2015;22:23-30.
11. Lim LG, Ho KY, Chan YH, et al. Urgent endoscopy is associated with lower mortality in high-risk but not low-risk nonvariceal upper gastrointestinal bleeding. Endoscopy. 2011;43:300-6.
12. Laine L, Yang H, Chang SC. Trends for incidence of hospitalization and due to Gİ caomplications in the United States from 2001 to 2009. Am J Gastroenterol. 2012;107:1190-95.
13. van Leerdam ME Epidemiology of acute upper gastrointestinal bleeding. Best Pract Res Clin Gastroenterol. 2008;22:209-24.
14. Di Fiore F, Lecleire S, Merle V, et al. Changes in charecteristics and outcome of acute upper gastrointestinal haemorrhage: a comparison of epidemiology and practices between 1996 and 2000 in a multicentre French study. Eur J Obstet Gynecol Reprod Biol. 2005;6:641-7.
15. Longstreth GF. Epidemiology of hospitalization for acute upper gastrointestinal hemorrhage: A population based study. Am J Gastroentesterol. 1995;90:206.
16. Rotondano G. Epidemiology and diagnosis of acute nonvariceal upper gastrointestinal bleeding. Gastroenterol Clin North Am. 2014;43:643-63.
17. Stanley AJ, Laine L, Dalton HR, et al. Comparison of risk scoring systems for patients presenting with upper gastrointestinal bleeding: international multicentre prospective study. BMJ. 2017;356:6432.
18. Shennak MM. ''Etiology of upper gastrointestinal bleeding in,Jordanian patients: A prospective study'' Ann Saudi Med. 1995;15:1-12
19. Dicu D, Pop F, Ionescu D, et al. Comparison of risk scoring systems in predicting clinical outcome at upper gastrointestinal bleeding patients in an emergency unit. Am J Emerg Med. 2013;31:94-9.
20. Wang CH, Chen YW, Yang CJ, et al. A prospective comparison of 3 scoring systems in upper gastrointestinal bleeding. Am J Emerg Med. 2013;31:775-8.
21. Mungan Z. An observational European study on clinical outcomes associated with current management strategies for non-variceal upper gastrointestinal bleeding (ENERGIB-Turkey). Turk J Gastroenterol. 2012;23:463-77.
22. Minakiri M, Badihian S, Jalalpour P, et al. Etiology and outcome in patients with upper gastrointestinal bleeding:study on 4747 patients in the central region of Iran. J Gastroenterol Hepatol. 2017;32:789-96.
23. Bozkurt S, Köse A, Arslan ED, et al. Validity of modified early warning, Glasgow Blatchford, and pre-endoscopic Rockall scores in predicting prognosis of patients presenting to emergency department with upper gastrointestinal bleeding. Scand J Trauma Resusc Emerg Med. 2015;23:109.
24. Mokhtare M, Bozorgi V, Agah S, et al. Comparison of Glasgow-Blatchford score and full Rockall score systems to predict clinical outcomes in patients with upper gastrointestinal bleeding. Clin Exp Gastroenterol. 2016;9:337–43.
25. Adrian J Stanley, Loren Laine, Harry R Dalton, et al. Comparison of risk scoring systems for patients presenting with upper gastrointestinal bleeding: international multicentre prospective study BMJ. 2017;356:6432.
26. Park SM, Yeum SC, Kim B-W, et al. Comparison of AIMS65 score and other scoring systems for predicting clinical outcomes in Koreans with nonvariceal upper gastrointestinal bleeding. Gut Liver. 2016;10:526–31.
27. Gölgeli H, Ecirli Ş, Kutlu O, et al. Üst gastrointestinal sistem kanaması nedeniyle izlenen hastaların değerlendirilmesi. Dicle Tıp Dergisi. 2014;41:495-501.
28. Okutur SK, Alkım C, Bes C, et al. Akut gastrointestinal sistem kanamaları: 230 olgunun analizi. Akademik Gastroenteroloji Dergisi. 2007;6:30-6.
29. Budimir I, Gradiser M, Nikolic M, et al. Glasgow Blatchford, pre-endoscopic Rockall and AIMS65 scores show no difference in predicting rebleeding rate and mortality in variceal bleeding. Scand J Gastroenterol. 2016;51:1375–79.
30. Robertson M, Majumdar A, Boyapati R, et al. Risk stratification in acute upper GI bleeding: comparison of the AIMS65 score with the Glasgow-Blatchford and Rockall scoring systems. Gastrointest Endosc. 2016;83:1151-60.
31. Günşar F. Üst gastrointestinal sistem kanamalı 502 olgunun değerlendirilmesi. Türk J Gastroenterolog. 1997;8:188-93.
32. Cheng DW, Lu YW, Teller T, et al. A modified Glasgow Blatchford Score improves risk stratification in upper gastrointestinal bleed: a prospective comparison of scoring systems. Aliment Pharmacol Ther. 2012;36:782-9.
33. Pang SH, Ching JY, Lau JY, et al. Comparing the Blatchford and pre-endoscopic Rockall score in predicting the need for endoscopic therapy in patients with upper GI hemorrhage. Gastrointest Endosc. 2010;71:1134-40.
34. Cander B, Ertekin B, Kara H, et al. Acil servise gastrointestinal kanama ile başvuran hastalarda hastane yatış süresini etkileyen faktörler. Fırat Tıp Dergisi. 2011;16:51-4.
35. Köseoglu Z, Kara B, Akın MS, et al. Evaluation of 364 Cases with Non-Variceal Gastrointestinal System Bleeding. JAEM. 2011;66:165-70.
36. Koçoğlu H, Okuturlar Y, Oğuz B, et al. Cost Analysis of Patients with Upper Gastrointestinal Hemorrhage. J Clin Anal Med. 2015;6:473-8.
37. Rockall TA, Logan RF, Devlin HB, et al. Risk assessment after acute upper gastrointesti-nal haemorrhage. Gut. 1996;38:316-21.
38. Sezgin O, Altıntaş E, Tombak A. Effects of seasonal variations on acute upper gastrointestinal bleeding and its etiology. Turk J Gastroenterol. 2007;18:172.
39. Gürel S, İmadoğlu O. Varis ve Malignite Dışı Üst Gastrointestinal Sistem Kanamalarının Değerlendirilmesi. Uludağ Üniversitesi Tıp Fakültesi Dergisi. 2004;30:87.

40. Chen C, Hung M, Chiu T, et al. Risk scoring systems to predict need for clinical intervention for patients with nonvariceal upper gastrointestinal tract bleeding. Am J Emerg Med. 2007;25:774–9.

41. Srirajaskanthan R, Conn R, Bulwer C, et al. The Glasgow Blatchford scoring system enables accurate risk stratification of patients with upper gastrointestinal hemorrhage. Int J Clin Pract. 2010;64:868-74.

42. Sorensen HT, Mellemkjaer L, Blot WJ. Risk of Upper gastrointestinal bleeding associated with use of low-dose aspirin. Am J Gastroenterol. 2000;95:2218-24.

43. Capet C, Czernichow P, Dupas JL, et al. Upper gastrointestinal bleeding in patients treated by low-dose aspirin. Gastroenterol Clin Biol. 2001;25:233-8.

Available online at www.medicinescience.org

ORIGINAL ARTICLE

Medicine Science International Medical Journal

Medicine Science 2021;10(1):153-6

Dermatologic findings in patients with exogenous obesity: A prospective- clinical investigation

Pelin Hizli[1], Ulker Gul[2], Muzeyyen Gonul[2], Yavuz Yalcin[3], Serdar Guler[4], Dilek Berker[5]

[1]Balikesir University, Faculty of Medicine, Department of Dermatology, Balikesir, Turkey
[2]Diskapi Training and Research Hospital, Department of Dermatology, Ankara, Turkey
[3]Memorial Hospital, Department of Endocrinology, Istanbul, Turkey
[4]Liv Hospital, Department of Endocrinology, Ankara, Turkey
[5]Ankara Bilkent City Hospital, Department of Endocrinology, Ankara, Turkey

Received 23 January 2021; Accepted 01 February 2021
Available online 09.02.2021 with doi: 10.5455/medscience.2021.01.023

Abstract

Obesity caused by overnutrition without any underlying organic problem is referred to as exogenous (primary) obesity. The aim of this study was to investigate dermatologic findings and their associations with anthropometric parameters in patients with exogenous obesity.From the patients with presenting symptom of obesity, we included 66 with the diagnosis of exogenous obesity. We excluded the patients with following diseases that might cause dermatologic symptoms: Diabetes mellitus, hyperthyroidism, hypothyroidism, polycystic ovarian syndrome, renal diseases, and hepatic diseases. After comprehensive dermatologic examination, we noted all findings for each patient. We performed a statistical analysis to assess the association between dermatological findings and body- mass index, waist circumference, hip circumference and waist/hip ratio.Sixty-four (97%) patients had at least one dermatologic finding. The most common dermatologic findings were plantar hyperkeratosis (63.6%), stria (56.1%), acrochordon (56.1%), and hyperhidrosis (54.5%). Presence of plantar hyperkeratosis, stria, and hyperhidrosis were significantly higher in females compared with males (p=0.013, p=0.004, p=0.032, respectively). The mean body mass index was significantly higher in patients with acanthosis nigricans and keratosis pilaris (p=0.016). The mean waist circumference was significantly higher in patients with hirsutism (p<0.039) and the mean hip circumference was significantly higher in patients with stria, intertrigo and acanthosis nigricans (p=0.012, p=0.045). The mean waist/hip ratio was significantly higher in patients with keratosis pilaris (p=0.024).Obesity has a significant association with various dermatologic findings as do main anthropometric parameters of obesity.

Keywords: Obesity, hyperkeratosis, acrochordon, hyperhidrosis, body-mass index, stria.

Introduction

Obesity, the excess of rational or total body fat, can cause many severe health problems [1,2]. Multiple etiologic factors may play a role in the mechanism of obesity[3]. According to the classification based on its causative mechanism, obesity caused by overnutrition without any underlying organic disorder is referred to as exogenous or primary obesity and the one caused by a hormonal or a genetic disorder is referred to as endogenous or secondary obesity [4, 5]. Obesity may lead multiple systemic complications including hypertension, coronary artery disease, cerebrovascular disease, sleep apnea, hiatal hernia, gallbladder stone, hepatic steatosis, colorectal carcinoma, metabolic dyslipidemia, type 2 diabetes mellitus, hyperuricemia, locomotor osteoarthritis and deep venous thrombosis. In addition to these systemic complications, obesity may have many different effects on the skin [6]. There exist multiple different mechanisms of the effects of the obesity on the skin. It may affect the barrier function, sebaceous glands, production of the sebum, sweat glands, lymphatics, collagenous structures and their functions, wound healing, microcirculation, macrocirculation, and the components of subcutaneous fat tissue. It may also cause many types of dermatosis, affecting the sensitivity of the skin, heat distribution and the structure of the feet [7].

In the prior literature, a limited number of studies focusing the effects of obesity on the skin are available [8, 9]. These prior publications usually focused on obesity together with other conditions such as diabetes mellitus [9, 10]. To the best of our knowledge, no study thus far has investigated the dermatologic findings particularly in the patients with exogenous obesity, in

***Coresponding Author:** Pelin Hizli, Balikesir University, Faculty of Medicine, Department of Dermatology, Balikesir, Turkey
E-mail: pelinhizli@gmail.com

the literature of English language. The goal of this prospective -multidisciplinary -clinical study was to investigate dermatologic symptoms occurring in patients with exogenous obesity, and the factors affecting these symptoms.

Materials and Methods

Patients and Study Design

This prospective, clinical study was conducted in line with the dictates of Helsinki Declaration and approved by the local ethical committee of Ankara Numune Training and Research Hospital) (IRB Number: 2011-137). From the patients with the presenting symptom of obesity between April 2011 and June 2011 in our tertiary institution, 66 with the diagnosis of exogenous obesity (age range: 19-69 years) were included in the study. The patients with exogenous obesity were referred us from the endocrinology clinic of our tertiary institution after taking a detailed patient history, a comprehensive physical examination and laboratory analysis, with a record of additional diseases.We excluded the patients with following diseases that might cause dermatologic symptoms: diabetes mellitus, hyperthyroidism, hypothyroidism, polycystic ovarian syndrome (PCOS), renal diseases and hepatic diseases. We noted all skin findings of every single patient after comprehensive dermatologic examination.

We confirmed the diagnosis of obesity calculating the body- mass index (BMI) for all patients using the well- known formula "[BMI = weight (kg) / height (m^2)]" [11]. Diagnosed as obesity were the patients with BMI more than 30. We noted the waist circumferences of all patients measuring at the level of belly, parallel to the ground. Additionally, we noted the hip circumferences measuring at the level of pubis anteriorly and at the level of the point at which greater gluteal muscle is most prominent posteriorly.

Of the patients with acrochordons, we noted the number of the lesions. To confirm the presence of any fungal infection, we performed a native fungus scanning for patients with lesions consistent with superficial fungal infections like tinea pedis and onychomycosis clinically.

We assessed the association between the gender and the frequency of dermatological findings. We excluded hirsutism (a female disease) from the comparison of males and females.Additionally, we investigated the association between the anthropometric data of the patients (BMI, waist circumference, hip circumference, waist/hip ratio) and the presence of any dermatologic finding.

Statistical Analysis

We presented the results of continuous variables as mean ± standard deviation (SD), sequential variables as median (minimum-maximum) and categorical variables as percentage (%). We tested the normality of the distribution of the continuous variables using Shapiro Wilk test. We tested the importance of the differences of mean values among the groups using independent T test and median values using Mann Whitney U test. We tested the associationof categorical variables among the groups using Pearson's Chi-square or Fisher's exact test. To assess the correlation between the number of acrochordons and anthropometric measurement results, we used Spearman's correlation test. For the statistical analysis, we used SPSS 11.5 software for Windows (SPSS Inc., Chicago, IL). A *P* value less than 0.05 was considered statistically significant.

Results

From 66 patients, 16 (24.2%) were male and 50 (75.8%) were female. The mean age of the study population was 41.7±11.7 (19 - 69) years and the mean BMI was 39.7±7.5 (30- 60.9). Of the 66 patients, 25 (37.8%) had no disease coexisting with obesity. However, 42 (63.6%) patients had coexisting diseases as shown in table 1.

Table 1. Coexisting diseases in patients with exogenous obesity

	Frequency (n=42)	
	n	%
Hypertension	12	18.1
Sleep apnea syndrome	7	10.6
Asthma	6	9
Depression	3	4.5
Lumbar hernia	2	3
COPD	2	3
Migraine	2	3
Renal stones	2	3
Aortic insufficiency	1	1.5
Coronary artery disease	1	1.5
Hepatitis B carrier status	1	1.5
Endometrial myoma	1	1.5
Thyroiditis	1	1.5
History of gynecologic surgery	1	1.5

Dermatologic examination revealed that 64 (97%) patients had at least one dermatologic finding whereas 2 (3%) had no dermatologic finding. The most common dermatologic findings were plantar hyperkeratosis (63.6%), stria (56.1%), acrochordon (56.1%) and hyperhidrosis (54.5%) as shown in table 2.

Table 2. Dermatologic findings of the patients

	Frequency (n=66)	
	n	%
Plantar hyperkeratosis	42	63.6
Stria	37	56.1
Acrochordon	37	56.1
Hyperhidrosis	36	54.5
Intertrigo	19	28.8
Tinea pedis	15	22.7
Onychomycosis	13	19.7
Hirsutism	13	19.7
Folliculitis	8	12.1
Acanthosis nigricans	8	12.1
Keratosis pilaris	5	7.6
Psoriasis	3	4.5
Acne	2	3

The frequency of dermatologic findings in males and females were shown in table 3. Presence of plantar hyperkeratosis, stria, and hyperhidrosis were significantly higher in females compared with males (p=0.013, p=0.004, p=0.032, respectively). The mean anthropometric data of the patients with and without every single dermatologic findingwas shown in table 4. The mean BMI was significantly higher in patients with acanthosis nigricans and keratosis pilaris compared with the patients without acanthosis

nigricans and keratosis pilaris (p=0.016). The mean waist circumference was significantly higher in patients with hirsutism compared with the patients without hirsutism (p=0.039). The mean hip circumference was significantly higher in patients with stria, intertrigo and acanthosis nigricans compared with the patients without stria, intertrigo and acanthosis nigricans (p=0.012, p=0.045). The mean waist/hip ratio was significantly higher in patients with keratosis pilaris compared to the patients without keratosis pilaris (p=0.024), but it was significantly lower in patients with plantar hyperkeratosis compared to the patients withoutplantar hyperkeratosis(p=0.008). The number of acrochordons varied from 1 to 50 among patients and it was not significantly associated with the BMI, waist circumference, hip circumference, and waist/hip ratio of the patients (p >0.05).

Table 3. The frequency of dermatologic findings in males and females

	Females (n=50)	Males (n=16)	*P value*
Plantar hyperkeratosis	36 (72%)	6 (37.5%)	**0.013**
Stria	33 (66%)	4 (25%)	**0.004**
Acrochordon	28 (56%)	9 (56.3%)	0.986
Hyperhidrosis	31 (62%)	5 (31.3%)	**0.032**
Intertrigo	16 (32%)	3 (18.8%)	0.362
Tinea pedis	11 (22%)	4 (25%)	1.000
Onychomycosis	9 (18%)	4 (25%)	0.719
Folliculitis	4 (8%)	4 (25%)	0.075
Acanthosis nigricans	7 (14%)	1 (6.3%)	0.668
Keratosis pilaris	5 (10%)	0 (0%)	0.325

Table 4. The mean anthropometric data of the patients with and without every single dermatologic finding.

	BMI			Waist Circumference			Hip Circumference			Waist/Hip Ratio		
	-	+	*p*	-	+	*p*	-	+	*p*	-	+	*p*
Plantar hyperkeratosis	39.3±7.7	39.9±7.5	0.753	114.4±13.3	110.8±13.8	0.312	122.5±11.1	129.0±14.7	0.067	0.92±0.11	0.85±0.10	0.008
Stria	38.0±6.5	41.1±8.0	0.099	111.3±14.0	112.8±13.4	0.658	121.9±12.2	130.3±13.9	0.012	0.90±0.12	0.86±0.10	0.091
Acrochordon	39.1±7.9	40.2±7.2	0.567	109.8±13.1	114.0±13.8	0.214	127.7±16.1	125.8±11.7	0.598	0.85±0.11	0.90±0.10	0.079
Hyperhidrosis	38.0±7.2	41.1±7.6	0.097	110.2±13.5	113.7±13.6	0.290	124.4±12.6	128.5±14.5	0.223	0.88±0.12	0.88±0.10	0.971
Intertrigo	38.7±7.2	42.3±7.9	0.076	111.0±12.6	114.9±15.7	0.295	124.5±12.0	131.9±16.5	0.045	0.88±0.11	0.87±0.10	0.715
Tinea pedis	39.4±7.4	40.9±7.8	0.500	111.8±13.6	113.1±14.0	0.746	125.9±14.5	129.1±10.9	0.440	0.88±0.12	0.86±0.10	0.529
Onychomycosis	39.5±7.6	40.7±7.1	0.593	112.7±13.3	109.9±15.1	0.519	126.5±14.1	127.2±12.5	0.863	0.88±0.11	0.85±0.16	0312
Hirsutism	39.3±6.2	44.2±9.8	0.117	109.2±11.3	117.4±14.0	0.039	126.3±12.2	134.2±17.5	0.079	0.86±0.10	0.88±0.10	0.508
Folliculitis	39.6±7.5	41.2±7.2	0.574	112.2±13.7	112.6±14.2	0.934	125.9±13.8	133.9±11.1	0.124	0.88±0.11	0.82±0.10	0.120
Acanthosis nigricans	38.9±7.4	45.6±4.9	0.016	111.2±13.6	118.6±12.2	0.150	125.1±13.6	137.9±9.5	0.012	0.88±0.11	0.86±0.10	0.604
Keratosis pilaris	39.1±7.1	47.4±8.3	0.016	111.2±13.4	123.2±11.6	0.057	126.7±13.8	126.0±14.5	0.915	0.87±0.10	0.98±0.16	0.024

- : absence, +: presence

Discussion

Dermatologic findings of the patients with obesity have an implication for physicians to find out the causative mechanisms of these findings and to keep the other associations of the obesity with different organ systems in mind. Despite this implication, prior studies focusing on the frequency and number of dermatologic findings are quite limited as are the studies about the causative mechanism of these findings. In the perspective of conducting a study with select patients of obesity, this is the first study in the literature,conducted only with exogenous obesity patients.In addition, this study investigated the association of dermatologic findings with anthropometric parameters, unlike previous literature.

Hidalgo et al. reported the most common dermatologic findings of the patients with obesity as acrochordons, stria, plantar hyperkeratosis, acanthosis nigricans and keratosis pilaris respectively [9]. However, Mutairi reported the most common finding as plantar hyperkeratosis, followed by acanthosis nigricans, acrochordons, stria, intertrigo, acne, hirsutism, folliculitis, tinea cruris, and hyperhidrosis [8]. In these studies, reported dermatologic findings were almost similar but we should bear in mind that they included patients with diabetes mellitus and other diseases that might cause dermatologic findings in their study population. Unlike these publications,we excluded the patients with diseases that might cause dermatologic findings like diabetes mellitus, hyperthyroidism, hypothyroidism, PCOS, renal diseases and hepatic diseases. In our study, we found the prevalence of acanthosis nigricans lower than in these studies. Because we excluded the patients with diabetes, this finding suggests that acanthosis nigricans might have an association with diabetes mellitus. Supporting this contention, Hud et al. reported a higher fasting plasma insulin level in patients with obesity and acanthosis nigricans, compared to the patients without acanthosis

nigricans, suggesting the presence of acanthosis nigricans as a marker of hyperinsulinemia [12]. Additionally, the reason for lower prevalence of acanthosis nigricans in our study might be the exclusion of the patients with PCOS.

In consistent with the prior literature, we found plantar hyperkeratosis as the most common dermatologic finding. Hills et al. reported that a higher pressure on the feet of the patients with obesity caused plantar hyperkeratosis and structural differences of musculoskeletal system between males and females might be the cause of higher incidence of plantar hyperkeratosis in females [13]. In consistent with this report, we found the prevalence of plantar hyperkeratosis higher in females than in males.

Kahana et al. reported that any association between the presence of acrochordons and obesity was not present, but presence of acrochordons might be associated with increased risk of diabetes mellitus and carbohydrate metabolism disorder [10]. Despite this report, we found acrochordons in 56% of our study group. Accordingly, presence of acrochordons might be directly associated with obesity as well as glucose intolerance, because we did not evaluate the glucose intolerance of the patients in our study group. Demir et al. supported this contention with their study reporting that presence of acrochordons was associated with glucose intolerance [14].

In consistent with the study of Yosipovitch et al. [15], we found a positive correlation between the presence of keratosis pilaris and BMI. However Barth et al. reported that obesity was not effective on the development of keratosis pilaris alone [16]. Because of different reports from various studies, the association of presence of keratosis pilaris with obesity remains a matter of debate.

We found a higher prevalence of tinea pedis and onychomycosis in our study than in the previous study of Şahin et al. that focus on general population [17]. Thus, we can hypothesize that,dermatophyte infections might be more common in patients with obesity compared to the normal population.

Hirsutism was a common finding in female patients of our study group with a frequency of 26%. Higher incidence of hirsutism despite the exclusion of the patients with PCOS might be associated with ethnic factors. Additionally, in contrast with previous publications [18], we did not found any significant association between BMI and presence of hirsutism, but found that presence of hirsutism was significantly higher in patients with higher waist circumference.

Although focusing on a limited population of obesity to determine absolute association of dermatological findings with obesity, this study has some limitations. The major limitation was the number of patients. The descriptive statistics might have been more meaningful if more patients had been included. The lack of comparison of dermatologic findings with another patient group with different features was another limitation for this study as well as the lack of a control group.

Conclusion

In conclusion, obesity has a significant association with dermatologic findings as do main anthropometric parameters of obesity. The most common dermatologic findings of the patients with exogenous obesity wereplantar hyperkeratosis, stria,acrochordons, and hyperhidrosis, respectively. Plantar hyperkeratosis and hyperhidrosis were more common in females than in males. Presence of acanthosis nigricans and keratosis pilaris were significantly associated with higher BMI. We found a significant association between the presence of hirsutism and waist circumference;presence of stria, intertrigo and acanthosis nigricans with hip circumference; and presence of plantar hyperkeratosis and keratosis pilaris with waist/hip ratio.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
All authors declare no financial support.

Ethical approval
All procedures performed in this study were in accordance with the ethical standards of local ethical committee of Ankara Bilkent City Hospital (formerly: Ankara Numune Training and Research Hospital) (IRB Number: 2011-137)

References

1. Hellerstein M, Parks E. Obesity & Overweight. In: Greenspan F, Gardner D (eds). Basic and clinical endocrinology, 7 Edition. New York: The McGraw-Hill Companies, Inc. 2004;794-813.
2. Klein S, Romijn J. Obesity. In: Kronenberg H, Melmed S, Polonsky K, Larsen P (eds). Williams textbook of endocrinology, 11 Edition. Philadelphia: Saunders Elsevier. 2008;1563-88.
3. Ersoy R, Çakır B. Obezite. Turk Med J. 2007;1:109-11.
4. Flier S, Folder D. Eating disorders: obesty, anorexia nervosa, and blumia nervosa. In: Wilson. Foster D, Kronenberg H, Larsen P (eds). Williams Textbook of Endocrinology, 9 Edition. Philadelphia: W. B. Saunders Company. 1998;1061-95.
5. Günöz H. Çocuk ve Adölesanlarda Obezite. Aktüel Tıp Dergisi. 2001;6:58-61.
6. Kopelman B. Defining overweight and obesity. In: Kopelman P, Dunıtz M (eds). The management of obesity and related disorders. London: Taylor & Francis e-Library, 2003;1-10.
7. Scheinfeld NS. Obesity and dermatology. Clin Dermatol. 2004;22:303-9.
8. Al-Mutairi N. Associated cutaneous diseases in obese adult patients: a prospective study from a skin referral care center. Med Princ Pract. 2011;20:248-52.
9. Garcia-Hidalgo L, Orozco-Topete R, Gonzalez-Barranco J, et al. Dermatoses in 156 obese adults. Obes Res. 1999;7:299-302.
10. Kahana M, Grossman E, Feinstein A, et al. Skin tags: a cutaneous marker for diabetes mellitus. Acta Derm Venereol. 1987;67:175-7.
11. Garrow JS, Webster J. Quetelet's index (W/H2) as a measure of fatness. Int J Obes. 1985;9:147-53.
12. Hud JA, Jr., Cohen JB, Wagner JM, et al. Prevalence and significance of acanthosis nigricans in an adult obese population. Arch Dermatol. 1992;128:941-4.
13. Hills AP, Hennig EM, McDonald M, et al. Plantar pressure differences between obese and non-obese adults: a biomechanical analysis. Int J Obes Relat Metab Disord. 2001;25:1674-9.
14. Demir S, Demir Y. Acrochordon and impaired carbohydrate metabolism. Acta Diabetol. 2002;39:57-9.
15. Yosipovitch G, Mevorah B, Mashiach J et al. High body mass index, dry scaly leg skin and atopic conditions are highly associated with keratosis pilaris. Dermatol. 2000;201:34-6.
16. Barth JH, Wojnarowska F, Dawber RP. Is keratosis pilaris another androgen-dependent dermatosis? Clin Exp Dermatol. 1988;13:240-1.
17. Sahin I, Oksuz I, Kaya I, et al. Dermatophytes in the rural area of Duzce, Turkey. Mycoses. 2004;47:470-4.
18. Ruutiainen K, Erkkola R, Gronroos MA, et al. Influence of body mass index and age on the grade of hair growth in hirsute women of reproductive ages. Fertil Steril. 1988;50:260-5.

Available online at www.medicinescience.org

ORIGINAL ARTICLE

Medicine Science International Medical Journal

Medicine Science 2021;10:157-61

Computational binding analysis and toxicity evaluation of estrogen receptor with estradiol and the approved SERMs raloxifene, tamoxifen, and toremifene

Esma Eryilmaz Dogan

Department of Biomedical Engineering, Faculty of Technology, Selcuk University, Konya, Turkey

Received 11 August 2020; Accepted 02 December 2020
Available online 20.01.2021 with doi: 10.5455/medscience.2020.08.161

Abstract

Estrogen receptor is a key feature of many complex disorders. Natural estrogen ligand, estradiol has been investigated in the pharmaceutical aspect of breast cancer, Parkinson's, Alzheimer's, risk of stroke in postmenopausal women, and dementia. From the similar manner, synthetic selective estrogen receptor modulators (SERMs) have been investigated, and their pharmaceutical effects have been evaluated in compared to the natural ligand, estradiol, in literature. To design better alternatives to the approved SERMs and to improve the clinical observations, it is crucial to understand the molecular basis of drug-target interactions of estrogen receptor with the natural and synthetic ligands in a comparative manner. We used molecular modeling softwares PyRX, Avogadro, and Arguslab for in silico calculations. The results were analyzed using PyMol. We, in this study, provided a computational binding analysis of the estrogen receptor with the endogenous ligand estradiol and the FDA approved SERMs raloxifene, tamoxifen, and toremifene. We investigated the toxicity profile of the SERMs and estradiol and interpreted the results according to the reported clinical observations. We found that designing new molecules based on the estradiol structure instead of the approved tamoxifen analogs could result in better clinical observations for future estrogen targeting therapeutics.

Keywords: Estrogen receptor; estradiol; in silico; tamoxifen; raloxifene; molecular docking; toxicity

Introduction

Breast cancer, described by uncontrolled growth of epithelial cells in breast is the second most common type of cancer in women. It is also seen rare cases in men. Over time, breast cancer has been classified based on the mechanism and the pathways of carcinoma, and these classifications have resulted in the fundamental targets for prognosis and treatment of the disease. Hormonal targets such as progesterone, androgen, and especially estrogen receptors (ER) constitute an important group of molecular targets as the hormone-receptor positive breast cancer constitutes two cases out of three diagnosis according to the American Cancer Society [1]. Estrogen receptor is actively used in today's diagnosis of breast cancer and the treatment has been based on the level of estrogen receptor found in the body.

***Coresponding Author:** Esma Eryilmaz Dogan, Department of Biomedical Engineering, Faculty of Technology, Selcuk University, Konya, Turkey
E-mail: eeryilmaz@selcuk.edu.tr

Estradiol, the natural and endogenous ligand, also known as E2 is a hormone binding the estrogen receptor, circulating within the human body, and acting as a main female sex hormone. Estradiol plays important roles in many biological process such as regulating ERα levels in hypothalamic neurons [2], signaling for estrogen dependent behavior [3], and protecting hippocampal neurons [4]. Its neuroprotective effect has also been clearly established from animal studies [5, 6]. Binding of estradiol with ER gives insight regarding binding energy, binding pocket, and other binding related parameters. Therefore, we used estradiol for investigating the binding dynamics of ER and comparing the results with the FDA approved synthetic ligands, raloxifene, tamoxifen, and toremifene, called selective estrogen receptor modulators (SERMs). Binding of estrogen receptor with a bioactive small molecule has been manipulated to control the functionality of estrogen with synthetic ligands. For that, tamoxifen has been approved by FDA in 1977 to treat ER+ breast cancer upon with the proven benefits of the molecule in clinic. However, later studies have shown that patients treated with tamoxifen have been found developing an

increased risk of liver tumor and endometrial cancers [7-9]. Those results have led to the search for better alternatives to tamoxifen. Therefore, its structural analogs toremifene and raloxifene have been approved later, and their clinical results of toxicity are not quite convincing yet.

Binding parameters of ER with a ligand could be experimentally determined by controlling equilibrium binding assays performed mostly with radiolabeled compounds. Computational investigation of binding details, however, is less time-consuming and relatively easy to perform. Therefore, we, in this study, investigated the binding parameters including the types of interaction, association constant, and the binding energy of the complex structure of estrogen with bounded ligands. We tried to understand the reported clinical results with the resulting molecular based computational analysis. Receptor protein estrogen is bound with the natural ligand estradiol, and synthetic SERMs, tamoxifen, toremifene and raloxifene. We, in this study, investigated the binding affinity and the types of binding between the natural and the synthetic ligands listed above in a comparative manner using computational technique, molecular modeling, and molecular docking procedure.

Materials and Methods

Ligand Structures Preparation

SMILES codes of the small molecule ligands estradiol, raloxifene, tamoxifen and toremifene were obtained from the website of PubChem, the National Institutes of Health (NIH), USA. Four ligand molecules approved by FDA, their DrugBank identification numbers, the first year of approval, and their SMILES codes were given in Table 1. The 2D and 3D structures of the ligands were provided in Figure 1. The sdf files of the ligands were downloaded from the DrugBank website, https://www.drugbank.ca/ [10], and the molecules were minimized to their stable 3D configuration using the geometry optimization tool of Avogadro software to be used in molecular docking procedure. The minimized 3D structures obtained from Avogadro were verified with the 3D structure provided in DrugBank. Geometry optimization was repeated many times till no change is seen in the molecular geometry meaning that a stable minimized structure was reached. ArgusLab [11] and PyRX [12] softwares were also used for energy minimization of the ligand structures, but they could not reach a stable configuration of their molecular geometry.

Table 1. The natural and the FDA approved synthetic ligands interacting with ER. The chemical names of the molecules, their ID codes, the year of approval, and the SMILES codes

Chemical name	Drug Bank ID	Year of approval	SMILES
Estradiol	DB00783	1954	[H][C@@]12CC[C@H](O)[C@@]1(C)CC[C@]1([H])C3=C(CC[C@@]21[H])C=C(O)C=C3
Raloxifene	DB00481	1997	OC1=CC=C(C=C1)C1=C(C(=O)C2=CC=C(OCCN3CCCCC3)C=C2)C2=C(S1)C=C(O)C=C2
Tamoxifen	DB00675	1977	CC\C(=C(/C1=CC=CC=C1)C1=CC=C(OCCN(C)C)C=C1)C1=CC=CC=C1
Toremifene	DB00539	1997	CN(C)CCOC1=CC=C(C=C1)C(=C(\CCCl)C1=CC=CC=C1)\C1=CC=CC=C1

Target Molecule Preparation

The crystal structure of ER was downloaded from the Protein Data Bank, http://www.rcsb.org/ [13] in a complex form of the protein molecule itself with different ligands and water molecules. For searching ER structure in Protein Data Bank, we restricted the database search to `Homo sapiens only', and the crystal structure of 6SQ0 at the resolution of 1.77 Å was downloaded [14]. The ER structure was cleaned by removing miscellaneous two groups using ArgusLab, a molecular modeling software package (http://www.arguslab.com/ arguslab.com/ArgusLab.html). We kept water molecules to able to observe possible hydrogen bindiureg with the ligands. The cleaned pdb file of the target molecule ER was saved to be used in docking procedure.

Molecular Docking

Molecular docking of the ligand molecules into the ER was performed by using PyRX, an open source virtual screening software, with an exhaustiveness value of 8 [12]. The minimized 3D structures of the ligands were opened in PyRX and converted to pdbqt file. Only chain A of all ligands was incorporated into the blind docking. Vina search space was selected as a cube of 25x25x25 Å3. The best possible interaction poses and their interaction energies were calculated by AutoDock Vina. Visualization and analysis of the docking poses of the complex structures were performed by PyMol, a molecular graphics system [15].

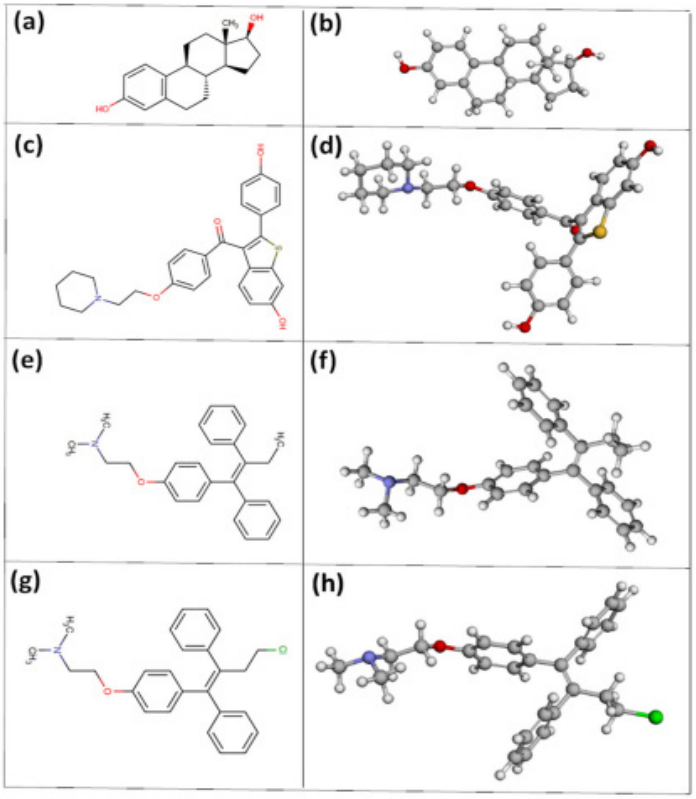


Figure 1. The 2D and 3D minimized structures of estradiol (a,b), raloxifene (c,d), tamoxifen (e,f), and toremifene (g,h)

Results

Molecular Docking

In silico molecular docking is often used to study the binding affinity of a drug candidate with a receptor molecule, mostly proteins. We, in this study, investigated the theoretical interaction profile of the estrogen receptor bounded with the natural ligand estradiol and the three FDA approved drugs raloxifene, tamoxifen, and toremifene to compare the binding parameters of the natural ligand with the synthetic ones and to understand their clinical observations better. The complex structure of the ER upon molecular docking of four ligand molecules was shown in Figure 2. The lowest energy binding poses of the three synthetic ligands were computationally observed as bounded at the same binding pocket of ER with estradiol as shown in Figure 2.

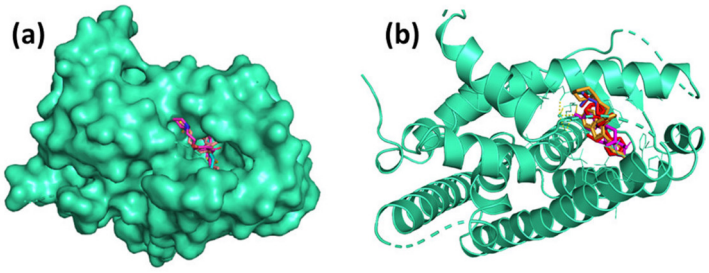


Figure 2. a) The overall topology of ER and b) the binding site of four ligands, estradiol, raloxifene, tamoxifen, and toremifene docked into the same binding pocket of ER (6SQ0).

The binding energies of the ER - ligand complex structures calculated by AutoDock Vina and shown in Figure 3 were provided in Table 2. Estradiol, as expected, was resulted in the highest number of polar bonds in the bond lengths of 3.2 Å, 2.4 Å, and 2.3 Å. Estradiol bound ER was resulted in one of the highest energy of -9.7 kcal/mol. Raloxifene which was approved in 1997 followed the natural ligand estradiol with the same binding energy and only one polar bond in a length of 3.2 Å. Tamoxifen and toremifene approved in 1977 and 1997, respectively, followed them with the interaction energy of -8.8 kcal/mol and with only one polar bond of 2.6 Å. An animal study performed on rats showed that raloxifene resulted in more stable down-regulation of ERβ and ERβ2 after 72 h of treatment compared to tamoxifen and toremifene [16]. The results of this animal study support our computational results leading to the more stable binding complex of raloxifene bound with estrogen than the other two ligands, tamoxifen and toremifene. Time dependent regulation of ODC (ornithine decarboxylase), an essential enzyme for cell growth was also studied with estradiol and the SERMs mentioned [16]. The enzyme activity study on the comparative efficacy of estradiol and the SERMS showed that tamoxifen and toremifene resulted in a similar time–dependent regulation of ODC, but the marked effect was less than that of estradiol. And yet, Raloxifene which was resulted in the same binding energy with natural estradiol showed even weaker ODC activity. When we compared the effect of estradiol and the synthetic SERMs on the induction of ODC genes, estradiol showed a quite high activity than those of SERMs. Moreover, another animal study showed that even though raloxifene increased the estrogenic effect in brain, that effect of raloxifene did not resulted in positive influence of estrogen in cognitive performance of brain [17]. That might be related to the less number of interactions with a specific binding site of estrogen performed by estradiol, but not by raloxifene. Neuroprotective effect of estradiol and some SERMs have also been studied on animals, and different mechanisms of neuroprotection have been found in SERMs and in estradiol [18]. Based on these animal tests, clinical reports, and our in silico results, estradiol structure could be used for designing new drug molecules and for searching better alternatives than that of tamoxifen analogs.

Table 2. The binding parameters of the structure of ligand-ER upon docking

Ligand molecule	Energy (kcal/mol)	Number of polar interaction	Polar bond lengths (Å)
Estradiol	-9.7	3	3.2, 2.4, 2.3
Raloxifene	-9.7	1	3.2
Tamoxifen	-8.8	1	2.6
Toremifene	-8.8	1	2.6

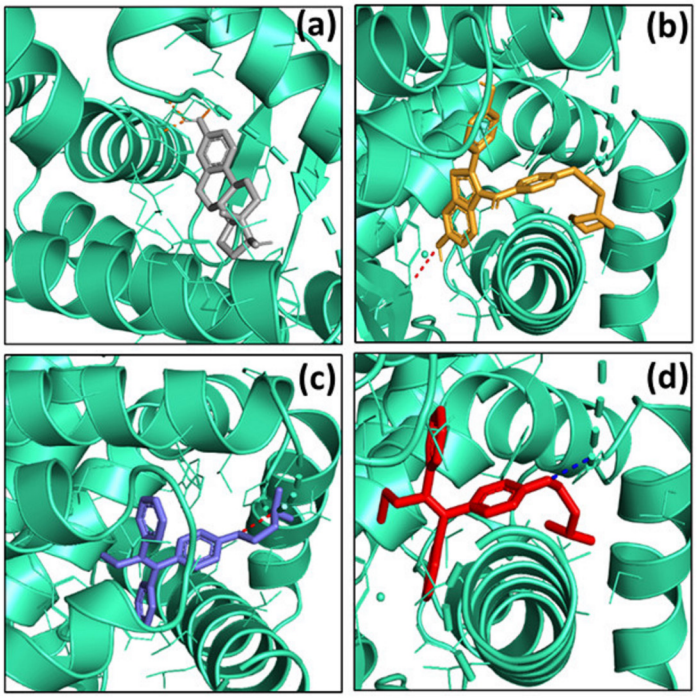


Figure 3. The binding site and the interactions of a) estradiol, b) raloxifene, c) tamoxifen, and d) toremifene with estrogen receptor (6SQ0).

Physico-chemical Properties

Calculating physico-chemical properties and evaluating its drug-likeness profile is a common way of investigating how a ligand is molecularly and pharmaceutically appropriate to be a bioavailable and effective drug. Based on this fact, we calculated the molecular structural properties of the ligands estradiol and SERMs listed above in order to help with understanding the clinical results of the natural and the synthetic ligands in a comparative manner. The results of the calculations were provided in Table 3. While the natural ligand estradiol gave appropriate drug-likeness properties explained in our previous study [19], the approved drug molecules, the synthetic ligands raloxifene, tamoxifen, and toremifene resulted in not a very convenient picture with a miLog P value above 6. A Log P value higher than five is considered as a violation of the 'rule of five' reported by Lipinski as a drug-likeness criteria [20]. A previous study performed on the patented molecules in between the year of 2000 and 2010, Log P value was ranged from 3.5 to 4.5 [21].

A higher Log P value meaning a higher molecular hydrophobicity could cause negative effects on the pharmacological properties of the molecule such as solubility and even toxicity [22]. Although docking results of raloxifene was promising, its molecular weight is also quite higher than the threshold of 500 g/mol in terms of the 'rule of five', the common drug-likeness criteria. So, the effort of lowering Log P value and lowering the molecular weight could be a good approach to designing new SERMs. Because of the higher Log P value, all synthetic ligands raloxifene, tamoxifen, and toremifene were resulted in one violation of drug-likeness criteria, although estradiol obeyed all of them.

Table 3. Physico-chemical properties of the natural and the synthetic ligand molecules

Ligand molecule	miLog P	TPSA	MW	NOH	NOHNH	Nvio
Estradiol	3.43	40.46	272.4	2	2	0
Raloxifene	6.22	70.00	473.5	5	2	1
Tamoxifen	6.06	12.47	371.5	2	0	1
Toremifene	6.06	12.47	405.9	2	0	1

MiLog P: Logarithm of partition coefficient, MW: molecular weight in the unit of gr/mol, TPSA: topological polar surface area in the unit of Å, NOH: the number of hydrogen bond donor, and NOHNH: the number of hydrogen bond acceptor

Toxicity Evaluation

We explored the potential toxicity of the ligand molecules in a color-coded manner using the Osiris Property Explorer program (www.organicchemistry.org/prog/peo/). Toxicity risk categories were classified in the program as mutagenic, tumorigenic, irritant effects, and reproductive effects. High risk of undesired effects was represented in red, whereas drug-like behavior is colored in green. The results showed that synthetic drugs did not really exhibit conform as of the natural ligand estradiol. Raloxifene and tamoxifen showed a safer profile in toxicity table (Table 4) except a high risk on reproduce effects, whereas toremifene showed a high risk of tumorigenicity and reproductive effect and a moderate risk on mutagenicity. Toremifene has been actually approved upon the undesirable effects of tamoxifen observed in the clinical trials. It was developed to produce a similar efficacy with tamoxifen but an improved safety profile. Several investigations showed that tamoxifen increased the risk of hepatocarcinoma in rats [23] and gastrointestinal and endometrial cancers in human [7, 24]. According to our toxicity analysis, toremifene had an even higher toxicity risk profile than that of tamoxifen. Clinical trials of toremifene and tamoxifen performed in 2014 have shown some common adverse effects such as hot flashes, vaginal dryness, discharge, bleeding, and vomiting [25]. More than that, phase III trials of toremifene have shown that efficacy and safety is comparable to that of tamoxifen in postmenopausal women with ER+ or ER- [26]. Moreover, the risk of endometrial cancer was evaluated for toremifene and tamoxifen, and almost the same number of incidence have been found in both group of patients [27]. The results showed that the molecular structure of the synthetic SERMS raloxifene, tamoxifen, and toremifene were not close enough to the best alternative the natural ligand estradiol. Instead of modifying the structure of tamoxifen approved in 1977 and not much been preferred for treatment any more (https://go.drugbank.com/drugs/DB00675), creating model drug structure on the lead of the molecular structure of estradiol would result in more effective clinical observations according to our in silico molecular drug-target interaction study.

Table 4. Physico-chemical properties of the natural and the synthetic ligand molecules

Ligand molecule	Mutagenic	Tumorigenic	Irritant	Reproductive
Estradiol	Green	Green	Green	Green
Raloxifene	Green	Green	Green	Red
Tamoxifen	Green	Green	Green	Red
Toremifene	Orange	Red	Green	Red

Discussion

Our computational results were analyzed in terms of three different aspect of molecular docking, physico-chemical properties, and toxicity evaluation. Molecular docking analysis provided that all of the ligands were bound with the same binding pocket of the ER molecule, however, more important point than that is the binding details with the number of polar bonds and polar bond lengths. Those details exhibited that estradiol has the best structure to bind with ER resulting with the highest binding energy and with three polar bonds. Raloxifene followed estradiol giving the same binding energy, but only one polar bond. Although these results were significant, ligands should be investigated in terms of drug-likeness profile and toxicity prediction.

Drug-likeness parameters with related physico-chemical properties were investigated for all of the ligand structure, and the results were meaningful. Tamoxifen analogs failed to obey one of the most important drug-likeness parameter, Log P value, although estradiol showed the best value of 3.43 leading to the reported range of Log P [21]. On the other hand, molecular weight of tamoxifen analogs is also close to the reported limit of 500 gr/mol [20]. For the ER targeted therapeutics, our results showed that tamoxifen analogs are not really best structure to continue with the investigation. Instead, based on the estradiol structure, its bioisosteric analogs with the new promising elements studied in recent medicinal chemistry such as silicon and/or boron are worth to investigate and could give a better pharmacological and toxicology profile [28].

Another important aspect of bioactive compounds to be a god oral bioavailable drug is toxicity evaluation. Although literature has a good number of ER targeted studies, they are lack of toxicity investigation [29]. Our results additionally provided a potential toxicity risk prediction for all ligands, and tamoxifen analogs exhibited one or more toxic effects on different fields. Tamoxifen and Raloxifene showed a relatively better toxic profile resulting in high risk of reproductive effect. Toremifene, on the other hand, exhibited even worse toxicity profile including mutagenic and tumorigenic effect in addition to the reproductive effect. These potential risk predictions are also consistent with the clinical cancer reports provided by patients taking the tamoxifen analogs.

Conclusion

We used the molecular docking procedure to investigate the binding interactions of estrogen receptor with a natural ligand estradiol and the synthetic ligands raloxifene, tamoxifen, and toremifene in a comparative manner. We computationally evaluated their relative toxicity profile and compared them with the reported clinical

observations. The most favorable binding pose was obtained with the details of the interaction types, and the coordinates of all ligands and target estrogen. The results showed that estradiol has the most appropriate structure to interact with estrogen receptor with the highest binding energy and three stable interactions among other ligands. Based on those in vitro studies and our computational toxicity and pharmacological results, we suggest that new design drug molecules using the estradiol structure as a lead molecule would be resulting in better pharmaceutical consequences both in vitro and in clinic. Our theoretical binding analysis of an hormone receptor, estrogen with experimentally studied natural and synthetic ligands is considered to give insight to the future estrogen-ligand interaction studies before performing costly experimental testing.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
All authors declare no financial support.

Ethical approval
Manuscript does not include any human or animal materials.

References

1. Cristofanilli M and Hortobagyi GN. Molecular targets in breast cancer: current status and future directions. Endocr Relat Cancer. 2002;9:249-66.
2. Dominguez R and Micevych P. Estradiol rapidly regulates membrane estrogen receptor α levels in hypothalamic neurons. J Neurosci. 2010;30):12589-96.
3. Dewing P, Boulware MI, Sinchak, K. et al. Membrane estrogen receptor-α interactions with metabotropic glutamate receptor 1a modulate female sexual receptivity in rats. J Neurosci. 2007;27):9294-300.
4. Ciriza I, Carrero, P, Azcoitia, I. et al. Selective estrogen receptor modulators protect hippocampal neurons from kainic acid excitotoxicity: differences with the effect of estradiol. J Neurobiol. 2004;61:209-21.
5. Azcoitia I, Sierra A, and Garcia-Segura LM. Estradiol prevents kainic acid-induced neuronal loss in the rat dentate gyrus. Neuroreport. 1998;9:3075-9.
6. Reibel S, André V, Chassagnon S. et al. Neuroprotective effects of chronic estradiol benzoate treatment on hippocampal cell loss induced by status epilepticus in the female rat. Neurosci Lett. 2000;281:79-82.
7. Fisher B, Costantino JP, Redmond CK. et al. Endometrial cancer in tamoxifen-treated breast cancer patients: findings from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14. JNCI: J Natl Cancer Inst. 1994;86:527-37.
8. Carthew P, Rich KJ, Martin EA. et al. DNA damage as assessed by 32P-postlabelling in three rat strains exposed to dietary tamoxifen: the relationship between cell proliferation and liver tumour formation. Carcinogenesis. 1995;16:1299-304.
9. Levenson AS and Jordan VC. The key to the antiestrogenic mechanism of raloxifene is amino acid 351 (aspartate) in the estrogen receptor. Cancer Res. 1998;58:1872-5.
10. Wishart DS, Feunang YD, Guo AC. et al. DrugBank 5.0: a major update to the DrugBank database for 2018. Nucleic Acids Res. 2018;46:1074-82.
11. Thompson MA. ArgusLab 4.0. 1. Planaria Software LLC, Seattle, WA, 2004.
12. Dallakyan S and Olson AJ. Small-molecule library screening by docking with PyRx. Methods Mol Biol. 2015;1263:243-50.
13. Berman HM, Westbrook J, Feng Z. et al. Th e protein data bank. Nucleic Acids Res. 2000;28:235-42.
14. Scott JS, Breed J, Carbajo RJ. et al. Building Bridges in a Series of Estrogen Receptor Degraders: An Application of Metathesis in Medicinal Chemistry. ACS Med Chem Lett. 2019;10:1492-7.
15. Schrodinger L. The PyMOL molecular graphics system, version 1.8. Schrodinger LLC, New York, NY, 2015.
16. Green AR, Parrott EL, Butterworth M. et al. Comparisons of the effects of tamoxifen, toremifene and raloxifene on enzyme induction and gene expression in the ovariectomised rat uterus. J Endocrinol. 2001;170:555-64.
17. Gibbs RB, Gabor R, Cox T. et al. Effects of raloxifene and estradiol on hippocampal acetylcholine release and spatial learning in the rat. Psychoneuroendocrinology. 2004;29:741-8.
18. Ciriza I, Carrero P, Azcoitia I. et al. Selective estrogen receptor modulators protect hippocampal neurons from kainic acid excitotoxicity: differences with the effect of estradiol. J Neurobiol. 2004;61:209-21.
19. Eryilmaz E. Multi-targeted anti-leukemic drug design with the incorporation of silicon into Nelarabine: How silicon increases bioactivity. Eur J Pharm Sci. 2019;134:266-73.
20. Lipinski CA. Avoiding investment in doomed drugs. Curr Drug Discov. 2001;1:17-9.
21. Leeson PD and St-Gallay SA. The influence of the'organizational factor'on compound quality in drug discovery. Nat Rev Drug Discov. 2011;10:749.
22. Waring MJ. Lipophilicity in drug discovery. Expert Opin Drug Dis. 2010;5:235-48.
23. Vancutsem PM, Lazarus P, and Williams GM. Frequent and specific mutations of the rat p53 gene in hepatocarcinomas induced by tamoxifen. Cancer Res. 1994;54:3864-67.
24. Rutqvist LE, Johansson H, Signomklao T. et al. Adjuvant tamoxifen therapy for early stage breast cancer and second primary malignancies. Stockholm Breast Cancer Study Group. J Natl Cancer Inst. 1995;87:645-51.
25. Vogel CL, Johnston MA, Capers C. et al. Toremifene for breast cancer: a review of 20 years of data. Clin Breast Cancer. 2014;14:1-9.
26. Milla-Santos A, Milla L, Rallo L. et al. Phase III randomized trial of toremifene vs tamoxifen in hormonodependant advanced breast cancer. Breast Cancer Res Tr. 2001;65:119-24.
27. Zhou W-B, Ding Q, Chen L. al. Toremifene is an effective and safe alternative to tamoxifen in adjuvant endocrine therapy for breast cancer: results of four randomized trials. Breast Cancer Res Tr. 2011;128:625-31.
28. Dogan, EE. Computational Bioactivity Analysis and Bioisosteric Investigation of the Approved Breast Cancer Drugs Proposed New Design Drug Compounds: Increased Bioactivity Coming with Silicon and Boron, Lett Drug Des Discov. DOI: 10.2174/1570180818666210114115415
29. Sayan M, Durjoy M. Computational molecular docking assessment of hormone receptor adjuvant drugs: Breast cancer as an example. Pathophysiology. 2009;16:19-29. .

Available online at www.medicinescience.org

ORIGINAL ARTICLE

Medicine Science International Medical Journal

Medicine Science 2021;10:162-8

DNA profiling for forensic identification in Bulgarian Turks

Elif Canpolat[1], Emel Hulya Yukseloglu[1], Fatma Cavus Yonar[1], Gulten Rayimoglu[1], Ozge Pasin[2], Ahmet Dirican[3], Onur Ozturk[4],

[1]Istanbul University-Cerrahpasa, Institute of Forensic Sciences and Legal Medicine Cerrahpasa, Istanbul, Turkey
[2]Department of Biostatistics and Medical Informatics, Health Sciences Institute, Istanbul University, Istanbul, Turkey
[3]Department of Biostatistics, Faculty of Medicine, Istanbul University Cerrahpasa, Istanbul, Turkey
[4]Deparment of Biophysics, Faculty of Medicine, Malatya Turgut Ozal University, Malatya, Turkey

Received 10 December 2020; Accepted 12 January 2021
Available online 26.01.2021 with doi: 10.5455/medscience.2020.12.254

Abstract

Forensic statistical parameters based on allelic frequencies of commonly used STRs (Short Tandem Repeats) were estimated for the Bulgarian Turks. The 6-dye GlobalFiler™ PCR amplification kit incorporates 21 autosomal STRs, providing reliable DNA typing results with enhanced the power of discrimination. Here, we analyzed the GlobalFiler™ STR loci in 150 unrelated individuals from Bulgaria Turks who was born in Bulgaria, lived there and then have settled in Turkey. A total of 329 alleles were observed ranging between 5 and 37 repeat units, and SE33 showed the greatest power of discrimination (40 alleles) in Bulgaria Turks population.
Blood and intraoral swab samples were collected from 150 Bulgarian Turks whose consent was obtained beforehand. DNA isolation was performed by using QIamp DNA Mini Isolation Kit. After quantification of the obtained DNA, the next step, PCR, was carried out using the GlobalFiler ™ STR kit. The DNA amplified after PCR was analyzed for profiling by running on ABI 3130 Genetic Analyzer. Allele frequencies and forensic statistical calculations were performed with Arlequin v 3.5.2.2 program. Allele frequencies were compared with Spain, Europe, Middle East, Africa, America, Central Asia, Japan, and Turkish populations. When the loci were examined in general, it was observed that the Turkish population had the closest frequency value to the group we studied, and the African and Central Asian populations had the farthest frequency value. The present study provides precise reference database for forensic applications and population genetic studies.

Keywords: Population genetics, allele frequency, STR, DNA analysis, globalfiler, forensic genetics, statistics, Bulgarian Turks

Introduction

DNA analysis, which is used routinely in basic sciences for various purposes, is used in the forensic sciences to present objective evidence in courts. In the forensic sciences, DNA analyzes are used in paternity and / or maternity detection cases, criminal cases, identification of missing persons and disaster victims [1,2]. DNA analysis consists of two steps: determination of DNA profile from biological samples and interpretation of evidence obtained from DNA. In order to interpret the evidence obtained from the DNA molecule correctly, it is necessary to know how often genetic signs are seen in the relevant population [3,4].

***Coresponding Author:** Elif Canpolat, Istanbul University-Cerrahpasa, Institute of Forensic Sciences and Legal Medicine Cerrahpasa, Istanbul, Turkey
E-mail: emelhulyayukseloglu@gmail.com

In the non-coding DNA regions (introns), especially the regions formed by repeating the number of nucleotide sequences of different lengths repeatedly, have a high polymorphic value [5]. All people have the same sequences, but the number of repeats varies from person to person. These repeated sequences are hereditary characters suitable for Mendelian inheritance and are polymorphic due to the variation in the number of repeats. In DNA profiling, these repeated sequences are used [4,5]. STR loci have been preferred in forensic sciences since 1993 because of their small allele length and short analysis time, yielding results even in old and poorly preserved biological samples, enabling multiple analyzes and their suitability for automation [6-8].

The microsatellites are preferred in forensic sciences because the fact that they are very small fragments, they can be obtained from

damaged or even small amounts of DNA, the obtained results can be repeated, that the mutation rate is low. In addition to these advantages, the fact that many STR regions are analyzed at the same time and the discrimination power has increased has made it one of the leading techniques used in forensic sciences [9].

The GlobalFiler ™ STR kit was created by upgrading the 13 CODIS (Combined DNA Index System) loci to 20 loci and was made available to the laboratories . In fact, the GlobalFiler ™ STR kit can be called a system created by combining and developing the Identifiler® Kit and NGM SElect ™ Kits. The NGM SElect ™ kit includes the STR regions defined by the ESS (European Standard Set of Loci), which is used mostly in Europe, while the Identifiler® Kit is a FBI and consequently a CODIS-based system. Since the last locus of CODIS is located within the ESS, the GlobalFiler ™ STR kit has become a global system combining CODIS and ESS regions [10]. Because of these distinctive features, GlobalFiler ™ STR kit was used in our study. One of the most important features of the GlobalFiler ™ STR kit is the use of the combination of Y-chromosomal DYS391 and Y-indel, which compensates for the deficiencies in highly degraded samples in which DYS391 may fail, and thus greatly assist in the determination of highly degraded samples. The use of this feature helps to identify the victim of the disaster, to identify generations / genealogies and to clarify cases of sexual assault. In addition, the inclusion of the SE33 locus within the ESS, which has a high discriminatory power, improves the quality of the studies [1,11,12].

The allele frequency of STR loci varies in all populations. Therefore, genetic frequencies of genetic markers used in forensic sciences should be determined for each population and a database should be established. In the statistical calculations made in the evaluation of the results of DNA analysis, it is important to use the exact community database[12-14]. Located on a major migration route and has hosted many civilizations territory of Turkey has many racial and ethnic groups. Bulgarian Turkish immigrants, who have a considerable population especially in the Marmara Region, are an effective resource for population studies as they are included in the ethnic and cultural diversity of our country. In this regard, the purpose of our study is to identify the gene frequency in the specified locus for Bulgaria Turks who was born in Bulgaria, lived there and then have settled in Turkey by using GlobalFiler ™ STR kit, and to provide a use in forensic laboratories.

Materials and Methods

Sample Collection

This study was conducted with the permission of Istanbul University, Cerrahpasa Faculty of Medicine Clinical Research Ethics Committee (No:381416, dated 03.12.2015). Blood samples and buccal cell swabs were collected from 150 unrelated healthy Bulgarian Turk donors following informed consent.

105 blood samples were taken into 2 mL EDTA tubes and brought to the laboratory in accordance with the cold transport chain. 45 intraoral swab samples were taken from the mouth with sterile swabs and dried at room temperature. The collected samples were stored at -20 ° C until the time of study. All the studies were carried out using devices and equipments in the Forensic Molecular Genetic Laboratory of Istanbul University-Cerrahpaşa Forensic Medicine Institute.

Application of the Method

DNA isolation and quantification

DNA isolation was performed with silica-based QIAamp® DNA Mini Kit (Qiagen, Stanford, CA, USA) from 2mL blood samples taken into EDTA tubes and intraoral swab samples taken from sterile swabs [16]. The DNA quantification of the isolates was determined using the Qubit® fluorometer (Applied Biosystems) using the Quant-iT dsDNA HS (High Sensetive) Assay kit (Invitrogen, Paisley, Renfrewshire, UK) [17].

Amplification of the Samples by Polymerase Chain Reaction

The GlobalFiler ™ STR kit, which was stored at -20ºC, was used at this stage of the study. PCR analysis was performed on the GeneAmp 9700 (Thermo Fisher Scientific Company) according to the parameters set forth in Table 1. A negative control was used for each amplification to control contamination during the PCR stage and a positive control was used to determine if the method was working correctly [18].

Table 1. Cycling Conditions

PCR Steps	Temprature	Time
Initial incubation	95°C	1 minute
Denate	94°C	20 seconds
Anneal	59°C	90 seconds
Extend		
Final Extension	60°C	10 minutes

Running Samples in Capillary Electrophoresis

Electrophoresis of PCR products was performed by using 4 capillary ABI PRISM® 3130 Genetic Analyzer (Applied Biosystems Foster City, California) in Istanbul University-Cerrahpaşa Forensic Molecular Genetics Laboratory.

Analysis of Capillary Electrophoresis Data

After electrophoresis, visualization, typing and evaluation of the raw data obtained from the samples were performed using GeneMapper® ID-X software v1.4 (Applied Biosystems) analysis program [19]. Statistical calculations of raw data (allele frequencies, Fst values obtained for comparison with other countries) were analysed with Excel based PowerStats and Arlequin v 3.5.2.2. analysis programs [20,21]. Allele frequencies were compared with Turkish, Spanish, European, Middle Eastern, African, American, Central Asian and Japanese populations.

Results

Blood samples and buccal cell swabs were collected from 150 unrelated healthy Bulgarian Turk donors following informed consent. The amount of DNA measured by fluorimetric method of all samples used in our study ranged between 0.88 and> 600 ng / µl. The silica based QIAamp® DNA Mini Kit (Qiagen, Stanford, CA, USA) was used for DNA isolation. PCR amplifications were performed using the GlobalFiler™ STR according to the manufacturers' recommendations. Amplified products were analyzed using ABI 3130 sequencers and allele designations

were made corresponding to GlobalFiler Allelic Ladder (Applied Biosystems).

Data from each study were analyzed using GeneMapper ID-X 1.4 software (Life Technologies / Thermo Fisher Scientific, USA) with a global cut-off value of 20%. This 20% cut-off filter removes small peaks less than or equal to 20% of the height of the highest peak in a given location. Electroprograms were checked using GeneMapper ID-X and, if necessary, a noise peak (s) such as plus and / or minus stutter peaks were manually removed. The low allele peaks, which are automatically removed by the 20% cut-off filter, are manually added. Electrophoregrams of 24 loci are shown in Figure 1 and Figure 2.

The allele frequencies (Table 2) and forensic parameters (Table 4) were determined for 21 STR autosomal loci (D8S1179, D21S11, D7S820, CSF1PO, D3S1358, TH01, D13S317, D16S539, D2S1338, D19S433, VWA, TPOX, D18S51, D5S818, FGA, D10S1248, D1S1656, D22S1045, D2S441, D12S391 and SE33). The allele frenquencies obtained from using Arlequin v 3.5.2.2 are shown in Table 2, the expected & observed heterozygosity rates, and Hardy-Weinberg equilibrium results from using Arlequin v 3.5.2.2 are shown in Table 3 [21].

Table 2. Allele frequencies of 21 autosomal STR loci obtained for a population of 150 Bulgarian Turk individuals genotyped using the GlobalFiler kit.

Alel	D3S1358	vWa	D16S539	CSF1PO	TPOX	D8S1179	D21S11	D18S51	D2S441	D19S433	TH01	FGA	D22S1045	D5S818	D13S317	D7S820	SE33	D10S1248	D1S1656	D12S391	D2S1338
5					0.007																
6				0.007	0.027					0.007	0.237	0.003				0.007					
6.3																	0.003				
7				0.027	0.010	0.003		0.003			0.160			0.007		0.037	0.010				
7.3					0.007						0.003										
8			0.047	0.010	0.073	0.020		0.003		0.007	0.100	0.003	0.003	0.007	0.180	0.193	0.003			0.003	
9			0.153	0.073	0.293	0.007	0.003	0.007	0.017	0.003	0.187	0.003		0.037	0.133	0.087	0.013				
9.3							0.007				0.223	0.003									
10		0.003	0.100	0.293	0.293	0.087		0.017	0.170	0.013	0.043		0.007	0.050	0.043	0.300	0.007				0.003
11			0.337	0.293	0.253	0.030		0.023	0.260	0.007	0.007		0.157	0.330	0.283	0.227	0.007	0.017	0.117		
11.2										0.013	0.003										
12	0.003	0.003	0.200	0.253	0.037	0.157		0.093	0.120	0.100	0.003		0.017	0.347	0.283	0.097	0.007	0.040	0.063		0.013
12.2										0.103											
12.3								0.003						0.003							
13	0.003	0.007	0.147	0.037		0.347	0.003	0.130	0.070	0.170	0.007		0.007	0.187	0.060	0.023	0.020	0.217	0.073	0.007	0.010
13.2										0.197											
13.3											0.003										
14	0.037	0.083	0.013	0.007	0.007	0.167		0.173	0.297	0.140		0.003	0.070	0.017	0.013		0.050	0.343	0.080		
14.2										0.063	0.003										
14.3										0.010	0.003						0.003		0.003		
15	0.253	0.097	0.003			0.123		0.133	0.060	0.090		0.010	0.373	0.007	0.003	0.003	0.053	0.160	0.183	0.060	0.003
15.2										0.023											
15.3																			0.023		
16	0.377	0.230				0.047		0.173	0.003	0.043		0.003	0.247	0.007			0.070	0.163	0.167	0.010	0.057
16.3																			0.027	0.003	
17	0.150	0.313				0.013		0.087	0.003	0.007		0.010	0.083	0.003		0.017	0.117	0.047	0.070	0.123	0.197
17.3								0.003											0.100	0.020	
18	0.150	0.147						0.070				0.003	0.020				0.070	0.007	0.050	0.180	0.093
18.3																			0.013	0.013	0.003
19	0.023	0.073						0.037				0.070	0.003				0.087		0.003	0.130	0.077
19.3												0.007								0.030	0.007
20	0.003	0.033						0.017			0.003	0.137	0.007			0.003	0.087		0.013	0.080	0.133
20.2												0.003									
20.3																				0.003	
21								0.010				0.163	0.003				0.033		0.003	0.137	0.037
21.2												0.003					0.007				
21.3												0.020									
22		0.003						0.007				0.193					0.017	0.003	0.003	0.073	0.060
22.2																	0.033				
22.3												0.003									
23		0.003						0.003			0.007	0.123	0.003							0.073	0.087
23.2																0.007	0.027				
23.3										0.003		0.010									
24		0.003									0.003	0.090					0.007			0.040	0.113
24.2							0.003										0.027		0.003		
24.3												0.003									
25							0.003					0.077					0.007		0.003	0.010	0.103
25.2																	0.020				
26							0.200				0.003	0.030					0.013			0.003	0.003
26.2																	0.023				
26.3												0.003									
27							0.017					0.007					0.003				
27.2																	0.017				
28							0.130					0.007					0.017				
28.2																	0.037	0.003			
28.3							0.003														
29							0.313	0.003				0.003									
29.2							0.007										0.040				
29.3							0.007														
30							0.173	0.003													
30.2							0.033										0.013				
31							0.043										0.007				
31.2							0.053										0.020				
31.3							0.003														
32							0.020					0.003									
32.2							0.110										0.013				
33.2							0.030														
34																	0.003				
34.2							0.007														
35																	0.003				
36							0.007														
36.2							0.003										0.003				
37																	0.003				

Using Arlequin v3.5.1.2, the Hardy-Weinberg Complete Test was performed to determine whether any tribal specimen exhibited detectable deviations from equilibrium expectations. The test phase used 1,000,000 Markov chains and 100,000 dememorization steps. The significance level was accepted as p = 0.05 (Table 3).

Table 3. Statistics obtained from using Arlequin v 3.5.2.2

	Na	Ne	I	Ho	He	uHe	F	P value	S.D.	Garza Williamson index
D3S1358	9	3.952916	1.550688	0.76	0.747022	0.749521	-0.01737	0.39091	0.00067	1,00000
VWA	13	5.115962	1.849563	0.806667	0.804533	0.807224	-0.00265	0.04300	0.00440	0,86667
D16S539	8	4.745334	1.707324	0.773333	0.789267	0.791906	0.020188	0.21300	0.00010	1,00000
CSF1PA	9	4.099854	1.589642	0.733333	0.756089	0.758618	0.030096	0.04000	0.00410	1,00000
TPOX	10	3.132832	1.420714	0.653333	0.6808	0.683077	0.040345	0.61818	0.00033	0,13158
D8S1179	12	5.052773	1.878937	0.84	0.802089	0.804771	-0.04727	0.03100	0.00520	1,00000
D21S11	24	6.058158	2.222919	0.853333	0.834933	0.837726	-0.02204	0.98000	0.00023	0,33333
D18S51	21	8.431703	2.35221	0.906667	0.8814	0.884348	-0.02867	0.05300	0.00302	0,45652
D2S441	10	4.824702	1.741015	0.773333	0.792733	0.795385	0.024472	0.00909	0.01401	1,00000
D19S433	18	8.127145	2.309121	0.793333	0.876956	0.879889	0.095355	0.04200	0.00355	0,32727
TH01	18	5.603985	1.919979	0.793333	0.821556	0.824303	0.034352	0.17020	0.00142	0,42857
FGA	29	8.490566	2.438231	0.853333	0.882222	0.885173	0.032746	0.87080	0.00039	0,38667
D22S1045	14	4.211117	1.719472	0.806667	0.762533	0.765084	-0.05788	0.11090	0.00262	0,87500
D5S818	12	3.727943	1.557305	0.786667	0.731756	0.734203	-0.07504	0.09701	0.00394	0,32432
D13S317	8	4.621072	1.673358	0.733333	0.7836	0.786221	0.064148	0.95000	0.00022	1,00000
D7S820	12	5.053341	1.835132	0.713333	0.802111	0.804794	0.11068	0.01500	0.00713	0,22222
SE33	40	18.51852	3.21684	0.926667	0.946	0.949164	0.020437	0.03400	0.00495	0,57143
D10S1248	10	4.520342	1.699022	0.74	0.778778	0.781382	0.049793	0.01421	0.00756	0,17857
D1S1656	18	9.127789	2.402548	0.873333	0.890444	0.893423	0.019216	0.03300	0.00508	0,37255
D12S391	19	9.3187	2.429389	0.8	0.892689	0.895674	0.103831	0.05132	0.00391	0,38776
D2S1338	17	9.041591	2.36577	0.786667	0.8894	0.892375	0.115509	0.39091	0.00067	0,37778
TOTAL MEAN	15.7619	6.46554	1.994247	0.795556	0.81652	0.81925	0.024298			0,58287
TOTAL SE	1.725032	0.74485	0.095406	0.014204	0.014414	0.014462	0.01186			

Na: No. of Different Alleles, Ne: No. of Effective Alleles = 1 / (Sum pi^2), I: Shannon's Information Index = -1* Sum (pi* Ln (pi)), Ho: Observed Heterozygosity= No. of Hets / N, He: Expected Heterozygosity= 1- Sum pi^2, uHe: Unbiased Expected Heterozygosity = (2N / (2N-1))*He, F: Fixation Index= (He-Ho) / He= 1-(Ho / He), S.d: Standart Deviation
Where pi is the frequency of the ith allele fort he population & Sum pi^2 is the sum of the squared population allele frequencies.

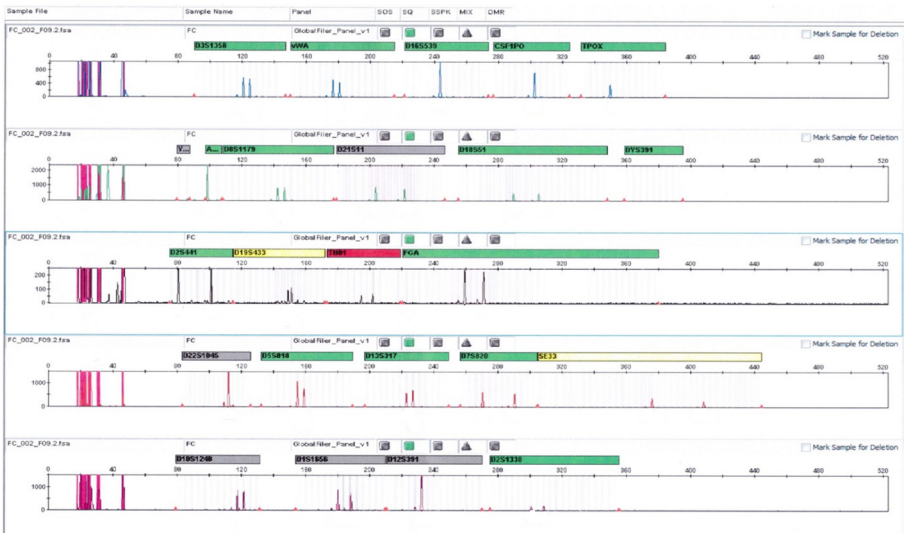


Figure 1. Female Electrophoregram

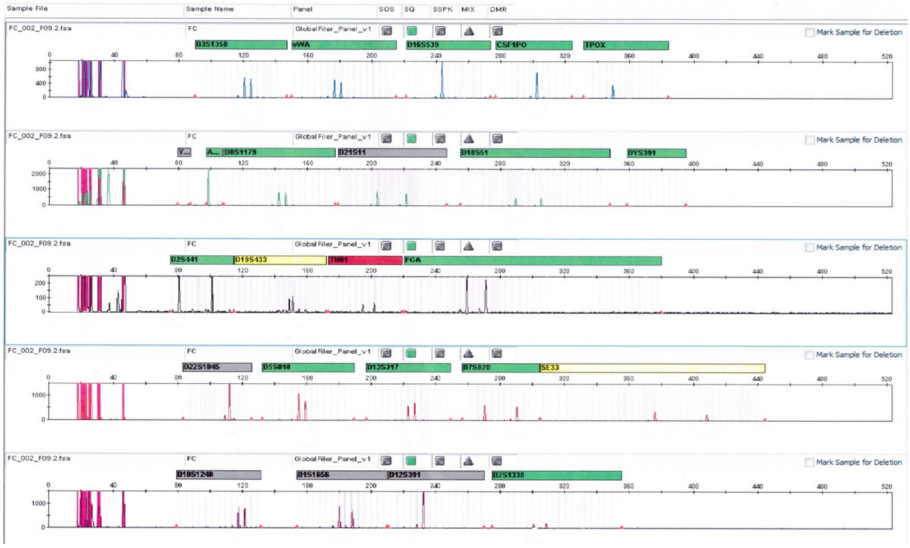


Figure 2. Male Electrophoregram

Probability of match (PM), power of discrimination (PD), polymorphism information content (PIC), power of exclusion (PE), typical paternity index (TPI) and Heterozygosity (He) were calculated roughly with the Excel based PowerStats (Table 4).

In the combined dataset, there were 9 loci that exhibited statistically significant deviations from HWE based on the exact test ($p<0.05$) which might be expected given population substructure. The marker SE33 exhibited the highest Hobs (0.92667), PD (0.9847), PIC (0.9418), PE (0.8471) and TPI values (6.6818) making it the most variable locus when compared to the other loci in this dataset. On the other hand, the less informative marker was TPOX (Table 4) .

Table 4. Forensic statistical parameters obtained from Power Stats

	PM	Expressed as 1 in ...	PD	PIC	PE	TPI	Homozygotes	Heterozygotes	Total Alleles
D3S1358	0.1188	8.4207	0.8812	0.7083	0.5270	2.0833	0.2400	0.7600	300
VWA	0.0716	13.9752	0.9284	0.7794	0.6115	2.5862	0.1933	0.8067	300
D16S539	0.0802	12.4723	0.9198	0.7604	0.5505	2.2059	0.2267	0.7733	300
CSF1PA	0.1089	9.1837	0.8911	0.7181	0.4817	1.8750	0.2667	0.7333	300
TPOX	0.1644	6.0811	0.8356	0.6302	0.3598	1.4423	0.3467	0.6533	300
D8S1179	0.0676	14.8026	0.9324	0.7790	0.6753	3.1250	0.1600	0.8400	300
D21S11	0.0720	13.8795	0.9280	0.8083	0.7031	3.4286	0.1458	0.8542	300
D18S51	0.0339	29.5276	0.9661	0.8699	0.8091	5.3571	0.0933	0.9067	300
D2S441	0.0868	11.5210	0.9132	0.7618	0.5478	2.1912	0.2282	0.7718	300
D19S433	0.0444	22.5350	0.9556	0.8646	0.5816	2.3871	0.2095	0.7905	300
THO1	0.0698	14.3312	0.9302	0.7973	0.5867	2.4194	0.2067	0.7933	300
FGA	0.0346	28.8700	0.9654	0.8693	0.6995	3.3864	0.1477	0.8523	300
D22S1045	0.1073	9.3206	0.8927	0.7299	0.6115	2.5862	0.1933	0.8067	300
D5S818	0.1297	7.7108	0.8703	0.6873	0.5745	2.3438	0.2133	0.7867	300
D13S317	0.0834	11.9936	0.9166	0.7510	0.4817	1.8750	0.2667	0.7333	300
D7S820	0.0747	13.3929	0.9253	0.7752	0.4492	1.7442	0.2867	0.7133	300
SE33	0.0153	65.2840	0.9847	0.9418	0.8471	6.6818	0.0748	0.9252	300
D10S1248	0.0856	11.6822	0.9144	0.7473	0.4928	1.9231	0.2600	0.7400	300
D1S1656	0.0291	34.4202	0.9709	0.8805	0.7396	3.9211	0.1275	0.8725	300
D12S391	0.0281	35.6356	0.9719	0.8825	0.5966	2.4833	0.2013	0.7987	300
D2S1338	0.0302	33.0882	0.9698	0.8795	0.5745	2.3438	0.2133	0.7867	300

Allelic frequencies were compared to previously published population data from Turkey (publication in preparation), as well as, others populations, namely, Spain, Middle East, Europe, Africa, America, Central Asia and Japan[22,23-26]. F-statics was performed Arlequin v3.5.1.2 and the results revealed that most of the molecular variation was due to variation between different populations. In the exact test of population differentiation, no major differences were observed with the populations of Turkey (FST=0,00014) and Middle East (FST=0,00027). Statistically significant differences were found with the populations of Japan (FST= -0,00001) and Spain (FST=0,00432) (Table 5).

Table 5. Computing conventional F-Statistics from haplotype frequencies

	BGTR	Turkey	Spain	Middleeast	Europe	Africa	America	Centralasia	Japan
BGTR	0.00000								
Turkey	0.00014	0.00000							
Spain	0.00432	0.00389	0.00000						
Middleeast	0.00027	-0.00003	0.00324	0.00000					
Europe	0.00051	0.00013	0.00375	0.00008	0.00000				
Africa	0.00090	0.00021	0.00383	0.00045	0.00049	0.00000			
America	0.00042	0.00007	0.00369	0.00010	0.00008	0.00027	0.00000		
Centralasia	0.00080	0.00078	0.00304	0.00051	0.00040	0.00136	0.00061	0.00000	
Japan	-0.00001	0.00010	0.00519	0.00017	0.00027	0.00058	0.00043	0.00064	0.00000

Discussion

The allele frequency of STR loci varies in all populations. For this reason, allele frequencies of genetic markers used in forensic sciences should be determined for each population and a database should be established. In the statistical calculations made in the evaluation of the results of DNA analysis, it is very important to use the accurate society database.

Combined with the need to get more information from the limited samples obtained and to finalize the procedures faster, studies have begun to analyze multiple STR systems together. To analyze multiple sites in the genome, multiple (Multiplex) PCR kits including the addition of multiple sets of PCR primers were able to implement this idea.

With this application depending on the principle that the primers used during PCR are labeled with fluorescent dyes and subsequently resolved spectrally, it is possible to amplify the labeled STR regions using different colored fluorescent dyes and to determine the size of the regions [14,27].

As a result of increasing 13 CODIS loci to 20 bymultiplying in the PCR following analyzing with electrophoresis and, a global system was established with the combination of CODIS and ESS regions and was made available to the use of the laboratories [14]. This system, called GlobalFilerTM STR kit, was first applied in the Forensic Molecular Genetic Laboratory of Istanbul University-Cerrahpaşa Forensic Medicine Institute, where the study was carried out, and optimized in our laboratory.

In our study, we preferred the GlobalFiler ™ STR kit to the Promega PowerPlex® 21 kit with similar features; Identifiler STR kit, which has been used in the forensic molecular genetics laboratory of Istanbul University Institute of Forensic Medicine for a while, has been used in routine analysis and project studies, since it is the same company, its primer indexes are similar and provide convenience in validation and optimization phase. Changes in primer sequences between commercial kits causes allele inconsistencies, allele losses and peak height ratio risk. This requires extra time to identify problems [13].

Conclusion

In conclusion, a Bulgarian Turks population database has been established for the 21 STR systems studied by using the GlobalFiler ™ PCR kit. The population data published in this paper can be freely used for any all state and privately funded forensic laboratory in the field of human identification and paternity testing. The obtained results support the idea that GlobalFiler ™ PCR kit is very informative for forensic purposes in Turkey Population and presents a very helpful tool for forensic reference samples analysis..

Acknowledgment

Supporting this work with the project numbered FYL-2016-20229, we would like to thank the Istanbul University-Cerrahpasa Scientific Research Projects Unit and GENOMED company who provided us the GlobalFiler™ (Applied Biosystems) Kit and ABI 3130 device with the software.

Conflict of interests

The authors declare that they have no competing interests.

Financial Disclosure

Supporting this work with the project numbered FYL-2016-20229, we would like to thank the Istanbul University-Cerrahpasa Scientific Research Projects Unit

Ethical approval

This study was conducted with the permission of Istanbul University-Cerrahpaşa Medical Faculty Clinical Research Ethics Committee (No:381416, dated 03.12.2015). Blood samples and buccal cell swabs were collected from 150 unrelated healthy Bulgarian Turk donors following informed consent..

References

1. Hares, DR. Addendum to expanding the CODIS core loci in the United States. Forensic Science International. 2012;6: e135.

2. Vijg, J. Aging of the genome: the dual role of DNA in life and death. Oxford University Press. 2021;10(1)162-8 168.

3. Rudin N, Inman K. An introduction to forensic DNA analysis. CRC press, London, 2001.
4. Semikhodskii, A. Dealing with DNA evidence: a legal guide. Routledge-Cavendish, 2007.
5. Balding, D J. When can a DNA profile be regarded as unique?. Science & Justice. 1999;39:257-60.
6. Scientific Working Group on DNA Analysis Methods (SWGDAM). SWGDAM interpretation guidelines for autosomal STR typing by forensic DNA testing laboratories. 2010.
7. Aşıcıoğlu F. X-Kromozomal STR Polimorfizmi (DXS8377, DXS101, DXS6789, STRX-1, HUMHPRTB) Ve Türk Toplumundaki Alel Frekansları. Ph.D. thesis, Istanbul University, Istanbul, 2006.
8. Ezkurdia, I, Juan D, Rodriguez et al. Multiple evidence strands suggest that there may be as few as 19 000 human protein-coding genes. Human Molecular Genetics. 2014;23:5866-78.
9. Butler J M. Forensic DNA Typing. Biology, Technology, and Genetics of STR Markers. 2nd edition. Elsevier Academic Press, USA, 2005;87-117.
10. Martín, P, de Simón, L F, Luque G, et al. Improving DNA data exchange: validation studies on a single 6 dye STR kit with 24 loci. Forensic Science International: Genetics. 2014;13:68-78.
11. http://www.thermofisher.com/order/catalog/product/4476135 access date 28.07.2019
12. Hares D. Expanding the CODIS core loci in the United States. Forensic Science International: Genetics. 2012;6:52-4.
13. Yükseloğlu E H, Kara U. Hukukçular ve Genetikçiler için Temel Adli Genetik, 1. Baskı. Nobel Tıp Kitapevi, İstanbul, Türkiye. 2015.
14. Butler, J.M., Hill, C.R. and Coble, M.D. Variability of New STR Loci and Kits in US Population Groups. Promega Corporation Web site. http://www.promega.com/resources/articles/profiles-in-dna/2012/variability-of-new-str-loci-and-kits-in-uspopulation-groups access date 03.08.2019
15. Butler J M, Hill C R, Kline M C et al. The single most polymorphic STR Locus: SE33 performance in US populations. Forensic Sci. Int. Genet. Suppl. Ser. 2009;2:23-4.
16. https://www.qiagen.com/us/resources/download.aspx?id=62a200d6-faf4-469b-b50f-2b59cf738962&lang=en access date 20.07.2019
17. https://www.thermofisher.com/order/catalog/product/Q33120 access date 22.07.2019
18. http://www.thermofisher.com/order/catalog/product/4476135 access date 22.07.2019
19. http://tools.thermofisher.com/content/sfs/manuals/cms_041469.pdf. access date 22.07.2019
20. Crow J F. Hardy, Weinberg and language impediments. Genetics. 1999;152:821-5.
21. http://cmpg.unibe.ch/software/arlequin35/Arlequin35.html access date 12.06.2019
22. García O, Alonso J, Cano J A, et al. Population genetic data and concordance study for the kits Identifiler, NGM, PowerPlex ESX 17 System and Investigator ESSplex in Spain. Forensic Sci. Int. Genet. 2012;6:78-9.
23. http://spsmart.cesga.es access date 17.06.2019

Available online at www.medicinescience.org

ORIGINAL ARTICLE

Medicine Science International Medical Journal

Medicine Science 2021;10(1):169-73

A novel approach for hepatocellular carcinoma detection with region merging segmentation method

Mustafa Koc[1], Firat Hardalac[2], Berkan Ural[2]

[1]Firat University, Faculty of Medicine, Department of Radiology, Elazig, Turkey
[2]Gazi University, Department of Electrical Electronics Engineering, Ankara, Turkey

Received 09 October 2020; Accepted 04 November 2020
Available online 21.01.2021 with doi: 10.5455/medscience.2020.10.213

Abstract

We present a noninvasive method for the detection and an advanced segmentation of Hepatocellular carcinoma (HCC) based on Computed Tomography (CT) images.This proposed method basically starts with the processing of the data set. 60 CT images are prepared for the segmentation process. Image data is divided into two groups; 50 CT images of the HCC, and 10 CT images of the normal liver. The ground truth images are created with the specialist abdominal radiologist. Images are in 256x256 µm size in JPEG format. For the segmentation part, the Statistical Region Merging method is used. The proposed method consists of three main parts, these are thresholding, segmentation, and estimation of ROC parameters. By using the database and the ground truth, according to the simulation results, the average of the sensitivity, specificity, and accuracy are obtained as 0.7476 %, 0.9723 %, and 0.9502 %, respectively. In conclusion, HCC is the most common primary malignant tumor in the liver. It is considered an important and life-threatening disease. Early detection of liver cancer has become very important for the patients. The Region Merging Segmentation Method is a very useful liver segmentation technique for detection of the HCC.

Keywords: Liver cancer, diagnosis, computed tomography, statistical region merging method

Introduction

The increase in imaging methods used to evaluate the abdominal region has led to an increase in the detection of liver lesions. Small lesions have become identifiable as a result of technical developments in the field of radiology. Focal lesions detected in the liver can be benign and malignant lesions. Hepatocellular carcinoma (HCC) is the leading cause of cancer-related deaths and is the most common primary malignant tumor of the liver.

HCC is sixth in incidence and third in cancer mortality worldwide [1]. It is the most common primary liver cancer, with approximately 3/4 of cases occurring in Asia [2]. Despite advances in screening, diagnosis with treatment, incidence, and mortality continue to increase [3]. Early diagnosed lesions potentially have treatment options. Because the early diagnosis of HCC is very important.

***Coresponding Author:** Mustafa Koc, Firat University, Faculty of Medicine, Department of Radiology, Elazig, Turkey.
E-mail: mkoc44@yahoo.com

Radiological imaging methods, biomarkers, and biopsy are used for diagnosis. Imaging plays a very important role in diagnosing HCC. In high-risk patients, noninvasive diagnosis can be obtained with imaging findings.

After analyzing the literature according to the topic of liver segmentation, results were classified. There are three techniques. The first technique is based on a common probability model used for the segmentation process. This technique explains the differences in liver structure [4]. The second technique is learning-based methods. This method is the process of defining and recognizing patterns in an image for segmentation via clustering, neural network, and support vector machine methods [5,6]. The other technique is a region-based method. In this method, the region is iteratively merged by comparing unallocated neighboring pixels to the region [7,8]. In this study, generally, HCC detection with the hybrid region merging segmentation algorithm is given and summarized in detail.

Materials and Methods

The clinical research ethics board approval was received from the

Non-Interventional Clinical Research Ethics Committee from the Institutional Ethics Committee.

Proposed Method

Statistical Region Merging block diagram is mainly given and information is given in detail (Figure 1).

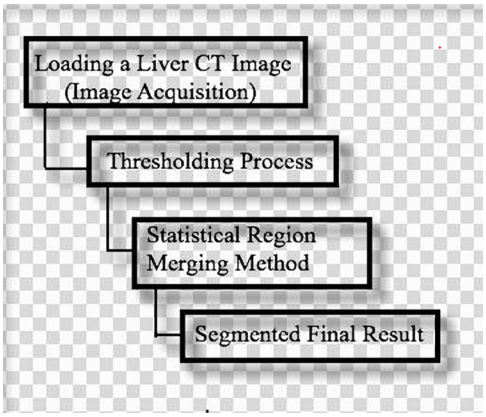


Figure 1. Proposed Statistical Region Merging Flowchart

Image Acquisition

This proposed method begins mainly with the process of the dataset 60 CT images are prepared for the segmentation process. Indeed, the image database which is used was collected from the university hospital and the ground truth images are created with a specialist abdomen radiologist. The images are in JPEG format, and 256x256 μm in a size. The image data are divided into two sets; 50 images of HCC and 10 images of normal liver CT.

Thresholding Process

Mainly, the image resizing process is achieved. The proper data set choose the whole process started with thresholding of the liver images which are done by analyzing the histogram of the image dataset and advanced thresholding techniques which are contrast/intensity-based and gray-scale image thresholding methods. The histogram processing of the image dataset to find the likelihood intensity of liver range is the most important part of the thresholding [9]. The histogram of the 60 gray images is also analyzed to find the range of liver. The liver pixels are separated from the abdomen CT image by using the two values k1 and k2, which represent the liver pixels, and the values before k1 and after k2 which represent the non-liver pixels will be assigned to zeros for elimination from the original image [10]. Finally, a binary image is obtained containing the liver pixel and all overlapping intensity with the liver pixel.

Statistical Region Merging Method

Because of the different shape of the liver, it is not possible to have an accurate segmentation in this step. The technique which is used in our proposed method is region merging that the pixel intensity is compared with a specific distance [11]. This technique starts with a definition of a specific pixel called the seed point. This can be chosen by using a common way. For each image, fixing a specific point in a way that will be very difficult for all images due to the liver shape variation [12]. Moreover, the region merging methods generally start by choosing a seed point. Then, the difference of a pixel's contrast/intensity value between the mean value of the region is added to the Region of Interest (ROI). This process will continue until the intensity value between the region and a new pixel becomes greater than a certain threshold.

Estimation of ROC Parameters

The receiver operating characteristic (ROC) has been developed to assess the balance between accuracy and sensitivity between the correct detection rate and the false detection rate of a receiver in a noisy channel in the signal detection theory [13]. Testing is often used to define their accuracy and to make the most accurate comparison among tests. In addition to being used mostly in medical decision-making processes, it is also being used effectively in research such as machine learning and data mining [14]. The receiver operating characteristic curves provide a good basis for analyzing the performance of the interpreter. A distinction must be made among the criterion that is used by the interpreter to determine the presence or absence of a condition and the ability of the interpreter to determine the condition. More simply, the receiver operating characteristic is the ratio of true positives to false positives. When a positive class p and a negative class are considered a binary classifier consisting of only two classes represented by n, the instances in the problem are mapped to one of classes n or p. In the binary classification, there are four different situations for a given example, as shown in Table 1.

Table 1. Performance segmentation measurements for Hepatocellular Carcinoma

TPR	TP / vessel number of pixels
FPR	FP / non-vessel pixel number
Specificity (SP)	TN / (TN + FP)
Sensitivity (SIN)	TP/(TP+FN)
Accuracy (Acc)	(TP+TN) FOV number of pixels

True Positive (TP) False Positive (FP)
True Negative (TN) False Negative (FN)

That is, when a pixel is classified as a precise reference (TP), it is classified as a true positive (TN). If it is classified as a definite reference. When the segmentation is regarded as a vein on the images, the classification is classified as a true negative (TN). One pixel in two misclassifications, false negative in a vein (FN). The vein is a segmented image and vein non-vein (FP) false positive in the image marked as absolute classified reference. TPR shows the proportion of positive samples (positive classification) among all positive samples (1) and FPR represents the proportion of positive samples (false classification) among all negative samples (2). The accuracy of the classification (Accuracy, ACC) is calculated by the ratio of correctly classified samples to all samples (3), (Table 2). That is, the correct positive ratio (TPR) represents the fraction perceived as the correct pixel vessel. False positivity rate (FPR) represents the fraction perceived as a false pixel vessel. Accuracy (ACC) is measured by the ratio of the number of pixels in the view image area (the sum of true positive and true negatives) to the total number of correctly classified pixels. Sensitivity (SN) reflects the algorithm's ability to detect pixels as veins. Specificity (SP) is the ability to detect non-vascular pixels.

Results

The proposed method for liver segmentation is applied to 60 CT images, respectively. These 60 images are divided into two parts. First, 50 liver CT images were used in different process training experiments, and 10 liver CT cases are used for the testing. During the thresholding process, some images are eliminated due to poor resolution and incorrect liver position. At the end of the process, excellent liver segmentation results are obtained from the approach. In Figure 2, one patient's original CT image (a), the segmented image (b), a ground truth image (c), the result of the statistical region merging in grayscale illustration (d) are given respectively. In the part of the 20 patients' estimation of ROC parameters, results which are sensitivity, specificity, accuracy is obtained and given in Table 3. It can be seen that the proposed segmentation method with adaptive thresholding and ROC result gives good results compared to manually segmented liver. Indeed, an average error percent of 5% for 10 test case studies is obtained and totally, the average success rate is calculated from the approach as approximately 95%. The sensitivity, specificity, and accuracy parameters are shown in a graph in detail (Figure 3).

Table 2. Calculation of sensitivity, specificity and accuracy

$$Sensitivity = \frac{TP}{TP + FN} \quad (1)$$

$$Specificity = \frac{TN}{TN + FP} \quad (2)$$

$$ACC = \frac{TP + TN}{TP + FN + TN + FP} \quad (3)$$

Table 3. The results of the sensitivity, specificity, accuracy

Number of Image	Sensitivity	Specificity	Accuracy
1	0.693743	0.984806	0.955713
2	0.59835	0.969622	0.94248
3	0.862632	0.97253	0.933944
4	0.757023	0.886511	0.945052
5	0.739277	0.820258	0.939693
6	0.680059	0.834271	0.950778
7	0.723745	0.718544	0.968658
8	0.913732	0.861778	0.968915
9	0.802457	0.88118	0.950662
10	0.741146	0.848047	0.951254
11	0.593823	0.976727	0.978815
12	0.752761	0.843156	0.9441
13	0.825041	0. 899431	0.941906
14	0.61513	0.934956	0.92719
15	0.827199	0.981036	0.959576
16	0.826387	0. 80997	0.945456
17	0.556886	0.823677	0.953867
18	0.550336	0.931828	0.94036
19	0.829104	0.952399	0.962364
20	0.864051	0.937879	0.944117

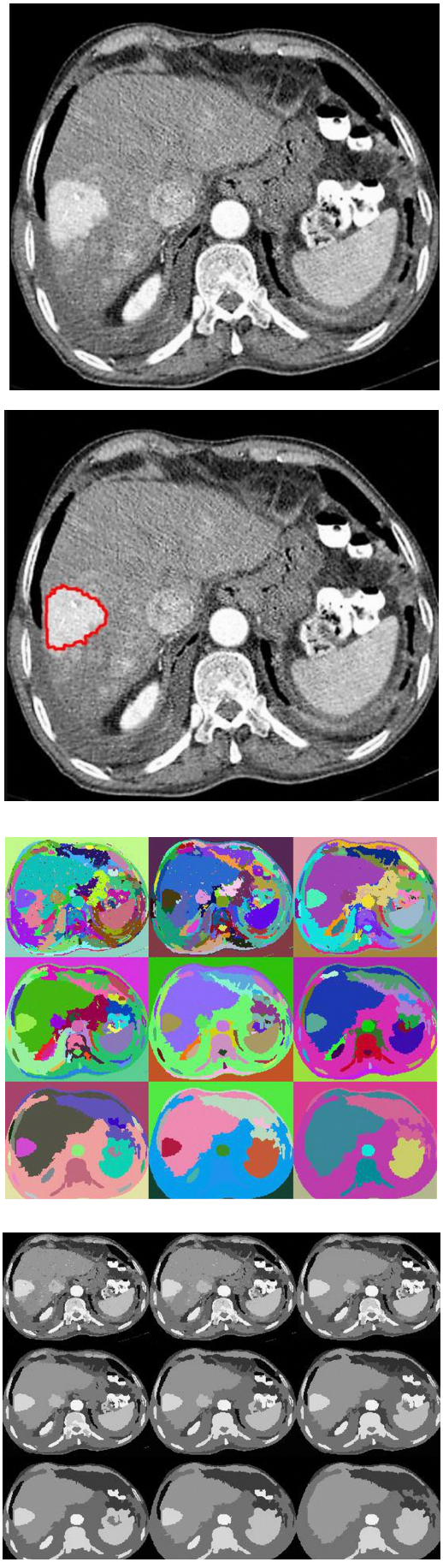


Figure 2. Original image (a), segmented area (b), ground truth image, statistical region merging in colored illustration (c), and in gray-scaled illustration (d)

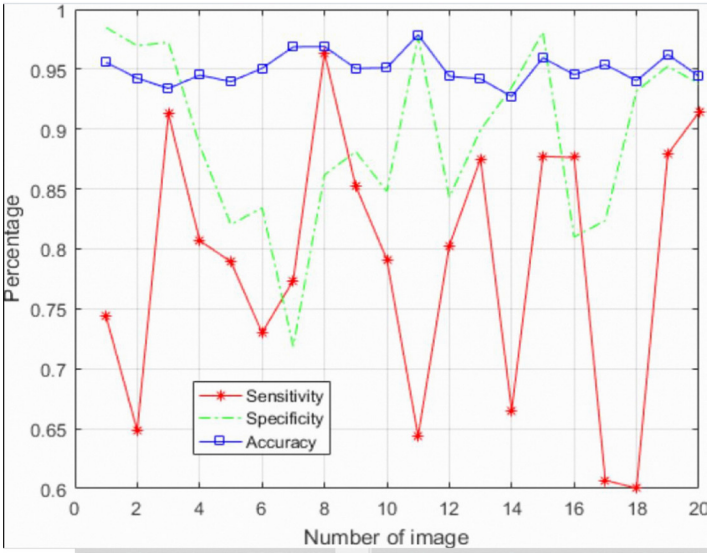


Figure 3. Comparison of sensitivity, specificity, and accuracy.

Discussion

Today; in medical imaging techniques; early diagnosis, diagnosis, and treatment of diseases are performed with radiological modalities. The analysis and interpretation of medical images in clinical studies are mostly done by specialist physicians. However, in recent years, medical doctors began to benefit from computer-assisted diagnosis and treatment assistance. With the applications of artificial intelligence, computers have made significant progress in automatically analyzing and explaining complex data.1 In the field of medicine, imaging data analysis is needed, especially in radiology [5,6,15,16], pathology [17] dermatology [18], and ophthalmology [19]. It has been widely used in medicine.

HCC can be diagnosed by ultrasonography (US), contrast-enhanced US, CT, and dynamic magnetic resonance imaging (MRI). Also, computerized assistive methods can be very useful in evaluating liver lesions. In retrospective studies, using models based on dynamic contrast-enhanced CT images in the arterial phase and delayed phase, a very high diagnostic performance was obtained. [5,6,20]. With these methods, HCC, metastasis, cyst, hemangioma, and other benign lesions in the liver, sensitivity rates were reached of 70-85-90 %, and it was considered quite successful.

Segmentation of liver vascular structure with CT is very important in vascular disease, liver surgeries, radiotherapy planning, liver transplantation planning, and analysis of tumor vascularization. Manual segmentation is time-consuming and human error may be possible. The automation-oriented process and the application of deep learning models have been examined by some researchers. [6,21] The portal veins, hepatic veins, hepatic artery structures are revealed by automatic programs. It enables the detection of vascular anomalies and variations if any, and the measurement of liver mass volumes with minimal error. Thus, high-security data are obtained for donor and recipient in interventional procedures, surgical planning, especially liver transplantation. The most appropriate safety is provided in terms of radiation therapies. Artificial intelligence (AI) programs developed in these areas are rapidly becoming widespread. It is used in surgical clinics dealing with radiology, transplantation, and radiotherapy units. With these automatic segmentation methods, clinical treatment becomes easier, and more precise medical data are obtained. There is serious debate about the time required to fully apply artificial intelligence methods obtained by deep learning methods in clinics. The period discussed varies from a few years to more. Automatic methods based on deep learning aim to solve the most common clinical problems that require long-term expertise or are too complex for humans. They need to develop a more advanced deep learning algorithm to solve the problems of their methods. Currently, a common drawback of existing AI tools is that they cannot solve multiple problems at once. Currently, there is no comprehensive information system that can detect multiple abnormalities in the human body. The existence of too many different data and their inability to bring them together at the same time also makes it difficult to develop appropriate programs quickly. [22] However, data validation of some applications may necessarily be done by humans.

To achieve healthier practices in the future, it is necessary to collect information about different parts of the world and from different geographies, including different demographic characteristics, and make them useful by coordinating them. Different patient data, diagnosis, and treatment methods should be updated. Developing new methods will facilitate the work of specialist physicians in many other branches, especially radiology specialists. By using these methods, both time gain, and healthier diagnosis and treatment will be made possible. The line of success will rise rapidly. AI applications, especially deep learning, are quickly becoming a promising aid in liver imaging. It provides improved performance in detecting and evaluating liver lesions, facilitating clinical therapy, and predicting response to treatment. There is rapid progress towards becoming an integral part of specialist physicians. It is necessary to work with many different modalities to expand and spread applications in the field of radiology.

In conclusion, in this study, the average of the sensitivity, specificity, and accuracy are obtained as 0.7476%, 0.9723%, and 0.9502%, respectively for automatic liver segmentation. The goal of this work is to create a computer-assisted diagnostic system by gathering or combining different kinds of measurements. To serve patients more, it is necessary to work on the development and use of AI applications.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
All authors declare no financial support.

Ethical approval
Ethics committee approval received from the Institutional Ethics Committee of University.

References

1. Ferlay J, Shin HR, Bray F, et al. Estimates of worldwide burden of cancer in 2008: Int J Cancer. 2010;127:2893-917.
2. Omata M, Lesmana LA, Tateishi R, et al. Asian Pacific Association for the Study of the Liver consensus recommendations on hepatocellular carcinoma. Hepatol Int. 2010;4:439-74.
3. Petrick JL, Braunlin M, Laversanne M, et al. International trends in liver cancer incidence, overall and by histologic subtype, 1978- 2007. Int J Cancer. 2016;139:1534-45.

4. Lamecker H, Lange T, Seebass M, et al. Automatic segmentation of the liver for preoperative planning of resections. Stud Health Technol Inform. 2003;94:171-3.

5. Özyurt F, Tuncer T, Avci E, et al. A novel liver image classification method using perceptual hash-based convolutional neural network. Arab J Sci Eng. 2019;44:3173-82.

6. Dogantekin A, Özyurt F, Avci E, et al. A novel approach for liver image classification: PH-C-ELM. Measurement. 2019;137:332-8.

7. Nayak A, Baidya Kayal E, Arya M, et al. Computer-aided diagnosis of cirrhosis and hepatocellular carcinoma using multi-phase abdomen CT. Int J Comput Assist Radiol Surg. 2019;14:1341-52.

8. Rafiei S, Karimi N, Mirmahboub B, et al. Liver segmentation in abdominal ct images using probabilistic atlas and adaptive 3d region growing. Conf Proc IEEE Eng Med Biol Soc. 2019;6310-3.

9. Huang W, Tan ZM, Lin Z, et al. A semi-automatic approach to the segmentation of liver parenchyma from 3D CT images with Extreme Learning Machine. Conf Proc IEEE Eng Med Biol Soc. 2012;3752-5.

10. Zhang X, Tian J, Deng K, Wu Y, Li X. Automatic liver segmentation using a statistical shape model with optimal surface detection. IEEE Trans Biomed Eng. 2010;57:2622-6.

11. Sun C, Guo S, Zhang H, et al. Automatic segmentation of liver tumors from multiphase contrast-enhanced CT images based on FCNs. Artif Intell Med. 2017;83:58-66.

12. Shiraishi J, Sugimoto K, Moriyasu F, et al. Computer-aided diagnosis for the classification of focal liver lesions by use of contrast-enhanced ultrasonography. Med Phys. 2008;35:1734-46.

13. Bogetti JD, Herts BR, Sands MJ, et al. Accuracy and utility of 3-dimensional computed tomography in evaluating donors for adult living related liver transplants, Liver Transpl. 2001;7:687-92.

14. Azmi R, Norozi N. A new markov random field segmentation method for breast lesion segmentation in mr images. J Med Signals Sens. 2011;1:156-64.

15. Hosny A, Parmar C, Quackenbush J, Set al. Artificial intelligence in radiology. Nat Rev Cancer. 2018;18:500-10.

16. Huang Q, Zhang F, Li X. Machine learning in ultrasound computer-aided diagnostic systems: a survey. Biomed Res Int. 2018;5137904.

17. Wong STC. Is pathology prepared for the adoption of artificial intelligence? Cancer Cytopathol. 2018;126:373-5.

18. Esteva A, Kuprel B, Novoa RA, et al. Dermatologist-level classification of skin cancer with deep neural networks. Nature. 2017;542:115-8.

19. Rahebi J, Hardalaç F. A new approach to optic disc detection in human retinal images using the firefly algorithm. Med Biol Eng Comput. 2016;54:453-61.

20. Yasaka K, Akai H, Abe O, et al. Deep learning with convolutional neural network for differentiation of liver masses at dynamic contrast-enhanced ct: a preliminary study. Radiology. 2018;286:887-96.

21. Ibragimov B, Toesca D, Chang D, et al. Combining deep learning with anatomical analysis for segmentation of the portal vein for liver SBRT planning. Phys Med Biol. 2017;62:8943-58.

22. 22. Lee JG, Jun S, Cho YW, et al. Deep learning in medical imaging: general overview. Korean J Radiol. 2017;18:570-84.

Available online at www.medicinescience.org

ORIGINAL ARTICLE

Medicine Science International Medical Journal

Medicine Science 2021;10(1):174-8

The effect of marital adjustment on mother-baby bonding and breastfeeding self-efficacy level

Sumeyye Altiparmak[1], Ayse Nur Yilmaz[2], Yesim Aksoy Derya[1]

[1]Department of Midwifery, Faculty of Health Sciences Inonu University, Malatya, Turkey
[2]Department of Midwifery, Faculty of Health Sciences Firat University, Elazig, Turkey

Received 19 October 2020; Accepted 24 December 2020
Available online 01.02.2021 with doi: 10.5455/medscience.2020.10.224

Abstract

This study was conducted to determine the effect of marital adjustment on mother-baby bonding and breastfeeding self-efficacy. This cross-sectional study is conducted on 510 postpartum women, who delivered a baby in a public hospital in the eastern region of Turkey, between January and June 2019. Data were collected using Personal Information Form, Marital Adjustment Scale (MAS), Mother-Infant Bonding Scale (MIBS) and Breastfeeding Self-Efficacy Scale Short Form (BSES). Data were analyzed by descriptive statistics and t test and Pearson correlation analysis were used in independent groups. The mean age was 29.2 ± 6.67 and it was found that 78.8% of the postpartum women had a desired / planned pregnancy, 48.4% breastfed their baby within the first half hour after birth, and 70.2% gave only breast milk within the first 24 hours after birth. The mean MAS score was 44.29 ± 8.06; the mean MIBS score was 22.97 ± 2.58; and the mean BSES score was 59.02 ± 9.84. It was found that postpartum women with an adjusted marriage relationship (59%) had a statistically higher level of mother-infant bonding and breastfeeding self-efficacy compared to postpartum women with non-adjusted marital relationships ($p < 0.05$). It was found that there was a weak positive correlation between the mean MAS score and the mean MIBS score ($r = 0.278$, $p = 0.000$). It was also found that there was a moderate positive correlation between the mean MAS score and the mean BSES score ($r = 0.507$, $p = 0.000$). It was found that postpartum women who had an adjusted marital relationship had higher levels of mother-infant bonding and breastfeeding self-efficacy than those leading a non-adjusted marital relationship. In addition, it was observed that mother-infant bonding and breastfeeding self-efficacy increased as marital adjustment increased in postpartum women.

Keywords: Marital adjustment, mother-baby bonding, breastfeeding self-efficacy

Introduction

Giving birth is a very special event and one of the most beautiful experiences in the lives of expectant mothers and fathers [1]. The postpartum period is a period that requires parents to learn their new roles, develop family sensitivity, create a safe environment for the baby, carry out baby care, communicate with the baby and deal with baby-related problems. This period can be a very positive period for the family, providing satisfaction and strengthening ties, but also can be a period of crisis [2]. During this period, the mother goes through a challenging process requiring adaptation to new roles and responsibilities, as well as the physiological and anatomical changes. In this process, mothers have to learn their new roles, communicate with the baby, care for the baby, and deal with baby-related problems. Many women easily adapt to physiological, psychological and social changes that occur during pregnancy and after delivery [2]. However, some women may not be able to adapt to this process easily. However, women may not be able to experience a positive postpartum period due to reasons such as low self-esteem of the mother, lack of support systems, fatigue that continues after birth and affects the care of herself and the baby, and marital problems [2].

Marital adjustment is one of the important factors that helps mothers to adapt to this complex process after the delivery and that helps coping with this process [3]. Marital adjustment is explained by the happiness and satisfaction in the marital life as a result of the adjusted partnership of the spouses [3,4]. Therefore, happiness, satisfaction and expectations can be realized with mutual adjustment in marriage [3,4]. Marital adjustment not only positively affects the adaptation process of the woman to the maternal role, but also increases her sensitivity to her baby and facilitates relationships with her relatives [3,5]. The women especially expect support from their suppouses in the postpartum period and the satisfaction of this expectation has a positive effect on the physical and mental well-being of the women [6]. Successful adaptation of women to

***Coresponding Author:** Yesim Aksoy Derya, Department of Midwifery, Faculty of Health Sciences Inonu University, Malatya, Turkey
E-mail: yesim.aksoy@inonu.edu.tr

motherhood and life changes in the postpartum period also affects the health of the mother and the baby. On the other hand, the lack of adjustment between spouses negatively affects the parenting roles of the mother and father [3]. It can be suggested that if the motherhood role of the woman is negatively affected, bonding and breastfeeding behavior will also be negatively affected.

Mothers should be ensured that they can develop bonding and breastfeeding behavior, in order to help them to adapt to the changing family balances and the new parenting role and to learn the strategies to cope with stress in this transitional process [7]. At this stage, healthcare personnel share the most important responsibility with the spouses and family members [2, 8]. From this point of view, the question of how the care and support that parents need in this period can be provided becomes more important. In this study, it was aimed to determine the effect of marital adjustment on mother-infant bonding and breastfeeding self-efficacy.

Materials and Methods

Study Design and Sample

This cross-sectional study was conducted on 510 postpartum women who gave birth to a baby in the maternity ward of a state hospital in Eastern Turkey, between January and June 2019. In the power analysis, it was calculated that the sample should include as at least 389 postpartum women to represent the universe with a 95% confidence interval with an error level of 0.05. Inclusion criteria for the study; all puerperant women who can communicate verbally, who do not develop any complications in the mother and newborn in the postpartum period and who do not have any diagnosed psychiatric diseases determined as.

Data Collection Tools

Data were obtained by using Personal Information Form, Marriage Adjustment Scale, Mother-Baby Bonding Scale and Breastfeeding Self-Efficacy Scale Short Form.

Personal Introduction Form

The Personal Information Form is created by the researchers and includes questions querying socio-demographic characteristics and some fertility characteristics of the postpartum women. The questions regarding socio-demographic characteristics included the age of, education level, employment status, income level, duration of marriage, obstetric characteristics, birth type, gender of the baby and breastfeeding attitude [9, 10, 11].

Marriage Adjustment Scale (MAS)

The marital adjustment scale is a 15-item scale developed by Locke and Wallace in 1959 [12]. The Turkish validity and reliability study of the scale was conducted by Tutarel-Kışlak (1999), in line with the scoring systems of Hunt (1978) and Freeston and Plechaty (1997). The total score obtained from the scale ranges between 0 and 60. The scores above 43.5 are considered to indicate adjusted marital relations, and the scores below this indicate a non-adjusted marital relationship. In the reliability study of the scale internal consistency coefficient was calculated as 0.84 and split half reliability as 0.84 [1]. In our research, the internal consistency coefficient was 0.86.

Mother-Infant Bonding Scale (MIBS)

MIBS was developed by Taylor et al., in 2005 [13] and adapted to Turkish by Karakulak Aydemir and Alparslan. It is a 4-point Likert scale consisting of 8 items [14]. The MIBS is organized in a way that can be applied from the first day after birth and allows the mother to express her feelings about her baby in a single word. This scale can be applied easily and quickly by the mother and father and indicates the relationship between the bond established between mother and baby and the mother's mood in the first period. The questions in the MIBS are scored between 0 and 3; the lowest total score is 0 and the highest total score is 24. The questions 1, 4, and 6 are expressions of positive emotion and scored as 0,1,2, and 3, while the questions 2,3,5,7 and 8 are expressions of negative emotions and are scored inversely as 3,2,1, and 0. The internal consistency coefficient of the scale was found to be 0.66 for the Turkish validity and reliability study [14]. In this study, the internal consistency coefficient was 0.72.

Breastfeeding Self-Efficacy Scale Short Form (BSES)

BSES was developed by Dennis, in 2003 [15] and consists of 14 items that evaluate breastfeeding self-efficacy. It is a 5-point Likert type scale and the items of the scale are answered as "1 =" not sure at all, 5 = "always sure". The lowest score that can be obtained from the scale is 14, and the highest score is 70; higher score indicates higher breastfeeding self-efficacy. The Turkish validity and reliability study of the scale was conducted by Aluş Tokat, Okumus and Dennis [16]. The internal consistency coefficient of the scale was found 0.86 in the Turkish validity and reliability study. [16]. In this research, the internal consistency coefficient was 0.91.

Data Collection

The data were collected by the researcher in the postpartum ward of the relevant public hospital by face to face interview method. The questions were asked and marked by the researchers. The data were collected by the researcher within the first 72 hours postpartum. The interviews were made on the weekdays and took an average of 10 minutes.

Evaluation of Data

The data were evaluated by using SPSS 25.0 package program. The compliance of the data to normal distribution was evaluated with the Kolmogorov Smirnov test. In statistical evaluation Cronbach's alpha, Pearson correlation and independent groups t test were used Percentage distribution, arithmetic mean, standard deviation and the data were expressed as mean, percentage and standard deviation. A value of $p<0,005$ was considered statistically significant.

Ethical Regulations

Ethical approval for the study was obtained from the Health Sciences Scientific Research and Publication Ethics Committee of Inonu University (Decision No: 2018 / 18-16). Verbal consent was obtained from all postpartum women before the study was started. The researchers informed the postpartum women that the data obtained from the participants would be published for scientific

purposes, anonymously, and that they could leave the study at any time they wish. Only the postpartum women who were volunteer to participate were included in the study.

Limitations of the Study

The sample of this study is limited to postpartum women hospitalized in the maternity ward of a state hospital in the eastern region of Turkey.

Results

The sociodemographic characteristics of the postpartum women included in the study were given in Table 1. It was determined that the average age of the participants was 29.24 ± 6.67, 53.3% of them were high school graduates, 62.4% did not work in any job. 67.8% of them stated that their income was moderate, 64.5% lived in the city center, 76.9% had nuclear family structure, and 52.5% had an arranged marriage. When the information about the spouses of the postpartum women is examined, it was determined that the average age was 33.10 ± 7.21 years, 34.3% of them were high school graduates, and 91.3% were employed in a job. It was determined that the mean marriage duration of the participants was 7.63 ± 6.58 years (Table 1).

The obstetric and postpartum characteristics of the postpartum women are given in Table 2. It was found that 72.9% of the postpartum women were multigravida, 78.8% wanted pregnancy, and 68% had a normal birth. In addition, it was determined that 57.1% of the postpartum babies were male, 48.4% breastfed their babies within the first half hour after birth, and 70.2% of the postpartum women fed their babies only with breast milk within the first 24 hours after birth. While 41.0% of women wanted their baby to be male, 50.2% of fathers stated that the gender of the baby did not matter, and 86.1% of women received support from their spouses, during the postpartum period (Table 2).

It was determined that the postpartum women got the lowest 12 and the highest 56 points on the MAS, the lowest 11 and the highest 24 on the MIBS, and the lowest 14 and the highest 70 points on the BSES. The mean total score of MAS was 44.29 ± 8.06, MIBS was 22.97 ± 2.58, and BSES was 59.02 ± 9.84. The distribution of the lowest and highest scores and mean scores that postpartum women got from MAS, MIBS, and BSES are shown in table 3.

The cut-off score of the MAS Scale was 43.5. The postpartum women who scored above the cut-off score can be considered to have an adjusted marriage. We found that, the rate of postpartum women with an adjusted marital relationship was 59% (n = 301) and those with a non-adjusted marital relationship was 41% (n = 209). It was determined that postpartum women who had an adjusted marital relationship had statistically higher MIBS and BSES scores, compared to those with non-adjusted marital relationships ($p<0.001$). In addition, it was determined that postpartum women with an adjusted marital relationship had a statistically higher BSES scores compared to those with a non-adjusted marital relationship ($p<0.001$). Comparison of MAS scores individually with MIBS and BSES scores are shown in Table 4.

It was determined that there was a statistically weak significant positive relationship between the mean MAS and MIBS scores; as the MAS increased, the MIBS increased significantly ($r = 0.278$; $p = 0.000$). It was also determined that there was a weak positive correlation between the mean MIBS and BSES scores; as the MIBS scores increased, BSES scores increased significantly $r = -0.336$; $p <0.336$). in addition, it was determined that there was a moderately significant positive correlation between the mean MAS and BSES scores; as the MAS score increased, BSES score increased significantly ($r = 0.507$; $p = 0.000$). The relationship between the total mean MAS, MIBS, and BSES scores are shown in Table 5.

Table 1. The Descriptive Characteristics of the Postpartum Women (n=510)

Descriptive Properties	**± SS**	
Age (years)	29.24 ± 6.67	
Spouse's age (years)	33.10 ± 7.21	
Duration of Marriage (years)	7.63 ± 6.58	
	n	**%**
Employment Status		
Employed	192	37.6
Unemployed	318	62.4
Educational Status		
Illiterate	14	2.7
Literate	19	3.7
Primary school	93	18.2
Secondary School	114	22.4
High school	170	33.3
University and above	100	19.6
Spouse training status		
Illiterate	2	0.4
Literate	12	2.4
Primary school	84	16.5
Middle school	95	18.6
High school	175	34.3
University and above	142	27.8
Spouse Employment Status		
Employed	475	93.1
Unemployed	35	6.9
Place of Residence		
Province	329	64.5
Town	112	22.0
Village	69	13.5
Income Status		
Good	128	25.1
Moderate	346	67.8
Poor	36	7.1
Family structure		
Nuclear Family	392	76.9
Extended family	116	22.7
Broken Family	2	0.4
Marriage Method		
Arranged	268	52.5
By meeting your own	194	38.0
Through friend	48	9.4
Total	**510**	**100.0**

Table 2. Distribution of Obstetric and Postpartum Characteristics of Postpartum Women (n = 510)

	n	%
Number of Pregnancies		
Primigravida	138	27.1
Multigravida	372	72.9
Desired Status of Pregnancy		
Yes	402	78.8
No	97	19.0
Unstable	11	2.2
Form of birth		
Normal birth	347	68.0
Cesarean section	163	32.0
Baby's gender		
Girl	219	42.9
Male	291	57.1
Mother's Baby Gender Preference		
Girl	180	35.3
Male	209	41.0
Not matter	121	23.7
Father's Baby Gender Preference		
Girl	127	24.9
Male	127	24.9
Not matter	256	50.2
Postpartum Spouse Support Asset		
Yes	439	86.1
No	71	13.9
First Breastfeeding Time		
Within the first half hour	247	48.4
Between Half Hour and One Hour	126	24.7
An hour later	119	23.3
Breastfeeding Did Not Happen	18	3.5
Nutrition in the First 24 Hours		
Only Breastfeeding	358	70.2
Formula Only Mama	18	3.5
Both Breast Milk and Formula Mama	134	26.3
Total	**510**	**100.0**

Table 3. The Distribution of the Lowest and Highest Scores that the Postpartum Women got from the MAS, MIBS and BSES

	The lowest and highest scores that can be obtained	The lowest and the highest scores obtained	Mean of the scores obtained (Ort.±SS)
Marriage Adjustment Scale	0-58	12-56	44.29±8.06
Mother-Infant Bonding Scale	0-24	11-24	22.97±2.58
Breastfeeding Self-Efficacy Scale	14-70	14-70	59.02±9.84

Table 4. Comparison of MAS scores with MIBS and BSES scores

	Adjusted Marital Relationship (n=301)	Non-adjusted Marital Relationship (n=209)	Test* and p value	
Scales	X±SD	X±SD	t	p
MIBS	23.41±2.15	22.39±2.99	-4.730	0.000
BSES	62.10±7.71	54.57±10.84	-9.166	0.000

***t: Independent-samples t-test p<0.001**

Table 5. Relationships Between MAS, MIBS and BSES Scores

Scales	*r	p
MAS - MIBS	0.278	0.000**
MIBS – BSES	0.336	0.000**
MAS - BSES	0.507	0.000**

***Pearson correlation analyze ** p<0.001**

Discussion

In this study, we aimed to determine the effect of marital adjustment on mother-infant bonding and breastfeeding self-efficacy. We found that the mean total MAS score of the postpartum women participated in our study was 44.29 ± 8.06 (Table 3). In several previous studies, it has been reported that the mean MAS score ranged between 41.99 ± 9.8 and 47.4 ± 8.2 [17- 21]. The women who scored above 43.5 on the marital adjustment scale were considered to have an adjusted marital relationship [14]. In this study, the rate of postpartum women who have an adjusted marital relationship is 59%. In the literature, the rate of postpartum women with an adjusted marital relationship has been reported to be between 54.5% and 73.6% [17, 18, 21]. The results of our study are similar to the literature.

In our study, the total mean MIBS score of the postpartum women was found to be 22.97 ± 2.58 (Table 3). In the study of Turhal (2019), the mean MIBS score was determined as 22.19 ± 2.63 [22]. In this study, it was determined that as marital adjustment increased, mother-infant bonding increased significantly (Table 5, r = 0.278; p = 0.000). Similarly, in the study of Mutlu et al. (2018), it was found that as the level of marital adjustment increased, the level of mother-infant bonding increased [23]. In a study conducted by Akkoca (2009) to investigate postpartum mother-baby bonding, it was found that marital non-adjustment negatively affected mother-infant bonding [24]. In the literature, it is stated that the relationship of mothers with their spouses affects their bonding with their babies, mothers who experience marital problems have difficulty in bonding with their children, and a healthy marital relationship is necessary for a healthy mother-baby bonding [25]. In the study conducted by Alan and Ege (2013), it was found that there was a significant relationship between perceived social support and mother-baby bonding in the postpartum period, and maternal bonding increased as the social support that received by the mothers increases [26]. These results support the findings of our study. We also suggest that marital adjustment strengthens the bond between mother and baby.

Breastfeeding is one of the important factors that will enable the mother to establish a deep, lasting and secure bond with her baby. [23, 27]. Breastfeeding self-efficacy refers to a postpartum mother's belief in her breastfeeding ability and requires interactions between the mother and infant [27]. In our study the mean total BSES score of the postpartum women was found to be 59.02 ± 9.84 (Table 3). Given that that the highest value of the scale is 70, we can say that the BSES scores of the mothers in our study were above the average. In the literature, it has been reported that the mean scores of BSES vary between 59.49 ± 8.46 and 38.71 ± 7.37 [28-31]. In our study, we determined that as

marital adjustment increased, breastfeeding self-efficacy increased significantly (Table 5, r = 0.507; p = 0.000). In the study conducted by Uludağ (2017), it was found that as the level of spousal support increased, the level of breastfeeding self-efficacy increased [32]. Similarly, in the literature, it has been reported that mothers who receive more support from their spouses and experience more marital satisfaction after birth had more breastfeeding self-efficacy and were more likely to start and continue breastfeeding [27]. Given the results of these studies and our study which support the literature, we also suggest that marital adjustment has a positive effect on breastfeeding self-efficacy.

Conclusion

In this study, it was found that women with adjusted marital relationships had statistically higher levels of mother-infant bonding and breastfeeding self-efficacy compared to women with non-adjusted marital relationships. In addition, it was observed that the MIBS and BSES scores as the MAS scores increased. Given these information; we suggest that the pregnant information classes and pregnancy schools should be provided with trainings about pregnancy, delivery and postpartum processes, in order to support marital adjustment, mother-infant bonding and breastfeeding self-efficacy. In this context, midwives and other healthcare professionals should support mothers by counseling and training spouses before the delivery. Spouses should be included in the mother-infant bonding process, and the importance of marital adjustment for both mother and baby should be emphasized during pregnancy follow ups and trainings. New mothers will be able to adapt to their new roles and responsibilities with the positive support of the spouse and family in the postpartum period. It would be appropriate for midwives to continue to provide support to mothers, in the postpartum period and to facilitate interaction between the mother and the baby and starting and continuing breastfeeding.

This research was presented as a summary oral presentation at the 2nd International / 3rd National Postpartum Care Congress (03 - 06 October 2019, Konya/Turkey).

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
All authors declare no financial support.

Ethical approval
Ethical approval for the study was obtained from the Health Sciences Scientific Research and Publication Ethics Committee of Inonu University (Decision No: 2018 /18-16).

References

1. Tutarel Kışlak Ş. Reliability and validity of the marital adjustment test. Journal of 3P. 1999;7:55-65.
2. Beydağ KB. Adaptation to motherhood in the postpartum period and the nurse's role. Kor Hek. 2007;6:479-84.
3. Çobanlar Akkaş S. Dyadic adjustment in pregnancy period. MSc dissertation, Adnan Menderes University, Aydın, 2014.
4. Erbek E, Bestepe E, Akar H, et al. Marital adjustment. Dusunen Adam The J Psychiat Neurological Sci. 2005;18:39-47.
5. Kiehl EM, White MA. Maternal adaptation during childbearing in norway, sweden and united states. Scand J Caring Sci. 2003;172:96-103.
6. Alan H. The influence of social support on mother-infant attachment in postpartum period. MSc dissertation, Selçuk University, Konya, 2011.
7. Dayan G. The relatıonshıp between maternal attachment and perceived socıal support ın postpartum depressıon. MSc dissertation, Near East University, Lefkoşa, 2019.
8. Çankaya S, Yılmaz Dereli S, Can R, et al. Effect of postpartum depressıon on maternal attachment. ACU Health Sci J. 2017;4:232-40.
9. Yiğitbaş Ç, Ada G. Mother baby bondıng regardıng self-effıcıency level on the fourth trımester. ESTUDAM Public Health J. 2019;4:343-53.
10. Tunçel NT, Süt HK. The effect of anxiety, depression and prenatal distress levels in pregnancy on prenatal attachment. J Gynecol- Obstetrics Neonatol. 2019;16:9-17.
11. Öztürk S, Erci B. Primipar mothers in postpartum period given maternity and newborn education increased attachment: post test with control group semi experimental research. Balikesir Health Sci J. 2016;5:129-34.
12. Locke HJ, Wallace KM. Short marital adjustment and prediction tests: Their reliability and validity. Marriage and Family Living. 1959;21:251-5.
13. Taylor A, Atkins R, Kumar R, et al. A new mother-to-infant bonding scale: Links with early maternal mood. Arch Womens Mental Health. 2005;8:45-51.
14. Aydemir HK, Alparslan Ö. Adaptation of mother to infant bonding scale to the turkish society: Aydın sample. J Contemporary Med. 2016;6:188-99.
15. Dennis CL. Breastfeeding self efficacy scale: psycho-metric assessment of the short form. JOGNN. 2003;32:734-43.
16. Tokat MA, Okumuş H, Dennis CL. Translation and psychometric assessment of the breast-feeding self-efficacy scale-short form among pregnant and postnatal women in Turkey. Midw. 2010;26:101-8.
17. Yekenkunrul D, Mete S. Investigation of relationsiıp in between nausea and vomiting in pregnancy, marital adjustment and spouse relationship. Dokuz Eylul University E-J Nursing Faculty. 2012;5:89-95.
18. Demirezen RD. Motherhood in pregnancy and effects of accepting pregnancy on marriage consistency. MSc dissertation, Cumhuriyet University, Sivas, 2016.
19. Dursun D. The effect of marital adjustment on fear of childbirth in pregnant women. MSc dissertation, Ordu University, Ordu, 2019.
20. Daş M. The relationship among spouse support, marital adjustment and psychological well-being in married individuals. MSc dissertation, İstanbul University, İstanbul, 2019.
21. Pekşen ZÇ, Şahin HA. Research of marital adjustment and domestic violence among physicians. Anatol J Psychiat. 2019;20:418-25.
22. Turhal A. Mother-baby attachment during pregnancy and the postpartum period and anxiety levels of mothers. MSc dissertation, Düzce University, Düzce, 2019.
23. Mutlu B, Erkut Z, Yıldırım Z, et al. A review on the relationship between marital adjustment and maternal attachment. Rev Assoc Med Bras. 2018;64:243-52.
24. Akkoca Y. Factors effecting bonding in the postpartum period. MSc dissertation, Gazi University, Ankara, 2009.
25. Durualp E, Kaytez N, Girgin BA. An analysis of the relation between marital satisfaction and maternal bonding. Anatol J Psychiat. 2017;18:129-38.
26. Alan H, Ege E. The influence of social support on maternal-infant attachment in Turkish Society. J Anatol Nursing Healt Sci. 2013;16:234-40.
27. Jasemi N, Mousavi P, Saki A, et al. Relationship between marital satisfaction with maternal infant attachment and breastfeeding self-efficacy in primiparous and multiparous nursing mothers. Intern J Women's Health Reproduction Sci. 2020;8:68-72.
28. Cömert Arslan C. Determining the self-efficacy breast feeding postpartum period and related factors. MSc dissertation, Selçuk University, Konya, 2011.
29. Yenal K, Tokat MA, Ozan YD, et al. The Relation Between Breastfeeding Self-Efficacy and Breastfeeding Successes of Mothers. J Educat Resn Nursing. 2013;10:14-9.
30. Küçükoğlu S, Çelebioğlu A, Coşkun D. Determination of the postpartum depression symptoms and breastfeeding self-efficacy of the mothers who have their babies hospitalized ın newborn clinic. Gümüşhane University J Health Sci. 2014;3.
31. Gökbulut N. The effects of women's satisfaction with their birth experience on breastfeeding sufficiency. MSc dissertation, Okan University, İstanbul, 2015.
32. Uludağ E. Influence of spousal support in early postpartum period on breastfeeding self-efficacy. MSc dissertation, Atatürk University, Erzurum, 2017.

Available online at www.medicinescience.org

ORIGINAL ARTICLE

Medicine Science International Medical Journal

Medicine Science 2021;10(1):179-83

Evaluation of trailer attached-two wheel tractor (Pat- pat) accident - related pediatric injuries in Turkey's western black sea region

Guleser Akpinar, Mehmet Cihat Demir

Duzce University, School of Medicine, Department of Emergency Medicine, Duzce, Turkey

Received 26 November 2020; Accepted 07 January 2021
Available online 01.02.2021 with doi: 10.5455/medscience.2020.11.245

Abstract

Traumatic injuries related to agricultural production can lead to serious illness, disability, and even death. Pediatric injuries due to trailer attached-two wheel tractor (Pat-pat) accidents occupy a scarce place in the literature. To contribute to the literature, we aimed to evaluate the demographic characteristics and analysis of pediatric injuries due to a Pat-pat accident admitted to our emergency department in the last decade. The study data were obtained by retrospectively examining patients younger than 18 years of age admitted to the Emergency Medicine Clinic between 01/01/2010 and 31/12/2019 with injuries due to Pat-pat accident. Demographic characteristics, injury sites, injury types, hospitalization status, length of hospital stay, injury severity score (ISS), and mortality status were recorded. Due to the Pat-pat accident, 32 children applied to the hospital. The male/Female ratio was 25/7. The median age of pediatric patients ranging from 9 to 18 years was 17 years. When evaluated according to the injury areas, extremity injuries were the most common. Admissions were most frequently in the summer season (n=21, 65.6%) and in July (n=13, 40.6%). These cases were admitted mostly on Tuesday (n=8, 25.0%) and between 16:00 and 23:59 (n=22, 68.8%). According to the ISS, 20 of the patients had a mild injury (ISS≤3), 3 had a moderate injury (4≤ ISS ≤8), and 9 had a severe injury (ISS≥9). To prevent accidents, the public should be made aware of this issue, and the authorities should be more careful in making the necessary administrative decisions and in implementation. For young agricultural workers, it should be an obligation to ensure proper education and job security. Pat-pat, which is not well known but often used in rural agricultural areas of the Western Black Sea region, can have dangerous consequences for children. Children should be kept away from such unsafe vehicles.

Keywords: Agricultural machine, pediatric injuries, pat-pat machine

Introduction

Agriculture is a hazardous industry considering occupational injury and death rates [1]. Traumatic injuries related to agricultural production can lead to serious illness, disability, and even death [2]. Agricultural tractors are the leading cause of occupational deaths in pastoral areas. Tractor accidents are a significant cause of motor vehicle-related injuries on farms, accounting for an estimated 4-14% of non-fatal injuries and a third of fatal agricultural injuries [3]. Trailer attached-two wheel tractor (Pat-pat) is similar in structure to an off-road vehicle; however, it is functionally identical to a farm tractor. The name of the Pat-pat machine derives from the sound it makes [4].This vehicle has two distinct structures: the fundamental part is an engine, and the other part is a trailer. It weighs an average of 300-350 kg, has a steering wheel or handlebar, and can carry 1 ton of cargo or 10-15 people [5].

Accidents linked to Pat-pat machine used for agricultural purposes in rural areas in Turkey's Black Sea region, in the presence of organs and blood vessel injury, can be seen high morbidity and mortality. Pat-pat accidents may include children accompanying their family, children allowed to attend the workers, and children working as agricultural workers. Children are affected more than adults in injuries due to Pat-pat accidents because; Children are less capable than adults in protecting themselves during accidents and preventing damage from the accident. In studies published on tractor-related deaths, the 0-19 age group's mortality rate was reported to be between 11.0% and 29.5% [6]. In the study conducted by Dogan et al., this rate was 36.1% [7].

Various scoring systems have been developed to use a common language for trauma patients outside the hospital and hospital settings. Scoring systems provide information about the relationship between treatment and outcomes [8]. The Injury Severity Score

***Coresponding Author:** Guleser Akpinar, Duzce University, School of Medicine, Department of Emergency Medicine, Duzce, Turkey
E-mail: guleserakpinarduman@gmail.com

(ISS) is the "gold standard" among anatomical indicators of injury severity in the trauma population [9, 10]. Glasgow Coma Scale (GCS), one of the physiological scoring systems used in patient follow-up from the moment of admission, is an easy, actual scoring system that can determine the level of consciousness and is widely used the reliable evaluation of the degree of mental status [11].

Duzce, plenty of nuts produced an agricultural city is in Turkey's western Black Sea Region. Especially in the mountainous parts of Duzce, Pat-pat is frequently used in hazelnut agriculture. Emergency services are the first places of application for injuries due to Pat-pat accidents. Publications on Pat-pat's pediatric injuries are scarce. By examining the children who came to our emergency service in the last ten years to contribute to the literature and who were injured in accidents related to Pat-pat, which is widely used in rural areas; Demographic data, and mortality rate related to these accidents were noted. We aimed to determine what kind of pediatric injuries occur in using these agricultural tools, convenient but not very safe for farmers, and make suggestions on this issue.

Materials and Methods

This research was a descriptive and retrospective study. The data of a total of 32 patients aged 18 and under, who were admitted to the emergency department with Pat-pat accident between 01/01/2010 and 31/12/2019, were obtained retrospectively via the hospital data processing system and emergency department records. There was no missing data. Patients older than 18 years were excluded.

It was conducted with the Ethics Committee of Duzce University's permission on 19/10/2020, numbered 2020/221.

According to the (GCS), the patients' consciousness level was evaluated. GCS consists of three parts: eye-opening and closing response, verbal response, and motor response. The score ranges from 3 to 15. The lower the score, the worse the patient's consciousness is [12].

The (ISS) was used while scoring the trauma severity of the patients. Patients presenting with multiple injuries were divided into six anatomical regions: head, neck, thorax, abdomen, extremity (including pelvis), and external injuries. It is a trauma scoring system calculated by summing the squares of each of the three most damaged body regions based on the results obtained by physical examination findings and trauma imaging examinations. The ISS was categorized into three groups: ≤ 3 mild, $4 \leq ISS \leq 8$ moderate, ≥ 9 severe [13,14].Patients' age, gender, injured body area, consultation notes, hospitalization status, length of hospital stay, (ISS), and mortality status were recorded. While defining the patient's trauma region, it was considered anatomically as the head - neck, thorax, abdomen, extremities, and whole-body trauma.

Statistical analysis

Non-normal variables were expressed as median (minimum value - maximum value). Categorical variables were represented with counts and percentages. The statistical software SPSS version 19 (SPSS Inc., Armonk, NY, USA) was used for frequency analyses.

Results

Between 2010 and 2019, 32 pediatric patients applied to our emergency department due to the Pat-pat accident. Male / Female patient ratio; It was 25/7. The median age of pediatric patients ranging from 9 to 18 years was 17 years, and 25 (78.1%) were male.

When the patients who applied with Pat-pat accident were evaluated according to the injury areas, extremity injuries were encountered most frequently. Of the 11 patients with extremity injuries, nine had injuries occurring only in their extremities and in 2 other parts. After the Pat-pat accident, soft tissue injury (STI) was the most common in patients. While 17 of these patients had only STI, 1 had head trauma and STI. All findings regarding the injury types of the patients were shown in Table 1.

Table 1. Injured body areas and diagnoses

	n	%
Injured body area		
Head-neck	5	15.6
Chest	4	12.5
Abdomen	2	6.3
Extremity	9	28.1
Multiple areas	12	37.5
Diagnosis		
Pulmonary contusion	1	3.1
Intrabdominal bleeding	1	3.1
Abdominal trauma	1	3.1
Cervical 1st (C1) vertebral fracture	1	3.1
Laceration in the extremities	2	6.3
Pneumothorax	1	3.1
Radial bone fracture	1	3.1
Radial + Ulnar bone fracture	1	3.1
Soft tissue injury	17	53.1
Multiple trauma	5	15.6
Total	32	100

The most frequent admissions of pediatric patients to the emergency department due to the Pat-pat accident were made in 2016. While there were no applications for 2010, it was observed

that applications increased since 2013 when only one admission was made, reaching 15 in 2016, and then declined again. Most frequently, admissions occurred in the summer season (n=21, 65.6%) and in July (n=13, 40.6%). No pediatric injury cases due to the Pat-pat accident were encountered in February, March, October, and December. Most of these cases were encountered on Tuesday (n=8, 25.0%) and at least on Monday and Wednesday (n=2, 6.3%) (Figure 1). Applications to the emergency department were made more frequently between 16:00 and 23:59 hours (n = 22, 68.8%).

According to the ISS, 20 patients had a minor injury (ISS≤3), 3 had a moderate injury (4≤ ISS ≤8), and 9 had a severe injury (ISS≥9). The median ages of patients with mild injury, moderate

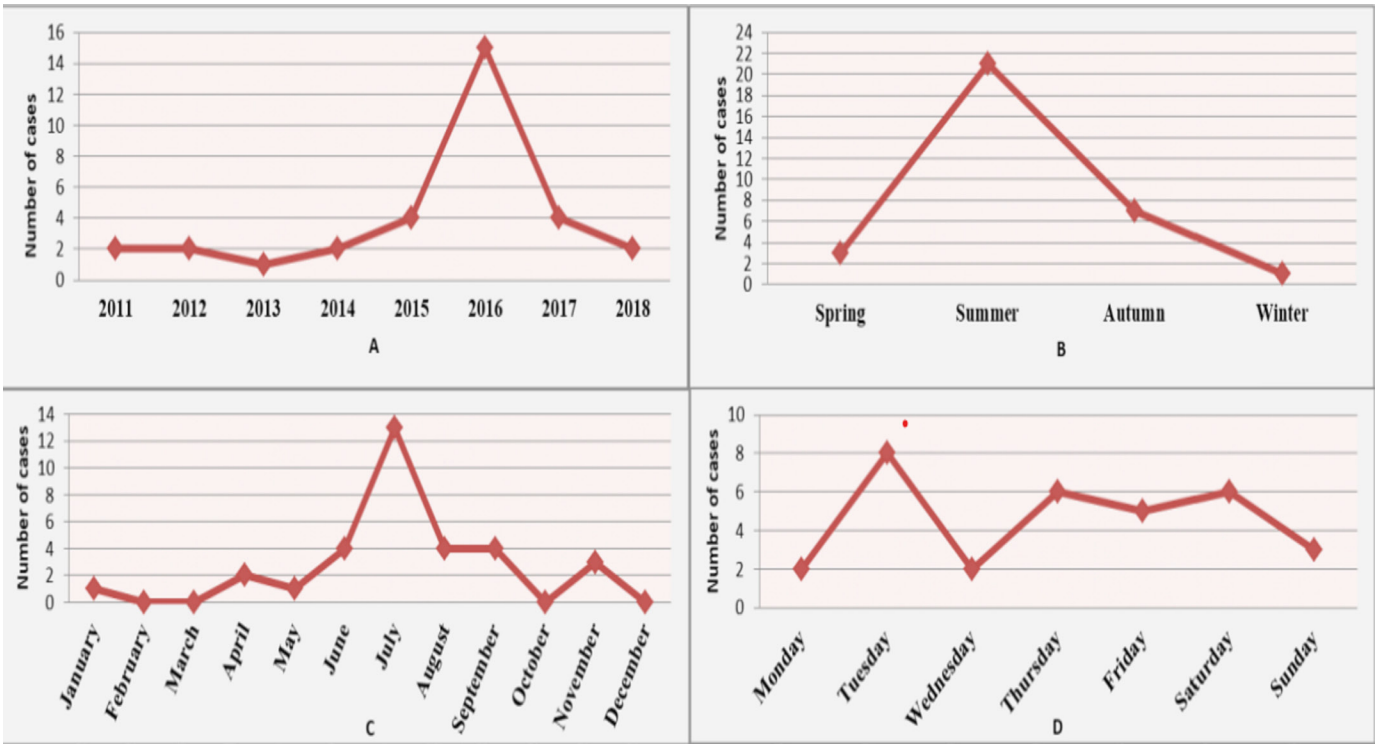


Figure 1. Number of pediatric patients admitted to the emergency department due to the Pat-pat accident A: By years, B: By seasons, C: By months, D: By days

injury, and severe injury were 17 (11-18), 16 (11-18), and 17 (9-18), respectively. 32% of boys and 14.3% of girls were seriously injured. 40% of the patients who applied to the emergency department between 08:00 and 15:59, and 22.7% of the patients admitted between 16:00 and 23:59 had severe injuries. Of the 15 patients consulted, 9 (60%) had severe injuries. The rates of severely injured patients were 37.5% (3/8) and 85.7% (6/7) in orthopedics and pediatric surgery departments, where consultation was requested most frequently. The severe injury was observed in 83.3% of the hospitalized patients and in 15.4% of the patients who were not hospitalized. All of the patients hospitalized in the neurosurgery clinic (NSC) and pediatric surgery clinic (PSC) and 66.7% of those hospitalized in the pediatric surgical intensive care unit (PICU) had severe injuries. The findings regarding the patients' hospitalization status was given in Table 2.

The GCS (GCS) was 15 in 30 (93.7%) patients and 8 in two patients. In the study, a boy who was obtained as GCS 8 and ISS 14 died.

Table 2. According to injury severity score, assessment of the patients' findings regarding gender, admission time, consultation requests, hospitalization status, and length of hospital stay.

	Injury Severity Score			
	3 or less	**4-8**	**9 or more**	**Total**
Age Median (min-max)	17 (11-18)	16 (11-18)	17 (9-18)	17 (9-18.0)
Gender n (%)				
Female	5 (71.4)	1 (14.3)	1 (14.3)	7 (100)
Male	15 (60.0)	2 (8.0)	8 (32.0)	25 (100)
Admission time n (%)				
08:00-15:59	5 (50.0)	1 (10.0)	4 (40.0)	10 (100)
16:00-23:59	15 (68.2)	2 (9.1)	5 (22.7)	22 (100)
Consultation				
No	17 (100)	0 (0)	0 (0)	17 (100)
Yes	3 (20.0)	3 (20.0)	9 (60.0)	15 (100)
Hospitalization n (%)				
No	20 (76.9)	2 (7.7)	4 (15.4)	26 (100)
Yes	0 (0)	1 (16.7)	5 (83.3)	6 (100)
Total	20 (62.5)	3 (9.4)	9 (28.1)	32 (100)

Discussion

Our study determined that accidents associated with Pat-pat, an agricultural tool, cause severe mortality and morbidity in Turkey (particularly in the western black sea region) and generated many injuries, chiefly extremity traumas, especially in the pediatric age group.

30% of our country's population works in agricultural activities. Due to a tractor accident in Turkey, the proportion of deaths due to Pat-pat-related accidents in fatalities is low. This low rate may be because the Pat-pat machine has less technological development than the tractor and is not used in every region of the country [4]. It has also been found that the most crucial cause of Pat-pat accidents is the overthrow of the Pat-pat [15,16].

A troubling aspect of this study is that a significant portion of the people involved in rural agriculture are children and that job security is less than children in other areas. By investigating unsafe working conditions and introducing necessary regulations, the rate of child accidents can be reduced. Still, emergency physicians must be prepared to handle a wide range of injuries in tractor-related incidents [17].

In accidents with agricultural implements such as the Pat-pat accident, the male gender is dominant. In these accidents, the ratio of male / female patients in admission to the emergency department and hospitalization was found to be 7: 3 and 5: 1; in our study, it was found in the ratio of 25: 7 and 5: 1, respectively. Due to the male gender of agricultural workers, there are more male patients in agrarian accidents [4, 17]. In our study, male patients were in the 10-18 age range, and there were 18 male patients over 15 years old. In our study, one patient who died was 18 years old and male. In Fulcher et al.'s study, they found the male patient mortality rate as 98% [18]. This shows us that young men are more active in agriculture. Our study's low number of mortality is due to our study population's shortage, which is the limitation of our research.

A series of scoring systems have been developed over the past few decades to assess the trauma's severity and estimate patient mortality and morbidity. ISS is one of the most commonly used scoring systems [19]. Although an exact score is not specified for the ISS score, it has been reported that as the score increases, the predictability of mortality and morbidity increases. An ISS score above 25 is directly associated with mortality [20]. Some studies highlight that data on injury severity and injured body areas play a crucial role in determining preventive measures [21]. Although fractures, soft tissue injuries, and extremity injuries are frequently reported in accidents with agricultural equipment, severe traumatic injuries are prominent in some studies [5]. In our study, 17 patients had STI, and the ISS was ≤3 in 20 patients. In 9 patients with a severe injury, it was ISS≥9. Also, 5 (83.3%) of 6 patients hospitalized, all hospitalized in NSC and PSC wards, and 66.7% of those hospitalized in PICU had severe injuries. Of the 15 patients who were consulted, 9 (60%) had severe injuries. The rates of severely injured patients were 37.5% (3/8) and 85.7% (6/7) in orthopedics and pediatric surgery departments, where consultation was requested most frequently. In our study, we saw that patients with high ISS scores were hospitalized and followed up. Despite the identified high ISS, we only observed one death, mainly because most injuries were to the extremities. Although such injuries are common, patients with high ISS should not be abandoned for other damages, and a routine Advanced Trauma Life Support protocol should be applied.

Carlson et al. determined that most tractor-related injuries (82%) occurred between 06:00 and 17:59 [22]. However, other studies have reported that most agricultural injuries happen in the afternoon and evening [5]. We found that accidents were most frequent on tuesday (n = 8, 25.0%) and between 16:00 and 23:59 (n = 22, 68.8%). The reason why most of the accidents occur in the evening is that the gathered product is transported for storage and the workers are exposed to increased road traffic during this time, and the Pat-pat is also used as a normal means of transport outside of agriculture. To prevent accidents, the public should be made aware of this issue, and the authorities should be more careful in making the necessary administrative decisions and implementation.

Unlike the tractor accidents that increased when planting and garden-field preparation operations were carried out in the spring, most of the Pat-pat incidents occurred in the summer and autumn months. However, Karapolat et al, reported the most frequent hospitalizations after injury was in July, August, and September; Brandenburg et al, stated that the most frequent applications were in July and August [4, 23]. In this study, the Pat-pat accident occurred most frequently in the summer season (n=21, 65.6%) and in July (n=13, 40.6%), especially during the harvest season. This period was compatible with the crop harvest time for our geography. The use of Pat-pat machines for human and material transfer increased during these periods. This seasonal situation was consistent with similar studies conducted in our country [7, 24]. According to the research of Rorat et al, it was determined that 65.8% of the accidents occurred between May and November. This difference has been attributed to the geographical location and climates of the places where the studies were conducted [25]. Information on body areas affected by injury is crucial to identifying and evaluating preventive actions. Akdur et al, noted that the most common injury sites are the upper extremities; Shults et al. reported that the arm-hand and leg-foot were the more common injury sites [21, 26]. Like other studies, we found that the most common types of injuries were extremity fractures and lacerations caused by overturning the Pat-pat. Of the 11 patients with extremity injuries, 9 had additional injuries only in their extremities and 2 in other parts. Agriculturalists should consider working with extremity protective equipment to protect the victim's extremities from damage.

Injuries to the head, chest, abdomen, or spinal cord often result in death in a Pat-pat or tractor-related accident [23, 27]. There was also chest trauma in our ex case. Pat-pat machines have an unbalanced center of gravity and do not have seat belts or a protected structure in case of overturning.

Limitations

We examined only the child casualties of all Pat-pat accidents in our city located in the Western Black Sea region. Besides, some of the injured may have been treated in other medical centers without ever coming to our hospital. Considering that our hospital provides specialist trauma care for serious injuries, we estimate that the number of injuries associated with Pat-pat machines in our area is significantly higher because we only evaluated child injuries and Pat-pat accidents. The casualties who died before admitting

to our hospital were also excluded from the evaluation. Another limitation was the small sample size. The last limitation was that the cost analysis could not be done.

Conclusion

This study showed that the use of Pat-pat is hazardous, especially for children. Appropriate legal regulations; additional engineering work on the mechanics, design, and safety of vehicles; having a license requirement for vehicles can prevent such accidents. Also, parents should be educated to protect children better and raise awareness of children against Pat-pat accidents. For young agricultural workers, it should be an obligation to ensure proper education and job security. Finally, emergency physicians, first responders, and other healthcare providers raise awareness of the dangers and possible consequences of Pat-pat-related injuries, particularly in rural health systems, leading to faster diagnosis-treatment times and more comprehensive care.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
All authors declare no financial support.

Ethical approval
Ethical approval obtained from the Duzce University Ethics Committee (numbered 2020/221; dated 19/10/2020).

References

1. Jawa RS, Young DH, Stothert JC et al. Farm machinery injuries: the 15-year experience at an urban joint trauma center system in a rural state. J Agromedicine. 2013;18:98-106.
2. Rathje C, Venegas A, Helmer SD et al. Pediatric farm injuries: morbidity and mortality. Kans J Med. 2017;10:92-5.
3. Swanton AR, Young TL, Leinenkugel K et al. Nonfatal tractor-related injuries presenting to a state trauma system. J Safety Res. 2015;53:97-102.
4. Karapolat S, Saritas A, Kandis H et al. The evaluation of Pat-Pat related injuries in the western black sea region of Turkey. Scand J Trauma Resusc Emerg Med. 2011:19;1-6.
5. Kahveci F O, Akca ASD, Piskin IE. Evaluation of occupational traumatic injuries in rural sectors of Turkey. Acta Med Int. 2015:2;87-91.
6. Bernhardt JH, RL Langley. Analysis of tractor-related deaths in North Carolina from 1979 to 1988. J Rural Health. 1999:15:285-95.
7. Dogan KH, Demirci S, Sunam GS et al. Evaluation of farm tractor-related fatalities. Am J Forensic Med Pathol. 2010:31;64-8.
8. Şengül AT, Kutlu T, Büyükkarabacak YB et al. Effects of trauma scores on prognosis in chest traumas. Türk Göğüs Kalp Dama. 2012;20:805-11.
9. Sultanoğlu H, Özkan S, Sultanoğlu TE et al. Comparison of trauma scoring systems in pediatric trauma patients. Eurasian J Med. 2019;18:1-8.
10. Champion HR, Copes WS, Sacco WJ et al. The major trauma outcome study: establishing national norms for trauma care. J Trauma.1990;30:1356-65.
11. Chan B, Guadry P, Gratton-Smıth TM et al. The use of glasgow coma scale in poisoning. J Emerg Med. 1993;11:579-82.
12. Jennett B, Bond M. Assessment of outcome after severe brain damage: a practical scale. Lancet. 1975;305:480-4.
13. Baker SP, O'Neill B, Haddon W Jr et al. The Injury Severity Score: a method for describing patients with multiple injuries and evaluating emergency care. J Trauma. 1974;14:187-96.
14. Nogalski A, Lübek T, Sompor J et al. Agriculture and forestry work-related injuries among farmers admitted to an Emergency Department. Ann Agric Environ Med. 2007;14:253-8.
15. Christopher BJ, Lesley D, Carolyn S. Trends in tractor related fatalities among adults working on farms in Victoria, Australia, 1985–2010. Accid Anal Prev. 2013;50:110-4.
16. Myers JR, Hendricks KJ. Agricultural tractor overturn deaths: assessment of trends and risk factors. Am J Ind Med. 2010;53:662-72.
17. National Farm Worker Ministry. Children in the fields. http://nfwm.org/farm-workers/farm-worker-issues/children-in-the-fields/ access date 22.10.2020.
18. Fulcher J, Noller A, Kay D. Farming tractor fatalities in Virginia: an 11-year retrospective review. Am J Forensic Med Pathol. 2012;33:377-81.
19. Köksal Ö, Özdemir F, Bulut M et al. Comparison of trauma scoring systems for predicting mortality in firearm injuries. Ulus Travma Acil Cerrahi Derg. 2009;15:559-64.
20. Taş H, Mesci A, Eryılmaz M et al. The affecting factors on the complication ratio in abdominal gunshot wounds. Ulus Travma Acil Cerrahi Derg. 2011;17:450-4.
21. Akdur O, Ozkan S, Durukan P et al. Machine-related farm injuries in Turkey. Ann Agric Environ Med. 2010;17:59-63.
22. Carlson KF, Gerberich SG, Church TR et al. Tractor-related injuries: A population-based study of a five-state region in the Midwest. Am J Ind Med. 2005;47:254-64.
23. Brandenburg MA, Brown SJ, Archer P et al. All-terrain vehicle crash factors and associated injuries in patients presenting to a regional trauma center. J Tra Acute Care Surg. 2007;63:994-9.
24. Erkol Z, Buken B, Hekimoglu Y et al. Analysis of tractor-related deaths. J Agromedicine. 2013;18:87-97.
25. Rorat M, Thannhauser A, Jurek T. Analysis of injuries and causes of death in fatal farm-related incidents in Lower Silesia, Poland. Ann Agric Environ Med. 2015;22:271-4.
26. Shults RA, West BA, Rudd RA et al. All-terrain vehicle–related nonfatal injuries among young riders in the United States, 2001–2010. Pediatrics. 2013;132:282-9.
27. Küçüker, H. Analysis of deaths caused by pat-pat accidents in Turkey. Traffic Inj Prev. 2012;13:209-11.

Available online at www.medicinescience.org

ORIGINAL ARTICLE

Medicine Science International Medical Journal

Medicine Science 2021;10:184-90

Investigation of antiphospholipid antibody syndrome markers in the etiology of recurrent miscarriage

Vildan Gorgulu, Orhan Cem Aktepe, Birol Safak

[1]*Department of Medical Microbiology, Antalya Public Health Laboratory, Antalya, Turkey*
[2]*Department of Medical Microbiology, Bahcesehir University Faculty of Medicine, Istanbul, Turkey*
[3]*Department of Medical Microbiology, Namik Kemal University Faculty of Medicine, Tekirdag, Turkey*

Received 22 August 2020; Accepted 02 November 2020
Available online 22.02.2021 with doi: 10.5455/medscience.2020.08.171

Abstract

This study aimed to determine the markers of antiphospholipid antibody syndrome (APS), which has an important place in the etiology of recurrent miscarriage, and to provide guidance for the treatment of the related disorders. This prospective observational study was performed on 120 female patients admitted to the Obstetrics and Gynecology outpatient clinics due to recurrent pregnancy loss. Blood samples were analyzed using the Enzyme-Linked Immunosorbent Assay (ELISA) technique to find out the levels of APS-associated anticardiolipin (ACA), anti-beta2-glycoprotein I (aβ2GPI), anti-annexin V (aANXV), anti-prothrombin (aPT), and antiphosphatidylserine (aPS) antibodies. A statistically significant difference was found between increased age groups and the number of miscarriages ($p=0.03$, $p<0.05$). There were no significant differences between the age groups by the time of miscarriage ($p=0.35$, $p<0.05$). ACA positivity (75%, n = 90) and anti-annexin V positivity (50.8%, n = 61) were higher than the positive results found in other tests($p=0.01$, $p<0.05$). Antiphospholipid antibodies (APAs) showed significantly different positivity levels by the age groups ($p=0.01$, $p<0.05$). The positivity levels of APAs were significantly different by the number of miscarriages ($p=0.01$, $p<0.05$). Other antibody levels were not statistically significantly different. The frequency of positive APA levels increases with advancing age and a high number of miscarriages in association with the etiology of recurrent miscarriage. Among the subgroups of these antibodies, ACA and anti-annexin V can serve as highly appropriate diagnostic markers in recurrent miscarriage.

Keywords: Antiphospholipid, recurrent miscarriages, etiology, anticardiolipin antibody

Introduction

Antiphospholipid antibody syndrome (APS) is an autoimmune disease that is characterized by the presence of antiphospholipid antibodies (APAs) and recurrent miscarriage, frequently occurring in the general population. Pregnancy complications in obstetric APS include unexplained recurrent pregnancy loss and fetal death due to severe preeclampsia, eclampsia, intrauterine growth restriction, or other consequences of placental failure [1]. In the literature, no relation was found between antiphospholipid antibodies (anticardiolipin, anti-beta2-glycoprotein I) and late fetal losses [2]. Failure to fully demonstrate the risk factors in the etiology of pregnancy loss hinders the application of appropriate interventions precisely for miscarriage prevention. Therefore, a clinical diagnosis of miscarriage is made at rates ranging from 8% to 15% in the presence of pregnancy loss [3]. Elucidation of the immunological causes in the etiology will contribute to the management of RPL(Recurrent Pregnancy Loss) patients. Studies have shown increased rates of APAs in RPL patients. These antibodies induce trophoblastic apoptosis and target the vascular endothelium, inducing the generation of anomalous spiral arteries [4]. The relationship between fertility disorders and autoimmune diseases is well described in the literature. However, it is very difficult to talk about humoral autoimmunity in the absence of any autoimmune disease criteria; This may involve the positivity of APA as there is little evidence in the literature [5]. Various types of evidence have shown that the risk of miscarriage increases in the presence of autoimmune diseases and associated autoantibody positivity. The most well-known autoimmune disease shown to be associated with this condition is antiphospholipid antibody syndrome [6]. APS is characterized by recurrent thrombosis or complications of pregnancy (miscarriage and fetal death, preeclampsia, placental insufficiency, and fetal growth restriction) in addition to the presence of antiphospholipid antibodies [7]. The antigenic targets of APAs are negatively charged phospholipids and phospholipid-binding proteins in the serum [7]. The antigens

***Corresponding Author:** Vildan Gorgulu, Department of Medical Microbiology, Antalya Public Health Laboratory, Antalya, Turkey
E-mail: gorgulu5@hotmail.com

to which APAs bind are partially understood. Autoimmune factors inducing the synthesis of antibodies targeting phospholipids (cardiolipin, phosphatidylserine, etc.) or plasma proteins (beta2-glycoprotein I, prothrombin, and annexin V, etc.) that bind to phospholipids are risk factors for recurrent miscarriage. However, the mechanisms of antiphospholipid antibody-mediated pregnancy failure remain to be a subject of research [8]. Recurrent miscarriage induces the synthesis of IgG, IgM, and IgA type antibodies against phospholipids. These antibodies disrupt cell functions, resulting in inflammation and coagulation. However, the relationship between antiphospholipid antibodies and spontaneous abortions of unknown etiology is unclear [6]. This study aims to identify APS markers that play an important role in the etiology of recurrent abortions and to guide clinical diagnosis and treatment.

Materials and Methods

Study Population

In the study, 310 pregnant women who applied to the gynecology and obstetrics outpatient clinic of Afyon Kocatepe University Faculty of Medicine were evaluated. Pregnant women with an etiological cause and a history of infection, systemic autoimmune rheumatic diseases (systemic lupus erythematosus, rheumatoid arthritis, etc.), and those who had a miscarriage 1 were excluded from the study. 190 pregnant women were excluded for these reasons. 120 patients who had 2 or more miscarriages were included in the study. The study included 120 patients 26,55±6,52 old, who were admitted to the obstetrics and gynecology outpatient clinic with recurrent miscarriage (miscarriage number ≥ 2) were included in the study. Patients were assigned into 4 age groups as follows: 20-25 years (n = 51), 26-30 years (n = 42), 31-35 years (n = 16), and 36 years and older (n = 11). This study was conducted prospectively in compliance with the Declaration of Helsinki after obtaining the approval of the institutional Ethics Committee. This study was done in Afyon Kocatepe University Medical Faculty's medical microbiology laboratory.

Ethical approval

This observational study was conducted by the ethical principles stated in the "Declaration of Helsinki" and permission was obtained from the Ethics Committee of Afyon Kocatepe University Faculty of Medicine for the use of patient data for publication purposes (Date-Decision no: 14.09.2007-115).

Power analysis

The prospective observational study universe comprised patients presenting to the obstetrics and gynecology outpatient clinic due to recurrent pregnancy loss. During the study period, 310 female patients were admitted to the obstetrics and gynecology outpatient clinic due to recurrent miscarriage. It was concluded that 118 patients to be included in the study using a simple random sampling method would be explanatory for the study universe in a 95% confidence interval and with a 3% error margin. In light of these data, the study was carried out on the samples collected from 120 patients. The patients included in the study provided a 0.95 sampling power at an effect size of 0.50 (studies having a 0.70 sampling power are considered to have a small, medium, or large effect size at an effect size of less than 0.10, 0.25, and 0.40). In summary, it is observed that the study is appropriately powered with a considerable appropriate effect size.

The statistical power of the study and the effect size was calculated with G*Power Version 3.1.7.

Laboratory analysis

The blood sample sera were separated by centrifugation at 5000 rpm for 5 minutes. Blood samples were screened for antibodies associated with APS using the Enzyme-Linked Immunosorbent Assay (ELISA) technique. The Orgentec kit (ORGENTEC Diagnostika GmbH, Germany) was used for measuring the antibody levels. The tests were automatically conducted using a fully automated Alegria device (ORGENTEC Diagnostica GmbH, Germany) based on the ELISA method. The test strips were designed for a single assay. The strips consisted of 8 wells with barcodes. The wells were coated with individual antigens (cardiolipin, beta2-glycoprotein, phosphatidylserine, prothrombin, and annexin V), depending on the test type. The assays were performed as indicated in the kit procedure. Quantitative results for each type of antiphospholipid antibody were interpreted based on the upper and lower limit values specified in the kit procedure. The positive cut-off levels (U/ml) specified for APAs were as follows; ACA IgM: ≥ 7 Positive, ACA IgG and IgA: ≥ 10, aβ2GPI IgM, IgG, and IgA: ≥ 5, Antiprothrombin IgM, IgG, and IgA: ≥ 10, Antiphosphatidylserine IgM and IgG: ≥ 10, Anti-annexin V IgM and IgG: ≥ 5.

Statistical Analysis

The numeric data were coded and entered into the statistical software. SPSS (Statistical Package for Social Science, Chicago, II, USA) 22.0 Windows package program was used for carrying out the statistical analyses. The critical decision-making value was set at 0.05. Descriptive statistics are presented with mean, deviation, frequency, and percentage. Also, a chi-square analysis was performed to examine the number and time of miscarriage by the patient's age. Kolmogorov-Smirnov test was performed to test the assumption of normality of distribution of mean age and a low number of patients. According to the results, it was determined that the distributions of age and number of lows showed normal distribution. Also, due to the sufficient number of samples and the appropriate average standard deviation rates, the tests performed were selected from the tests that show a parametric test approach. Correlation analysis was applied to examine the relationship between the patients' ages and their abortion numbers.

Results

The study was conducted on 120 female patients, who were examined for recurrent pregnancy loss. The mean age of the patients was found to be 26,55±6,52, and their number of miscarriages found to be 3,42±1,38 (Table 1). The distribution of the study patients by the age groups was as follows: 43% (n = 51) were 20-25 years old, 35% (n = 42) were 26-30 years old, 13% (n = 16) were 31-35 years old, and 9% (n = 11) were 36 years or older.

Table 1. Patient characteristics

Age	Mean ± SD
	26.5±6.52
Number of Miscarriage	Mean ± SD
	3.42±1.38
Type of Miscarriage (n:120)	
Early miscarriage	108 %90
Late miscarriage	2 %2
Early and late miscarriage	10 %8

The distribution of the study patients by the number of miscarriages was as follows: 1% (n = 1) of the patients had 7 miscarriages, 1% (n = 1) had 6, 2% (n = 2) had 5, and 6% (n = 7) had 4 miscarriages. Those patients having a history of 4, 5, 6, or 7 miscarriages were brought together to form a single group. Of the patients who had recurrent pregnancy loss, 53% (n = 63) had 3 and 38% (n = 46) had 2 miscarriages. Early miscarriage was observed in 90% (n = 108) of the patients and late miscarriage was observed in 2% (n = 2) of the patients. A history of both early and late miscarriage was present in 8% (n = 10) of the patients.

The number and time of spontaneous abortions were analyzed by the age groups. The number of miscarriages by the age groups was statistically significant. The patients having 2 (n = 21) and 3 (n = 29) miscarriages comprised 46% of the age group of 20-25 years and the proportion of patients having 4 or more miscarriages (n=5) was 45% in the age group of 36 years and older (p=0.03, p<0.05) (Table 2).

Table 2. Relationship between the number of miscarriages and age

Number of Miscarriages		20-25 years	26-30 years	31–35 years	≥36 years	p
2 miscarriages	n	21	17	6	2	0.03*
	%	46%	37%	13%	4%	
3 miscarriages	n	29	23	7	4	
	%	46%	37%	11%	6%	
≥ 4 miscarriages	n	1	2	3	5	
	%	9%	18%	27%	45%	

Those patients having a history of 4, 5, 6, or 7 miscarriages were brought together to form a single group.

It was observed that the mean age of the patients was not at different levels according to their early or late miscarriage (p = 0.16) (Table 3).

Table 3. Relationship between the time of miscarriage and age

Time of miscarriage	n	X±s.d.	p
Early miscarriage	108	26.08±7.54	0,16
Early and Late Miscarriage	10	27.05±9.22	

*Late Miscarriage n=2 excluded from the analysis

There were no significant differences between the age groups and the time of miscarriage (p=0.35, p>0.05) (Table 4).

There was a significant difference between the sensitivity of the tests. ACA (anticardiolipin antibody) total (IgM%/IgG%) seropositivity was 75% (n = 90) and anti-annexin V total (IgM%/IgG%) seropositivity was 50.8% (n = 61). The seropositivity of ACA and that of anti-annexin V were higher than those of other tests. Moreover, the positivity of ACA IgM isotype (42.5%, n = 51) and the seropositivity of anti-annexin V IgM isotype (40%, n = 48) were higher than the other isotypes (p=0.01, p <0.05) (Table 5) (Figure 1).

The distribution of antiphospholipid antibody positivity was different in 4 different age groups. ACA was positive at the lowest percentage (56%) in the 31-35 age group compared to the other age groups. aβ2GPI (anti-beta2-glycoprotein I) showed positivity in more patients in the age groups of 20-25 years (12%) and 31-35 years (13%). Compared to the other age groups, antiphosphatidylserine positivity was the highest (9%) in the patient group at the age of 36 years and older. Antiprothrombin positivity rates were higher in the age group of 31-35 years (38%) and the patient group at 36 years of age or older (36%) compared to the other age groups. Anti-annexin V positive patients were found at the highest ratio (64%) in the patient group at 36 years of age and over compared to the other age groups (p=0.01, p<0.05) (Table 6) (Figure 2).

Table 4. Relationship between the time of miscarriage and age

Time of miscarriage		20-25 years	26-30 years	31–35 years	≥36 years	p
Early miscarriage	n	48	37	13	10	0.35
	%	44%	34%	12%	9%	
Early and Late Miscarriage	n	3	4	3	0	
	%	30%	40%	30%	0%	
Late Miscarriage	n	0	1	0	1	
	%	0%	50%	0%	50%	

The distribution of antiphospholipid antibody positivity was different from the number of miscarriages. Both ACA and aβ2GPI positivity rates were the highest (71% and 13% respectively) in the patients having 3 miscarriages compared to the other groups. Antiphosphatidylserine positivity was also the highest (5%) in the patient group with 3 spontaneous abortions. Antiprothrombin positivity was found at the lowest percentage (22%) in the patient group with 2 spontaneous abortions. Anti-annexin V was positive at the highest percentage (60%) in patients with 3 spontaneous abortions (p=0.01, p<0.05) (Table 7) (Figure 3).

Table 5. IgM-IgG-IgA analysis of antiphospholipid antibodies in the patients

APAs		IgM / IgG / IgA	IgM	IgG	IgA	IgG+IgM+IgA	p
Early miscarriage	n	90	51	28	0	11	
	%	75%	42.5%	23.3%	0%	9.2%	
Early and Late Miscarriage	n	12	2	3	6	1	
	%	10%	1.7%	2.5%	5.0%	0.8%	
Late Miscarriage	n	4	4	0	0	0	0.01*
	%	3.3%	3.3%	0%	0%	0%	
Anti-prothrombin	n	30	21	4	4	1	
	%	25%	17.5%	3.3%	3.3%	0.8%	
Anti-annexin V	n	61	48	8	0	5	
	%	50.8%	40.0%	6.7%	0%	4.1%	

Table 6. The frequencies of antiphospholipid antibodies by the age groups

			Ages				
APAs		**Positive**	**20-25 years**	**26-30 years**	**31–35 years**	**≥36 years**	**p**
ACA	n	90	37	36	9	8	
	%	75%	73%	86%	56%	73%	
aβ2GPI	n	12	6	3	2	1	
	%	10%	12%	7%	13%	9%	
antiphosphatidylserine	n	4	2	0	1	1	0.01*
		3.3%	4%	0%	6%	9%	
Anti-prothrombin	n	30	9	11	6	4	
	%	25%	18%	26%	38%	36%	
Anti-annexin V	n	61	25	20	8	7	
	%	51%	49%	48%	50%	64%	

*Chi-square analysis

Table 7. Antiphospholipid antibody positivity by the miscarriage number

APAs		Positive	2 miscarriage	3 miscarriage	≥4 miscarriage	p
ACA	n	90	29	45	7	
	%	75%	63%	71%	64%	
aβ2GPI	n	12	3	8	1	
	%	10%	7%	13%	9%	
Antiphosphatidylserine	n	4	1	3	0	0.01*
	%	3.30%	2%	5%	0%	
Anti-prothrombin	n	30	10	17	3	
	%	25%	22%	27%	27%	
Anti-annexin V	n	61	19	38	4	
	%	51%	41%	60%	36%	

*Chi-square analysis

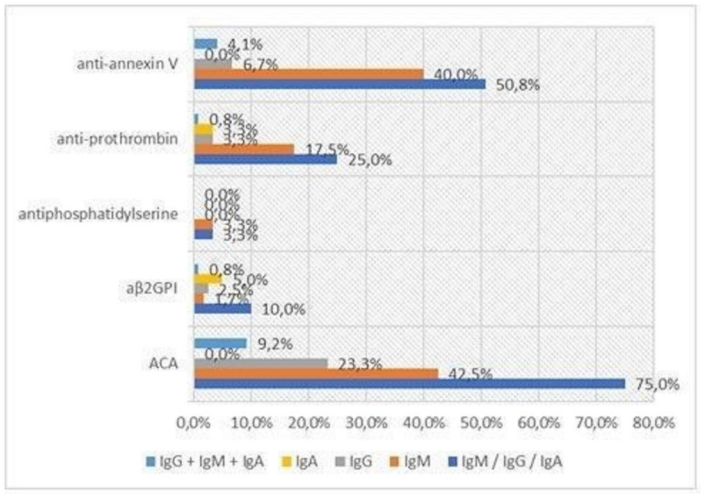


Figure 1. Test analysis results by the age groups

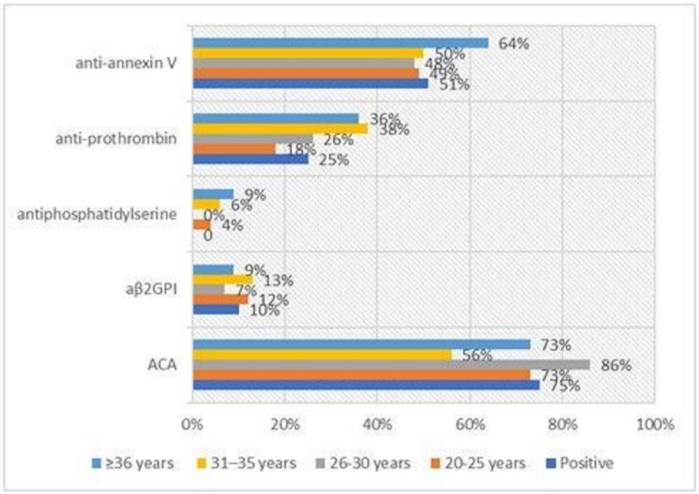


Figure 2. The frequencies of antiphospholipid antibodies by the age groups

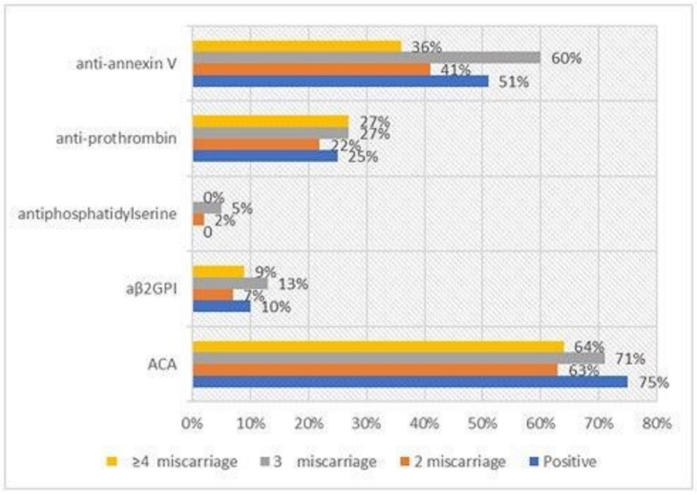


Figure 3. Antiphospholipid antibody positivity by the miscarriage number

Discussion

The coexistence of recurrent miscarriage and positivity of antiphospholipid antibodies is continuously stressed as characteristics of APS. If we think that 80% of the miscarriages are in the first trimester; APS may be considered as the most important treatable cause of recurrent first-trimester miscarriage. Also, It is a major cause of early-onset preeclampsia and intrauterine growth restriction due to abnormal placental function. It is observed that APAs may not directly affect the early stages of embryonic implantation in this patient group but it may affect subsequent trophoblast migration and implantation based on the time of miscarriage [9]. Phospholipids are found in the cell membrane and they help the transformation process into syncytiotrophoblasts. However, disorders in implantation and trophoblast defects develop in association with the antiphospholipid antibodies, resulting in miscarriage. The relationship between placental dysfunction and antiphospholipid antibody positivity has been the focus of many studies and is still a matter of debate [6].

This study investigated the role of APAs in the etiology of recurrent miscarriage. The positivity of antiphospholipid antibodies was analyzed in four age groups by the number and time of spontaneous abortions. In our study, statistically significant differences were found in the number of abortions by the age groups of the patients. In this study, it was observed that pregnant women who had 2 and 3 miscarriages were mostly in the age range of 20 to 30 years. Women with 4 or more miscarriages were more likely to be 36 years or older. This finding might result from the age of pregnancy mostly occurring from 20 and 30 years of age and also due to the high ratios of antiphospholipid antibody positivity in women having 2 and 3 miscarriages. This finding was similarly positive in the pregnant women group having 4 or more miscarriages, showing a high patient ratio with antiphospholipid antibody positivity. This study also examined the relationship between the time of miscarriage and the age of the patients. It was observed that 90% of the patients had an early miscarriage. In the literature, the rate of early miscarriage was 80% [3]. This study could not find out a relationship between the age groups and early or late spontaneous abortions. This finding may be due to the factors associated with the time of emergence of the antiphospholipid antibodies, suggesting that the time of APAs synthesis is an independent parameter of the age of the patient. Franklin et al. conducted a study on 79 recurrent miscarriage patients in 2002 and they examined the role of APAs in women with 2 or more miscarriages by the pathophysiology and obstetric history. Their study could find no significant associations among the patient's age, previous pregnancies, and previous spontaneous abortions based on the comparison of the demographic characteristics of the patients [10]. Another study on APS patients was conducted by Van den Boogaard et al., finding out no significant differences by the clinical obstetric parameters. That study could not find out a significant variable in association with the gestational age, the number of spontaneous abortions, and the type of positive antiphospholipid antibodies. Furthermore, that study demonstrated that women with two consecutive miscarriages are at the same risk as women with three or more spontaneous abortions [11]. Currently, it is not known whether diagnostic test results for APS can be supported by clinical determinants derived from obstetric history [11].

Antiphospholipid antibody positivity is associated with recurrent miscarriage and is used as diagnostic criteria. Also, determining APA positivity is important in the evaluation of autoimmune pregnancy losses. However, the results are highly variable among patients [12]. In our study, APA positivity was different among the age groups. While the APAs were positive in patients having 2

spontaneous abortions, the ratio of patients with APA positivity increased in patients with 3 miscarriages. This finding shows that the ratio of patients with APA positivity increases with the increasing number of spontaneous abortions, explaining the direct relationship between recurrent miscarriage and APA positivity. When the percentage of patients with positive APA levels were examined by the number of spontaneous abortions, significantly high ratios of patients with especially the positivity of ACA and the positivity of anti-annexin V antibodies were observed in the group of pregnant women with 2, 3, 4, and more spontaneous abortions. This finding indicates that; of the APAs, mostly ACA and annexin V antibodies were associated with recurrent miscarriage. However, in patients with recurrent miscarriage, ACA and annexin V antibodies should be tested and these antibodies should be included in diagnostic tests.

Several studies have found out statistically significant relationships between ACA and RPL. It has been reported that the risks of fetal growth delay and preeclampsia increase in pregnant women with ACA positivity. These antibodies cause thrombosis of placental vessels. Nielsen et al. performed a study on 147 patients in 2005, reporting a 41% ACA positivity rate based on ELISA test results. Of these positive ACA antibodies, 32% were ACA IgM and 13% were ACA IgG. It has been found out that ACA IgM is more sensitive than ACA IgG and, consequently, ACA IgM is more strongly correlated with recurrent miscarriage compared to ACA IgG [13]. In our study, ACA was found to be 75% positive. Of these ACA positive antibodies, 42.5% were ACA IgM and 23.3% were ACA IgG. ACA IgM and ACA IgG positivity were found in combination with a ratio of 9.2%. Based on our study results, we can argue that ACA IgM antibodies are found with higher ratios and should be considered as the main parameter for making the diagnosis.

IgM antibodies in these patients are found in high concentrations in the primary immune response but IgM positivity in APS should not be considered transient as it is in infectious diseases. IgM positivity is long-term in APS. The IgM isotype of APAs is the most important biological marker for recurrent miscarriage and is associated with pathogenicity. A literature review shows that the IgM isotype of antiphospholipid antibodies is considered a potential clinical risk for APS and it shows a more significant correlation with thrombosis. Despite the already defined diagnostic criteria for APS, difficulties remain in identifying patients at risk for thrombosis. A study reviewed 1288 articles in the literature in Pubmed and reported the results by the antibody types (ACA, aβ2GPI), the isotypes (IgM, IgG), and the type of thrombosis. It has been reported that strong evidence is obtained about the relationship between thrombosis and the ACA IgM isotype and the aβ2GPIantibodies [14]. aβ2GPI inhibits the proliferation of trophoblasts and maternal spiral artery invasion. Consequently; large necrosis, infarcts, and thrombosis occur in the placenta [14]. We believe that this study of ours will be guiding for the researches in developing a better classification system in the future.

Most antiphospholipid antibody studies have focused on the detection of IgM and IgG isotypes and a few studies are reporting the pathogenic importance of the IgA isotype [15]. The association between APS and IgA is observed, albeit slightly. This study also shows that IgA isotypes are less commonly found positive compared to the other antibody isotypes [15].

Several pathogenic mechanisms have been identified in APS, reporting the important role of annexin V. Annexin V is a phospholipid-binding protein that is highly expressed by the vascular endothelium and placental syncytiotrophoblasts, showing strong anticoagulant characteristics in antithrombotic activities. Annexin V, also known as the placental anticoagulant protein, is a strong vascular anticoagulant protein. APAs reduce annexin V quantities on cell surfaces and consequently accelerate coagulation in trophoblasts and endothelial cells. This may cause thrombotic events and pregnancy loss in APS [16]. Studies have reported that the anti-annexin V positivity results in placentation disorders in recurrent miscarriages [17]. It has been reported that anti-annexin V plays a role in recurrent miscarriage [18]. Bizzaro et al. conducted a study in 2005, examining samples from 1038 patients by the ELISA method. They reported that 25% of the patients had anti-annexin V IgG and 27.5% had anti-annexin V IgM [19]. In our study, anti-annexin V was found to be 50.8% positive in total. While 40% of these were anti-annexin V IgM, 6.7% were anti-annexin V IgG. This high ratio of anti-annexin V positivity in our study and the findings from other studies in the literature suggest that investigation of the role of anti-annexin V in miscarriage will unfold a better understanding of the placental physiology.

Phosphatidylserine is a phospholipid on the inner surface of the cell membrane and anti-phosphatidylserine autoantibodies have been detected in patients with APS. Studies in animal models show that antiphosphatidylserine antibodies cause pathogenic events in trophoblasts. One study reported the positivity rates for antiphosphatidylserine and aβ2GPI antibodies as 4% and 12%, respectively; suggesting that antiphosphatidylserine and aβ2GPI antibodies should be considered as risk factors in recurrent miscarriage [20]. Velayuthaprabhu et al. in 2005 found the ACA IgA and antiphosphatidylserine IgG levels were 40% and 19%, respectively, in women with recurrent miscarriage [21]. A study has reported that anti-prothrombin IgG and IgM isotypes may be associated with pregnancy loss in recurrent miscarriage. These antibodies are suggested to play an important role in the etiology and pathogenesis of miscarriage [22]. Anti-prothrombin and aβ2GPI antibodies have prothrombotic properties and their potential relationships with recurrent miscarriage have been reported [23]. Prothrombin (coagulation factor II) is a plasma protein having a phospholipid structure and it triggers the conversion of fibrinogen to fibrin. Anti-prothrombin antibodies are associated with thrombosis in patients with APS. Prothrombin antibodies cause prothrombin aggregation on the surface of the activated cell. Singh et al. study on 50 patients with a history of recurrent miscarriage found the positivity rates for aβ2GPI and anti-prothrombin as 12% and 6% respectively; highlighting the relationship between APS and thrombotic events in pregnant women. That finding shows the varying rates of APA positivity in patients with recurrent miscarriage [24]. Our study found out that the frequencies of anti-prothrombin, aβ2GP, and antiphosphatidylserine positivity were 25%, 10%, and 3.3% respectively. In light of our study findings and the results reported by previous studies in the literature, we think that these antibodies (anti-prothrombin, aβ2GPI, and antiphosphatidylserine) will be guiding for the management of spontaneous abortions and enable to make the diagnosis easily.

The data suggest that ACA and anti-annexin V may be more strongly associated with APS and may be more common in this disorder. The positivity for aβ2GPI, anti-prothrombin, and antiphosphatidylserine are observed at low rates. In our study, we observed that ACA and anti-annexin V antibodies correlated better with the clinical symptoms of the patients in our geographical region. Our results showed the major role played by APAs in recurrent miscarriage.

Conclusion

This study may guide for obtaining a better understanding of the etiology of APS in recurrent miscarriage in women having no history of chromosomal or anatomic malformations in the fetus. It can be argued that ACA and anti-annexin V antibodies play an important role in the etiology of recurrent miscarriage. Therefore, they are highly suitable diagnostic markers for recurrent miscarriage. Anti-prothrombin, aβ2GPI, and antiphosphatidylserine antibodies may be seen at low rates in the etiology of miscarriage. We think that the investigation of these antibodies may help in diagnosis and treatment. IgM and IgG isotypes of antiphospholipid antibodies were observed more frequently than the IgA isotype. In particular, the IgM isotype is an important marker and should be used as a diagnostic tool; however, the role of the IgA isotype in APS is very low.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
All authors declare no financial support.

Ethical approval
This observational study was conducted in accordance with the ethical principles stated in the "Declaration of Helsinki" and permission was obtained from Ethics Committee of Afyon Kocatepe University Faculty of Medicine for the use of patient data for publication purposes (Date-Decision no: 14.09.2007-115).

References

1. Schreiber K, Hunt BJ. Managing antiphospholipid syndrome in pregnancy. Thromb Res. 2019;181:41-6.
2. Jinfeng Xu, Daijuan Chen, Xia Duan, et al. The Association Between Antiphospholipid Antibodies and Late Fetal Loss: A Systematic Review and Meta-Analysis. Acta Obstet Gynecol Scand. 2019;98:1523-33.
3. Prine LW, MacNaughton H. Office management of early pregnancy loss. Am Fam Physician. 2011;84:75-82.
4. Grimstad F, Krieg S. Immunogenetic contributions to recurrent pregnancy loss. Assist Reprod Genet. 2016;33:833-47.
5. Wackenheim C, Hoffman P, Dumestre-Pérard C et al. [Prevalence and characteristics of serum autoantibodies in patients followed for infertility at Grenoble University Hospital]. Presse Med. 2019;48:307-15.
6. Zhu H, Wang M, Dong Y et al. Detection of non-criteria autoantibodies in women without apparent causes for pregnancy loss. Clin Lab Anal. 2019;33:e22994.
7. Krivonos MI, Kh Khizroeva J, Zainulina MS et al. The role of lymphocytic cells in infertility and reproductive failures in women with antiphospholipid antibodies. J Matern Fetal Neonatal Med. 2020;25:1-7.
8. Litvinova E, Darnige L, Kirilovsky A et al. Prevalence and Significance of Non-conventional Antiphospholipid Antibodies in Patients With Clinical APS Criteria. Front Immunol. 2018;14:2971.
9. Rai RS. Antiphospholipid syndrome and recurrent miscarriage. J Postgrad Med. 2002;48:3-4.
10. Franklin RD, Kutteh WH. Antiphospholipid antibodies (APA) and recurrent pregnancy loss: treating a unique APA positive population. Hum Reprod. 2002;17:2981-5.
11. Van den Boogaard E, Cohn DM, Korevaar JC et al. Number and sequence of preceding miscarriages and maternal age for the prediction of antiphospholipid syndrome in women with recurrent miscarriage. Fertil Steril. 2013;99:188-92.
12. Gris JC, Bouvier S, Nouvellon E et al. Antiphospholid antibodies and the risk of pregnancy complications. Thromb Res. 2017;151:34-7.
13. Nielsen HS, Christiansen OB. Prognostic impact of anticardiolipin antibodies in women with recurrent miscarriage negative for the lupus anticoagulant. Hum Reprod. 2005;20:1720-8.
14. Kelchtermans H, Pelkmans L, de Laat B et al. IgG/IgM antiphospholipid antibodies present in the classification criteria for the antiphospholipid syndrome: a critical review of their association with thrombosis. J Thromb Haemost. 2016;14:1530-48.
15. Meijide H, Sciascia S, Sanna G et al. The clinical relevance of IgA anticardiolipin and IgA anti-β2 glycoprotein I antiphospholipid antibodies: a systematic review. Autoimmun Rev. Autoimmun Rev. 2013;12:421-5.
16. Danisik H, Bogdanova N, Markoff A. Micromolar Zinc in Annexin A5 Anticoagulation as a Potential Remedy for RPRGL3-Associated Recurrent Pregnancy Loss. Reprod Sci. 2019;26:348-56.
17. Demetriou C, Abu-Amero S, White S, Peskett E et al. Investigation of the Annexin A5 M2 haplotype in 500 white European couples who have experienced recurrent spontaneous abortion. Reprod Biomed Online. 2015;31:681-8.
18. Rand J, Eerden PV, Wu XX et al. Defective annexin A5 crystallization: a mechanism for pregnancy losses in the antiphospholipid syndrome. Thromb Res. 2005;115:77-81.
19. Bizzaro N, Antico A, Musso M et al. A prospective study of 1038 pregnancies on the predictive value of anti-annexin V antibodies for fetal loss. Ann N Y Acad Sci. 2005;1050:348-56.
20. Alijotas-Reig J, Ferrer-Oliveras R, Rodrigo-Anoro MJ et al. Anti-beta (2)-glycoprotein-I and anti-phosphatidylserine antibodies in women with spontaneous pregnancy loss. Fertil Steril. 2010;93:2330-6.
21. Velayuthaprabhu S, Archunan G. Evaluation of anticardiolipin antibodies and antiphosphatidylserine antibodies in women with recurrent abortion. Indian J Med Sci 2005;59:347-52.
22. Sabatini L, Torricelli M, Scaccia V, et al. Increased plasma concentrations of antiprothrombin antibodies in women with recurrent spontaneous abortions. Clin Chem. 2007;53:228-32.
23. Kdous M, Hachicha R, Lombroso R et al. Antiphospholipid antibodies and pregnancy. Tunis Med. 2005;83:1-5.
24. Singh A, Nangia A, Sharma S et al. A Study of Anti Beta-2 Glycoprotein I and Anti-Prothrombin Antibodies in Patients with Unexplained Recurrent Pregnancy Losses. Indian J Hematol Blood Transfus. 2016;32:198–201.

Available online at www.medicinescience.org

ORIGINAL ARTICLE

Medicine Science International Medical Journal

Medicine Science 2021;10:191-5

Relationship between preoperative pulmonary risk assessment and postoperative pulmonary complications in patients undergoing cranial surgery in the presence of chronic disease

Usame Rakip[1], Aydin Balci[2]

[1]Afyonkarahisar Health Sciences University, Faculty of Medicine, Department of Neurosurgery, Afyonkarahisar, Turkey
[2]Afyonkarahisar Health Sciences University, Faculty of Medicine, Department of Chest Diseases, Afyonkarahisar, Turkey

Received 27 October 2020; Accepted 20 November 2020
Available online 01.02.2021 with doi: 10.5455/medscience.2020.10.229

Abstract

Postoperative complications are becoming more and more important than the risk given in preoperative pulmonary evaluation due to the increase in patients requiring surgical intervention. Patients undergoing craniotomy are routinely evaluated preoperatively, but the role of these evaluations in predicting outcomes has not been adequately studied. We aimed to investigate the effect of preoperative pulmonary risk assessment and the type of operation performed on postoperative complications and mortality concerning the presence of chronic disease in patients undergoing cranial surgery in the light of the literature. Preoperative pulmonary consultation data and postoperative pulmonary consultations, if any, of cranial surgery patients who were operated on in the neurosurgery clinic of a tertiary hospital were retrospectively analyzed. 85 (43.8%) of the surgical patients were male and 109 (56.2%) were female, and the average age of 194 people was 74 (35-90). 83 (42.7%) of the patients had at least one chronic disease. Considering the preoperative pulmonary risks, 72 (37.1%) patients were given medium risk. Statistically, the mortality rate was higher in those with ICU beds. Atelectasis in 10 (5.15%) patients, pneumonia in 7 (3.608%) patients, embolism in 3 (1.5%) patients, respiratory failure in 3 (1.5%) and bronchospasm in 2 (1%) patients, respectively. Postoperative pulmonary complications developed in 25 (12.9%) patients. Prediction of respiratory complications with effective preoperative pulmonary evaluation is important in terms of decreasing morbidity and mortality and decreasing the length of hospital stay. Since most of the complications are seen in patients given high risk in the preoperative period, close follow-up of high-risk patients in the postoperative period is important.

Keywords: Postoperative complications, pulmonary risk, cranial surgery, chronic disease, geriatric

Introduction

Pulmonary complications that develop in a short and long time in patients who undergo non-pulmonary surgical intervention lead to significant morbidity and mortality and increase the duration of hospital stay [1]. PPCs cause higher mortality, a longer stay in both hospital and ICU, a dramatic increase in medical cost and socioeconomic burden [2].

Today, studies are reporting that postoperative morbidity and mortality can be reduced and hospital costs can be reduced with a careful preoperative pulmonary evaluation in patients undergoing surgery in pulmonology practice [3,4].

***Coresponding Author:** Usame Rakip, Department of Neurosurgery, Faculty of Medicine, Afyonkarahisar Health Sciences University, Afyonkarahisar,Turkey
E-mail: usamerakip@gmail.com

Postoperative pulmonary complications (PPC) are the complications that cause the most mortality and morbidity in the postoperative period [5]. The incidence, clinical effect, and risk factors of individual PPCs are not fully known. To maximize the effectiveness of new interventions, detailed knowledge of mild to severe PPCs is needed to identify modifiable risk factors [6,7]. In these patients, preoperative spirometry and chest radiography may not be routinely requested to determine the risk of postoperative pulmonary complications, but chronic obstructive These tests may be useful in patients with a history of lung disease or asthma [8].

Postoperative complications are becoming more and more important according to the risk given in preoperative pulmonary evaluation due to the increase in patients requiring surgery. All these data reveal the importance of developing strategies for patients scheduled for surgery to increase quality and minimize complications. Patients undergoing cranial surgery are evaluated routinely before surgery. However, the role of these evaluations in predicting outcomes has not been sufficiently studied. We aimed to investigate the effect of preoperative pulmonary risk

assessment and the type of operation performed on postoperative complications and mortality concerning the presence of chronic disease in patients undergoing cranial surgery in the light of the literature.

Materials and Methods

194 cranial surgery patients were included in the study from 870 patients who were operated on in the Neurosurgery Clinic of Afyonkarahisar Health Sciences University, Faculty of Medicine, between 2014-2019. Preoperative pulmonary consultation data and postoperative pulmonary consultations of cranial surgery patients were analyzed retrospectively. Age, gender, existing diseases, preoperative pulmonary risk class, operation type and duration, type of anesthesia (all patients were operated on under general anesthesia), perioperative, and postoperative complications were recorded.

This study had been carried out with the decision dated 2020/395 (2011-KAEK2) by Afyonkarahisar Health Sciences University Clinical Research Ethical Board.

Statistical analysis

SPSS Windows 20 program was used for statistical analysis. Descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, maximum) were used to evaluate the study data. Compliance of quantitative data to normal distribution was tested with Kolmogorov-Smirnov, Shapiro - Wilk test, and graphical evaluations. Student-t-test was used to compare the quantitative data of the two groups with the normal distribution, and the Mann-Whitney U test was used to compare the two data groups with the abnormal distribution. Pearson's Chi-Square test and Fisher's Exact test were used to comparing qualitative data. Significance was set at $p < 0.05$.

Table 1. Demographic characteristics of the patients

	Chronic diseases have	Chronic diseases have'nt	Total	P
	n=83 %42.8	n=111 %57.2	n=194	
Age	74(46-89)	74(35-90)	74(35-90)	
Gender				
Woman	36(%43.4)	49(%44.1)	85(%43.8)	
Male	47(%56.6)	62(%55.9)	109(%56.2)	
Cigaret	38(%48.8)	45(%54.2)	73(%37.6)	
AveragHospitalization Days	15(1-100)	15(1-145)	15(1-145)	
Saturation	94(75-99)	94(84-99)	94(75-99)	
Pulse / Minute	80(60-172)	80(47-170)	80(47-172)	

Results

Of the 194 patients included in the study, 85 (43.8%) were male and 109 (56.2%) were female, and the average age was 74 (35-90). 73 (37.6%) of the patients were active smokers. During the examination, the saturation values of the patients who were evaluated preoperatively for pulmonary examination were 94 (75-99) and the heart rate values were measured as 80 (47-172) / minute (Table 1).

83 (42.7%) of the patients had at least one chronic disease. The most common chronic diseases are essential hypertension (HT) and coronary artery disease (CAD) in 36 (43.4%) patients, chronic respiratory diseases (asthma and chronic obstructive pulmonary disease, etc.) in 25 (30.2%) patients, respectively. Diabetes mellitus (DM) was present in 25 (30.2%) patients. When the operated patients were compared, no statistically significant difference was observed in terms of the total presence of chronic diseases.

When the patients who had a chronic disease in the preoperative period and died in the postoperative period, a statistically significant difference was observed in terms of death rates in the presence of malignancy alone (Table 2) ($P < 0.001$).

Considering the types of cranial surgery applied to the patients, the intracranial mass operation was performed most frequently in 83 (42.7%) patients, while Arnold Chiari malformation surgery was performed with at least 1 (0.5%) patient. In terms of postoperative mortality rates, it was statistically insignificant in terms of postoperative complications and mortality rates after surgical interventions ($P = 0.135$, $P = 0.185$, respectively) (Table 3).

Table 2. Chronic disease rates by gender

	Chronic Diseases Have n=83	
	n	%
Hypertension And Coronary Artery Disease	36	43.4
Diabetes	25	30.2
Congestive heart failure	17	20.5
Chronic obstructive pulmonary disease	14	16.9
Asthma	11	13.3

Table 3. The count of cranial surgeries applied to geriatric patient groups

	Chronic Diseases Have N=83		Chronic Diseases Have'nt N=111		Total n=194		P
	n	%	n	%	n	%	
Intracranial tumor	32	38.6	51	45.9	83	42.8	0.732
Intracranial hemorrhage	34	41	39	35.1	73	37.6	
Shunt(cyst etc)	8	9.6	13	11.7	21	10.8	
Hydrocephalus	8	9.6	8	7.2	16	8.2	
Chiari malformation	1	1.2	0	0	1	0.5	
Malignancy	10	12					
Neurological Disease	8	9.6					
Benign prostatic hypertrophy	5	6					
Thyroid dysfunction	3	3.6					
Osteoporosis	3	3.6					
Chronic renal failure	1	1.2					
Total	83	100					

In the preoperative period, 162 (98.7%) patients were asked to have posteroanterior chest (PA) x-ray and 100 (51.5%) patients had normal findings in 65 (33.5%) patients and 7 (3.6%) had an appearance consistent with a solitary pulmonary nodule or malignancy.

In physical examination, 8 (4.12%) patients had rhoncus and 9 (4.63%) patients had ral. In 3 (1.54%) patients, nasal oxygen saturation was followed due to long-term oxygen therapy use due to chronic respiratory failure.

Considering the preoperative pulmonary risks, 72 (37.1%) patients were given medium risk, while 58 (29.9%) patients were given severe risk. When the risks given to the patients were evaluated, it was observed that the increase in the risk given to the patient was not significant as the age increased according to the risks given to the patients (P = 0.114).

While 128 (66%) of the patients applied to the polyclinic, 66 (34%) of them were made as an emergency service application. Among the emergency service applications, 8 (12.12%) people applied for a traffic accident. When patients who were admitted for emergency surgery and those who underwent elective surgery were compared, there was no statistically significant difference in mortality rates (P = 0.053).

In the postoperative period, 147 (75.8%) of the patients were followed up and treated in the neurosurgery service, while 47 (24.2%) were followed up and treated in the intensive care (ICU). (P <0.001) 46 of the patients receiving treatment. Various postoperative complications were caused by death. Statistically, the mortality rate was higher in patients with ICU beds. (P <0.001) Only 7 (3.6%) of these deaths died due to postoperative pulmonary complications, and there was a significant statistical difference between hospitalization or hospitalization in deaths due to postoperative pulmonary complications. not followed. (P: 0.057).

Table 4. Preoperative risk and postoperative complications according to geriatric patient groups

	Chronic Diseases Have N=83		Chronic Diseases Have'nt N=111		Total n=194		P
	n	%	n	%	n	%	
Preop Given Risk							
Light	3	3.6	7	6.3	10	5.2	0.331
Light-Medium	6	7.2	14	12.6	20	10.3	
Middle	28	33.7	44	39.6	72	37.1	
Medium-Heavy	18	21.7	16	14.4	34	17.5	
Heavy	28	33.7	30	27	58	29.9	
Hospital Application Status							
Normal	57	68.7	71	64	128	66	0.206
Emergency	26	31.3	40	36	66	34	
Section Lying							
Service	63	75.9	84	75.7	147	75.8	0.554
Intensive Care	20	24.1	27	24.3	47	24.2	
Postoperative Respiratory Complication	15	18.1	10	9	25	12.8	0.05
Discharge Type							
With Healing	39	47	63	56.8	102	52.6	0.283
As A	24	28.9	22	19.8	46	23.7	
Death	20	24.1	26	23.4	46	23.7	

Atelectasis in 10 (5.15%) patients, pneumonia in 7 (3.608%) patients, embolism in 3 (1.5%), respiratory failure in 3 (0.87%) and bronchospasm in 2 (1%) patients, respectively. Postoperative pulmonary complications developed in a total of 25 (12.9%) patients. Of the patients who had an embolism, 2 (1%) passed away. As the duration of hospitalization increased, a positive correlation was observed in mortality. (P = 0.02) Also, there was a positive correlation between the increase in the number of hospitalization days and having an embolism (p = 0.040) (Table 4).

Discussion

Chest diseases consultation is performed for two purposes: preoperative evaluation and due to any pathology. The preoperative pulmonary evaluation aims to determine possible serious respiratory dysfunction that may occur after anesthesia and surgery before the operation [9,10]. Estimation of postoperative pulmonary complications (PPCs) allows for individually administered preventive measures and even early treatment if a PPC eventually begins to develop [11]. The parameters that should be evaluated in the preoperative pulmonary anamnesis phase; Age, smoking and drug history, occupational exposure, immobilization, comorbidities, and pulmonary embolism are risk factors. Also, sleep-apnea symptoms and the presence of recently passed respiratory tract infections should be questioned. With a detailed evaluation, findings of undefined lung disease can be obtained and can help determine the basal state before surgery [12]. In a past study conducted by Balcı A. et al in terms of preoperative evaluations in spinal surgery patients and the preoperative risks given to patients in our hospital. They divided the preoperative risks into 5 (mild, mild-moderate, moderate, moderate-severe, severe). The most common risk scale given to patients in the preoperative period was the medium-risk group with a value of 50.3% [13]. In our study, the most common risk value given to patients who were evaluated preoperatively was 37.1%, while this was a severe risk with 29.9%. In our study, while the preoperative risk was given to the patients, it was mostly carried out by considering the clinical conditions and anamnesis of the patients, which is similar to the risk ratios in previous studies.

Preoperative chest radiography is useful, especially in the presence of new or unexplained symptoms and signs, when sudden worsening of the symptoms and signs of the underlying disease is detected or if thoracic surgery is to be performed [14]. In our study, Posteroanterior (PA) chest x-ray of nearly all patients was evaluated in the preoperative period, and no obstacle was found for the operation. Besides, when our study was evaluated, the PFT test was excluded from the evaluation, since the pulmonary function test (PFT) was not requested from most of the patients in the preoperative period. However, in many studies conducted in recent years, it has been concluded that PFT disorder is not a good indicator of complications, and a good clinical evaluation is much more important [15,16]. In our study, patients were given the risk of operation with clinical findings and anamnesis.

The frequency of postoperative pulmonary complications (PPC) varies between 6-79% in the case of series due to various publications and different surgical interventions [17-19]. This wide range is that the patients in the studies were exposed to different surgical procedures and the postoperative pulmonary risks in the studies were different. However, in terms of specific surgeries, examples of preoperative pulmonary evaluations and postoperative pulmonary complication rates in cranial surgery patients forming the basis of our study are few in the literature. For example, in a study conducted on 931 patients who underwent cranial surgery, postoperative pulmonary complications (PPC) was observed in 14.3% of the patients [20]. However, different studies are showing that the probability of developing PPC following elective cranial surgery is 11.2-24.6% [21,22]. In our study, this rate was found to be 12.9% when PPCs after cranial surgery were examined, and it is consistent with similar literature information. This is how the PPCs are defined here: In most studies, PPC is defined as atelectasis, pneumonia, pulmonary edema, exacerbation of the underlying chronic lung disease, or respiratory failure in patients after surgery [23,24]. Neurosurgery operations are accepted as high risk for the formation of PPC [25]. A plausible explanation for this increased risk is the reduction in lung volumes and arterial blood gas tension secondary to the operation, with changes in breathing patterns occurring after craniotomy [26].

Early reports of respiratory complications in patients undergoing neurosurgical procedures include respiratory depression, reintubation, bronchospasm, laryngospasm, and upper airway obstruction occurring in 2.8% of patients [27]. In a study conducted by Hooda B. et al., 3.1% atelectasis occurred in 2.1%, tracheobronchitis in 2.1%, ARDS in 1.4%, and pneumothorax in 0.7% in terms of PPC [28].

Sogame's prospectively studied 236 cranial surgery patients and 58 patients (24.6%) (tracheobronchitis, pneumonia, bronchospasm, and atelectasis) PPC formation and 23 (10%) deaths were reported [29]. When we evaluated the PPCs in our study, 10 of 29 patients had atelectasis, 8 had pneumonia, 5 had tracheobronchitis, 3 had a pulmonary embolism, and 2 had respiratory failure. In our study, it can be shown that all patients who needed long-term mechanical ventilation as a possible reason for the absence of bronchospasm, receiving regular bronchodilator nebulization therapy as an institutional protocol in the intensive care unit. Besides, considering the complications of bronchospasm in patients in the preoperative period, the prediction of nebular and intravenous steroid therapy according to the risk prediction is descriptive to assume that no bronchospasm events occur in patients, but in the light of the retrospective nature of the study, it is largely speculative. Therefore, we suspect that the bronchospasm status was underreported for our study.

Prolonged hospital stays in the postoperative period is an important burden in terms of pulmonary dysfunction, morbidity, mortality, and increased cost of care [30]. As a matter of fact, in our study, the duration of ICU and hospital stay of the patients with PPC was significantly longer. It is independently associated with PPCs. These findings are in line with other studies conducted on neurosurgical patients [29,31].

Conclusion

As a result, postoperative respiratory complications are one of the causes of morbidity, mortality, and intensive care hospitalization in cases undergoing surgical operations. Therefore, it is important to evaluate patients in the preoperative period, and to predict respiratory complications, to reduce morbidity and mortality, and to decrease postoperative hospital stay. Since most of

the complications are seen in patients given high risk in the preoperative period, close follow-up of high-risk patients in the postoperative period is important.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
All authors declare no financial support.

Ethical approval
This study had been carried out with the decision dated 2020/395 (2011-KAEK2) by Afyonkarahisar Health Sciences University Clinical Research Ethical Board.

References

1. Delisser HM, Grippi MA. Ch 40 Perioperative respiratory considerations in the surgical patient. Fishman's Pulmonary Diseases and Disorders,third ed. Fishman AP., Elias JA., Fishman JA., Grippi MA., Kaiser LR., Senior RM. (ed) McGraw-Hill1998;Sf: 619-629.
2. Boden I, Skinner EH, Browning L, et al. Preoperative physiotherapy for the prevention of respiratory complications after upper abdominal surgery: pragmatic, double blinded, multicentre randomised controlled trial. BMJ 2018;360:j5916.10. Okada S, Shimada J, Kato D, et al. Long-term prognostic impact of severe postoperative complications after lung cancer surgery. Ann Surg Oncol 2019;26:230–7
3. Manku K, Bacchetti P, Leung J. Prognostic significance of postoperative in-hospital complications in elderly patients. I. Long Term Survival. Anesth Analg. 2003;96:583-9
4. Harari D, Hopper A, Dhesi J et al. Proactive care of older people undergoing surgery('POPS'): designing, embedding, evaluating and funding a comprehensive geriatric assessment service for older elective surgical patients. Age and Ageing. 2007;36:190- 6
5. Lawrence VA, Dhanda R, Hilsenbeck SG et al. Risk of pulmonary complications after elective abdominal surgery. Chest. 1996;110:744-50.
6. Vetter TR, Ivankova NV, Goeddel LA, et al Perioperative Surgical Home Group. An analysis of methodologies that can be used to validate if a perioperative surgical home improves the patient-centeredness, evidence-based practice, quality, safety, and value of patient care. Anesthesiology. 2013;119:1261–74.
7. Anderson AD, McNaught CE, MacFie J, et al. Randomized clinical trial of multimodal optimization and standard perioperative surgical care. Br J Surg. 2003;90:1497–504.
8. Smetana GW, Conde MV. Preoperative pulmonary update. Clin Geriatr Med 2008;24:607-24.
9. Zamani A. Selçuk üniversitesi araştırma hastanesi'nde göğüs hastalıkları konsültasyonu yapılan olguların değerlendirilmesi. Tüberküloz Ve Toraks Dergisi 1996;44:139-44
10. Woerlee GM. Common perioperative problems and the anasesthetist: Kluwer academic Publishers 1988;179.
11. Nijbroek SG, Schultz MJ, Hemmes SNT. Prediction of postoperative pulmonary complications. Curr Opin Anaesthesiol. 2019;32:443-51.
12. Erdinç E. Preoperatif Pulmoner Değerlendirme. TTDO Mesleki Gelişim Kursu. 2007:24-7.
13. Balci A, Rakip U, Cengiz A. Preoperative pulmonary evaluation and evaluation of postoperative pulmonary complications in geriatric patients undergoing spinal surgery. Journal of Health, Medicine and Nursing. 2020;78:27-35
14. Anonymous. A rational approach to radiodiagnostic investiga¬tions. World Health Organ Tech Rep Ser. 1983;689:1-49.
15. Smetana GW. Preoperative pulmonary evaluation. N Engl J M 1999;340:937-44.
16. Doyle RL. Assessing and modifying the risk of postoperative pulmonary complications. Chest 1999;115(Suppl 5):77-81.
17. Goldman L, Caldera DL, Nussbaum SR, et al. Multifactorial index of cardiac risk in noncardiac surgical procedures. N Engl J Med. 1977;297:845-50.
18. Rock AK, Opalak CF, Workman KG, et al. Safety Outcomes Following Spine and Cranial Neurosurgery: Evidence From the National Surgical Quality Improvement Program. J Neurosurg Anesthesiol. 2018;30:328-36.
19. Edwards AE, Seymour DG, McCarthy JM, et al. A 5-year survival study of general surgical patients aged 65 years and over. Anaesthesia 1996;51:3-10.
20. Bharati SJ, Pandia MP, Rath GP, et al. Respiratory complications in the early post-operative period following elective craniotomies. J Neuroanaesth Crit Care. 2015;2:114–20.
21. Manninen PH, Raman SK, Boyle K, et al. Early postoperative complications following neurosurgical procedures. Can J Anaesth. 1999;46:7–14.
22. Sogame LC, Vidotto MC, Jardim JR, et al. Incidence and risk factors for postoperative pulmonary complications in elective intracranial surgery. J Neurosurg. 2008;109:222–7.
23. Hall JC, Tarala RA, Hall JL, et al. A multivariate analysis of the risk of pulmonary complications after laparotomy. Chest. 1991;99:923–7.
24. Smetana GW, Lawrence VA, Cornell JE American College of Physicians. Preoperative pulmonary risk stratification for noncardiothoracic surgery: Systematic review for the American College of Physicians. Ann Intern Med. 2006;144:581–95.
25. Qaseem A, Snow V, Fitterman N, et al. Risk assessment for and strategies to reduce perioperative pulmonary complications for patients undergoing noncardiothoracic surgery: A guideline from the American college of physicians. Ann Intern Med. 2006;144:575–80.
26. Franceschini J, Sogame LC, Gazzotti MR, et al. Pulmonary function and thoraco-abdominal configuration after elective craniotomy. Neurosurg Q. 2008;18:22–7.
27. Manninen PH, Raman SK, Boyle K, et al. Early postoperative complications following neurosurgical procedures. Can J Anaesth. 1999;46:7–14.
28. Hooda B, Chouhan RS, Rath GP, et al. Incidence and predictors of postoperative pulmonary complications in patients undergoing craniotomy and excision of posterior fossa tumor. J Anaesthesiol Clin Pharmacol. 2019;35:254-60.
29. Sogame LC, Vidotto MC, Jardim JR, et al. Incidence and risk factors for postoperative pulmonary complications in elective intracranial surgery. J Neurosurg. 2008;109:222–7.
30. Marda M, Pandia MP, Rath GP, et al. Post-operative pulmonary complications in patients undergoing transoral odontoidectomy and posterior fixation for craniovertebral junction anomalies. J Anaesthesiol Clin Pharmacol. 2013;29:200–4.
31. Flexman AM, Merriman B, Griesdale DE, et al. Infratentorial neurosurgery is an independent risk factor for respiratory failure and death in patients undergoing intracranial tumor resection. J Neurosurg Anesthesiol. 2014;26:198–204.

Available online at www.medicinescience.org

ORIGINAL ARTICLE

Medicine Science International Medical Journal

Medicine Science 2021;10(1):196-201

P16 staining patterns and their relationships with clinical parameters in cases of cervical intraepithelial neoplasia

Muruvvet Akcay Celik[1], Havva Erdem[1], Soner Cankaya[2], Yeliz Kasko Arici[3]

[1]Ordu University, Faculty of Medicine, Department of Pathology, Ordu, Turkey
[2]Ondokuz Mayis University, Faculty of Sport Sciences, Department of Sports Management, Samsun, Turkey
[3]Ordu University, Faculty of Medicine, Department of Biostatistics and Medical Informatics, Ordu, Turkey

Received 22 December 2020; Accepted 31 January 2021
Available online 22.02.2021 with doi: 10.5455/medscience.2020.12.259

Abstract

The aim of this study is to investigate the contribution of the p16 immunohistochemical marker in the cervical intraepithelial neoplasia (CIN) cases in the distinction between CIN1, CIN2, CIN3 and the relationship of CINs with age, localization. CIN1, CIN2, CIN3 preparations of 2015 in the pathology department were retrospectively analyzed. New sections of 3 µm thickness were obtained on polylysine slides from paraffin blocks of these tissues. Samples with immunohistochemical staining with p16 were evaluated under a light microscope.p16 expression was semiquantitatively assessed according to staining intensity with 4 staining levels as score 0,1,2,3. As a result of the Kruskal-Wallis test, a significant difference was found between the scores in the CIN groups (p <0,001). As a result of the multiple comparison test, p16 scores of patients in the CIN2 and CIN3 group were found to be significantly higher than in the CIN1 group (p <0.001). While the mean age of patients in the CIN3 group was significantly higher than those in the CIN2 group (p <0.05), it was not different from the patients in the CIN1 group (p> 0.05). The variations between CIN groups and anatomical locations on the cervix were examined with Chi-square test. There was no change in the frequency distribution of CIN groups in the anatomical locations on the cervix (p> 0.05). In cervical intraepithelial neoplasms, p16 was found to show increased staining with the severity of the lesion. It was observed that p16 expression is important in CIN evaluation and reduces subjective evaluation.

Keywords: Cervical intraepithelial neoplasia, p16, cervical precancerous lesion

Introduction

Preinvasive cervical intraepithelial neoplasm (CIN) is the precursor of invasive cervical cancer [1]. World Health Organization (WHO) guidelines have adopted the use of the term squamous intraepithelial lesion (SIL) of the Bethesda System, used for screening and treatment of precancerous lesions [2]. In the latest classification system of the World Health Organization (WHO); SIL is divided into low grade squamous intraepithelial lesion (LSIL) and high grade squamous intraepithelial lesion (HSIL) [1]. While a low grade squamous intraepithelial lesion (LSIL) is an infectious lesion created by HPV, a high squamous intraepithelial lesion (HSIL) is a neoplasia that may contain CIN2 and CIN3 [3]. However, according to the degree of epithelial involvement, CINs are classified as CIN1 (mild), CIN2 (moderate), and CIN3 (severe) [4].

**Corresponding Author: Muruvvet Akcay Celik, Ordu University, Faculty of Medicine, Department of Pathology, Ordu, Turkey
E-mail: drmakcaycelik@gmail.com

In CIN1, undifferentiated cells are limited to the lower layer of the epithelium [4]. Maturation loss, cytological atypia, and mitosis are observed in the lower two-thirds of the epithelium in CIN2 and in the full layer of the epithelium in CIN3. CIN's progress to cancer is a dynamic process and represents a morphological continuity. CIN3 is the most advanced precancerous lesion [5]. CIN1 patients should be followed without treatment because most cases of CIN1 regress spontaneously and progress at a low rate [6,7].Excisional treatment or close observation approaches differ between clinics for CIN2 due to the high regression rate of CIN2 [8].CIN3 lesions are associated with a high risk of cervical cancer and these are typically treated with cervical excision or ablation. Excisional procedures can lead to negative obstetric outcomes for women who plan future childbearing [9,10]. In particular, the differential diagnosis of CIN1, CIN2 with immature squamous metaplasia, as well as the differential diagnosis of low grade lesions (CIN1) and high grade lesions (CIN2 and CIN3) can be difficult [4].

Despite well-defined criteria, histopathological diagnoses may show variations among pathologists [11].Cervical screening programs can also be used to detect cervical precancerous

lesions [12]. Cytology, histology, and colposcopy are important in detecting preinvasive cervical intraepithelial neoplasm lesions [13,14]. Early detection and treatment of cervical intraepithelial neoplasia (CIN) are beneficial in preventing cervical cancer [15,16].

Related research shows that the human papilloma virus (HPV) can greatly increase the incidence of cervical cancer [17]. When HPV continues to infect the cervical region and invade mucosal squamous epithelial cells, CIN1, CIN2, and CIN3 lesions gradually develop. When the basement membrane is invaded,it is transformed into invasive cervical cancer [18].

p16, a cyclin-dependent kinase inhibitor, is a cell cycle regulating protein. p16 is also known as p16INK4a [19,20]. Its function is to regulate cell proliferation in the G1-S phase and p16 negatively affects cell proliferation in a mutual relationship with another tumor suppressor protein, pRb. Over-expression of p16 can be found in cells with inactive pRb commonly found in HPV infection [21].

There is no expression of p16 in the normal cervical squamous epithelium [22] or it is rarely observed as focal positive [23]. Overexpression of protein p16INK4a encoded by the tumor suppressor gene INK4a is a feature of dysplastic and neoplastic changes of the cervical epithelium. The degree of staining of P16INK4a-positive samples increases according to the order of CIN1- CIN2- CIN3- invasive carcinoma [1,24].p16-positive immunohistochemical reactivity is widely used as a biomarker to identify HPV in cervical squamous neoplasms [25].However, CIN1 and CIN2/3 sometimes show similar p16 expression, and p16 can also be found in inflammatory cervical lesions [19,20].

Personal experience is very important in the diagnosis of CIN. Histomorphological examination of Hematoxylin&Eosin (H&E) stained preparations or evaluation with immunohistochemical findings are in question [3,12].

Grading of cervical intraepithelial neoplasia (CIN) with p16 immunoscore system is so useful in reducing variations among pathologists for CIN1,2,3 differentiation in current CIN grading. Accurate colposcopy and histological evaluation of cervical precursor lesions are important to determine clinical management [5].

In our study, it was aimed to emphasize the importance of p16 in the classification of CIN, to reveal its usefulness in planning treatment, and also to examine the relationship between age and localization in CIN.

Materials and Methods

Before beginning the study, permission was granted by the Clinical Research Ethics Committee dated 23/05/2016 and numbered 2016/48.

This study used 80 preparations with CIN diagnosis in 2015 in the Training and Research Hospital Pathology Department and 41 CIN1, 16 CIN2, 23 CIN3 cases were detected.

Preparations were removed from the archive and reevaluated in line with the study aims. New sections with 3µm thickness were obtained on polylysine slides from paraffin blocks of the collected CIN cases.

Immunohistochemical staining was performed with Leica Bond automatic tissue staining device with p16 antibody (Anti-p16-rabbit clonal antibody, R19-D, (1: 100) DB BIOTECH). Stained samples were assessed with a light microscope (BX51, Olympus, Tokyo, Japan).

H&E stained preparations were examined by light microscopy and the areas with the most dysplastic features of the epithelium were selected and CIN areas were evaluated with p16 especially in those regions.

p16 immunoreactivity was evaluated positively when both nuclear and cytoplasmic diffuse staining were seen in basal or parabasal cells. [26].

p16 staining was rated as 4 scores; score 0 (no staining), score 1 (seldom staining of singly scattered cells), score 2 (patchy but strong staining, usually not continuous from basement membrane), and score 3 (strong and diffuse staining, often continuous staining from the basement membrane and extending upward in proportion to lesion grade) [27].

In our study, sites, where lesions were detected on the cervix of each patient after conization or biopsy were determined and then the cervix was divided into anatomical location

The cervix was grouped as upper quadrant (from 10 to 3 o'clock), lower quadrant (from 4 to 9 o'clock), upper + lower quadrant, unknown localization, ECC (endocervical curettage).

Statistical Analysis

Normal distribution control of data with Kolmogorov-Smirnov test, homogeneity control of group variances with Levene's test were done. Groups for the variables providing assumptions were compared with the one-way ANOVA following Tukey's test. The groups that did not provide assumptions were compared with the Kruskal-Wallis test following Dunn-Bonferroni test.

The relationship between categorical variables was examined with Chi-square test.All calculations were made with SPSS v26 statistical software.

Results

A total of 80 cases were included in the study. The average age of patients is 45.24 ± 9.61 and their ages vary between 29-66. According to One-way ANOVA, the mean age of the patients varied according to the CIN groups (Table 1).While the average age of patients in the CIN3 group was significantly higher than those in the CIN2 group ($p < 0.05$), it was not different from patients in the CIN 1 group ($p > 0.05$).At the same time, there was no difference in the mean age of patients in the CIN1 group and in the CIN2 group ($p > 0.05$) (Figure1-3).

Frequency distributions of CIN groups according to scoring are given in Table 2.Chi-square test scores were observed to vary according to CIN groups ($p < 0.001$).While the percentage of CIN1 group with p16 scores of 0 was higher (41.5%), CIN2 (43.8%) and CIN3 (39.1%) groups had a higher percentage of p16 scores of 3(Figure 4-6).

Table 1. Age distribution and comparison results of CIN groups

	n	Mean	SD	Min.	Max.	P
CIN1	41	44.927[ab]	9.501	31	66	
CIN2	16	40.533[b]	9.92	28	61	0.029*
CIN3	23	48.870[a]	8.46	32	63	

*:<0.05, Means that do not share a letter are significantly different (p<0.05)
CIN: cervical intraepithelial neoplasia

Table 2. Comparison results of CIN groups with p16 staining scores

		CIN1	CIN2	CIN3	Total	P
p16 scoring	0	17 (41.5%)	1 (6.3%)	3 (13.0%)	21 (26.3%)	<0.001
	1	13 (31.7%)	3 (18.8%)	3 (13.0%)	19 (23.8%)	
	2	10 (24.4%)	5 (31.3%)	8 (34.8%)	23 (28.7%)	
	3	1 (2.4%)	7 (43.8%)	9 (39.1%)	17 (21.3%)	
Total		41 (100.0%)	16 (100.0%)	23 (100.0%)	80 (100.0%)	

***:<0.001
CIN: cervical intraepithelial neoplasia

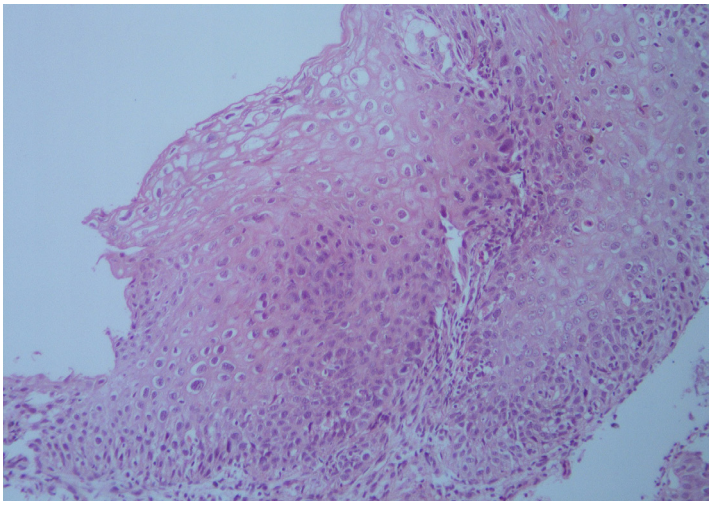


Figure 1. CIN1 lesion (H&Ex200)

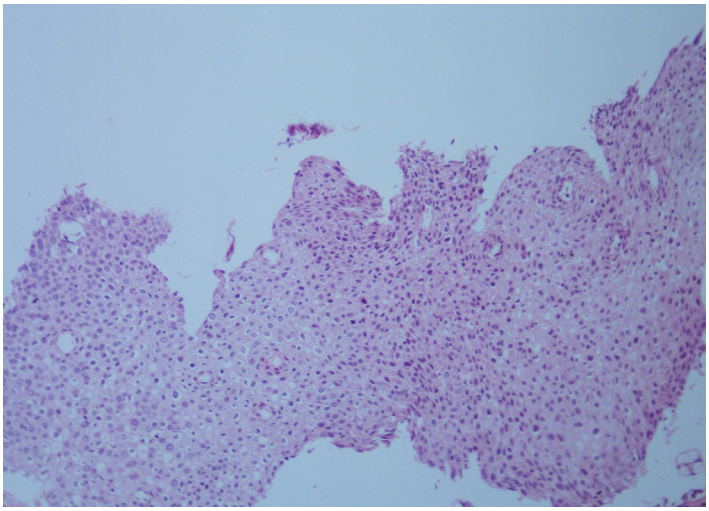


Figure 2. CIN2 lesion (H&Ex200)

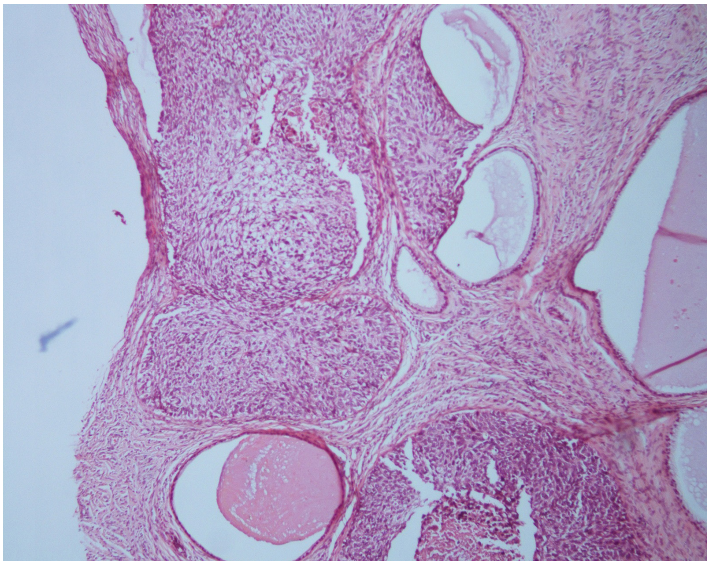


Figure 3. CIN3 lesion (H&Ex200)

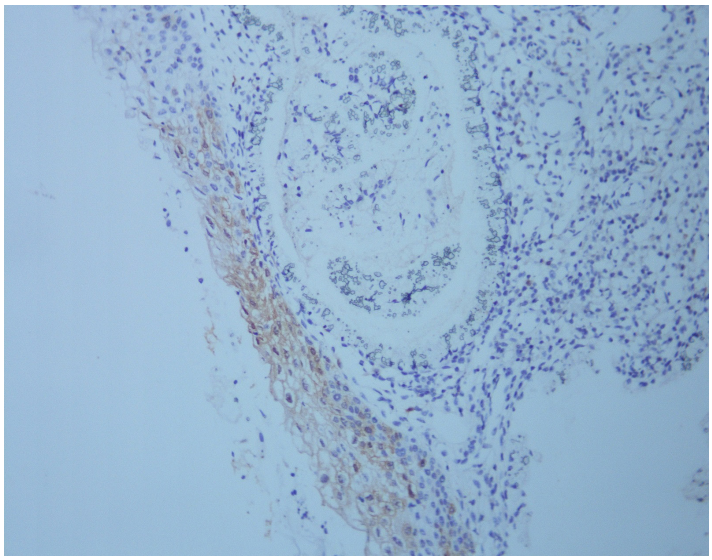


Figure 4. Immunohistochemical staining with p16 in CIN1lesion, mild cytoplasmic staining is seen (p16x100)

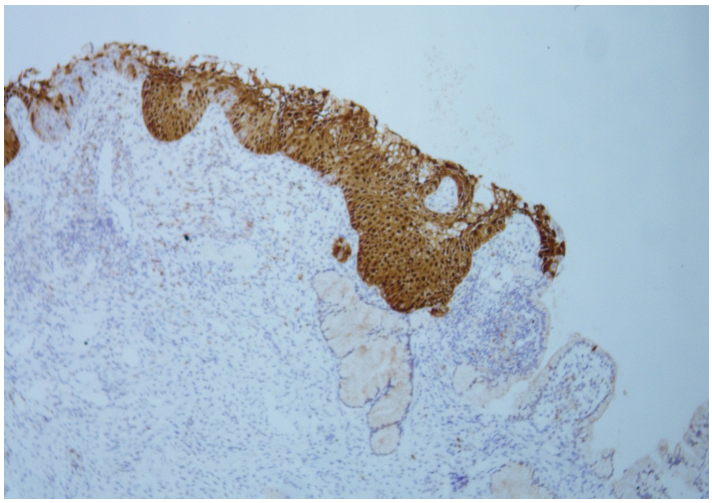


Figure 5. Immunohistochemical staining with p16 in CIN2 lesion, moderate cytoplasmic and nuclear stainings are seen (p16x100)

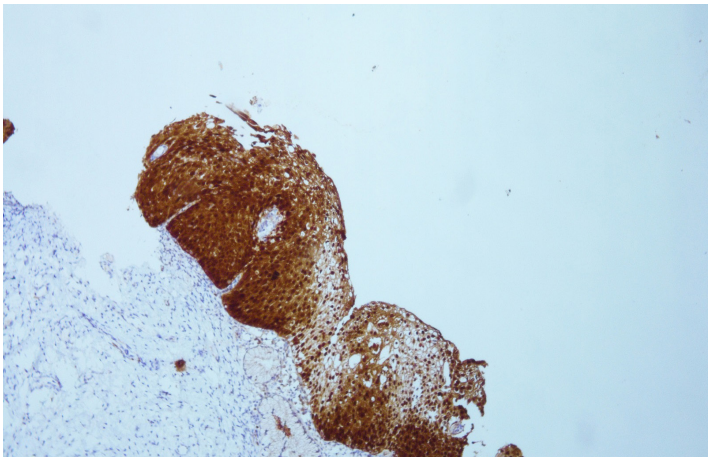


Figure 6. Immunohistochemical staining with p16 in CIN3 lesion, severe cytoplasmic and nuclear stainings are seen (p16x100)

As a result of the Kruskal-Wallis test, a significant difference was found between the scores in the CIN groups (p <0.001, Table 3). As a result of the multiple comparison test, the scores of patients in the CIN2 and CIN3 group were significantly higher than those in the CIN1 group (p <0.001).

The variation between CIN groups and anatomical locations on the cervix were examined with Chi-square test. There was no change in the frequency distribution of CIN groups in the anatomical locations on the cervix (p> 0.05, Table 4).

Table 3. Comparison results of CIN groups with p16 staining scores

		n	Mean	SD	Min.	Max.	Mean (Rank)	p
p16 scoring	CIN1	41	1.878	0.872	1	4	28.83[b]	<0.001
	CIN2	16	3.125	0.957	1	4	54.25[a]	
	CIN3	23	3	1.044	1	4	51.74[a]	

Means that do not share a letter are significantly different (p<0.001)
CIN: cervical intraepithelial neoplasia

Table 4. Frequency distributions of CIN groups in the anatomical locations on the cervix

	Anatomical Locations On The Cervix						
	Lower quadrant	Upper quadrant	Lower- upper quadrant	Unknown	ECC	Total	p
CIN1	8(53.3%)	8(50.0%)	9(60.0%)	11(44.0%)	5(55.6%)	41(51.2%)	0.729
CIN2	5(33.3%)	2(12.5%)	2(13.3%)	6(24.0%)	1(11.1%)	16(20.0%)	
CIN3	2(13.3%)	6(37.5%)	4(26.7%)	8(32.0%)	3(33.3%)	23(28.7%)	
Total	15(100.0%)	16(100.0%)	15(100.0%)	25(100.0%)	9(100.0%)	80(100.0%)	

(p> 0.05) ECC: endocervical curettage, CIN: cervical intraepithelial neoplasia

Discussion

Preinvasive cervical intraepithelial neoplasm (CIN) is the precursor of invasive cervical cancer.SIL is divided into the two-tiered degreeas low grade squamous intraepithelial lesion (LSIL) and high grade squamous intraepithelial lesion (HSIL) in the latest classification system of the World Health Organization (WHO)[3]. Cervical SIL's generally affect women of reproductive age [28,29]. According to Heatley et al., correct colposcopy and histological evaluation of cervical precursor lesions are important to determine clinical management [5].

Since approximately two-thirds of the CIN1 lesion is expected to regress naturally, these lesions are usually followed up by cytology and colposcopy and it is not treated by excision or ablation methods (such as conization) [30,31]. According to Baak et al., excisional treatment or close surveillance approaches may differ between clinics due to the regression rate of CIN2 [8].

According to Vink et al, CIN2 and CIN3 lesions are at a higher risk of progression to cervical cancer if left untreated. Therefore, these lesions are usually treated with conization [31].So the treatment approach differs between low and high grade SIL.

The cytological approach also has some advantages, as long as it allows the patient to avoid surgical procedures [32]. Recently, immunochemical staining for p16INK4a in cytological smears has also been proposed [33].Therefore it is important to classify their malignant potential to accurately diagnose precancerous lesions, to apply the correct surgical approach, and to avoid unnecessary surgical treatment that may increase the risk of miscarriage or premature birth [34].

Kanjana et al emphasized the importance of performing the immunohistochemical evaluation with p16 in addition to H&E staining in the diagnosis of SIL [35].

In our study, the mean age of the patients in the CIN3 group was significantly higher than the patients in the CIN2 group. Since the progress from CIN1 to CIN3 is a dynamic process, this finding was considered to be compatible with the findings of the literature [5].

In our study, p16 scores of patients in the CIN2 and CIN3 group were found to be significantly higher than in the CIN1

group (p <0.001).The progression of CIN to cancer represents a morphological continuity [5]. In the progression from CIN1 to CIN3, since CIN3 is the most advanced precancerous lesion, high p16 scores in CIN2 and CIN3 have been interpreted to support the literature findings [1,24].

Despite well-defined criteria, histopathological diagnoses may show variations among pathologists [11].The immunohistochemical staining of P16INK4a allows precise identification of even small CIN or cervical cancer lesions in biopsy sections and reduces the inter-observer variation in histopathological interpretation of cervical biopsy specimens [36].

Most cancers of the cervix are squamous cell carcinoma originating from the transformation zone. As age increases, transformation zone sampling becomes less accessible [37].

Foote et al. found that biopsies from the anterior and posterior cervix are more likely to have more CIN grade 3 lesions than biopsies taken from lateral angles[38]. According to He et al, the distribution of CIN lesions was not randomly observed across the cervix. The most common CIN location was at 12 o'clock and the least common CIN location was at 2 o'clock [39].

According to Zhao et al, 4 o'clock and 7 o'clock sites should be preferred especially during biopsy[40]. However, to date, there is no clear consensus on the importance of the distribution pattern of the CIN throughout the cervix.

In our study, no significant result was found in cervical intraepithelial neoplasia cases in terms of cervical distribution. This was thought to be related to the small sample size.

Conclusion

Overexpression of p16 protein is considered one of the important prognostic factors for CIN.Grading of cervical intraepithelial neoplasia (CIN) with the p16 immunoscore system provides convenience for pathologists.Numerous prospective studies with p16 immune staining have shown a good agreement between p16-positive staining and an increased degree of the intraepithelial lesion.However, p16 staining is not sufficient in some cases to provide an accurate diagnosis and accurate differentiation.

It should be noted that CIN1 and CIN2 / 3 can sometimes show similar p16 expression and also p16 may be present in inflammatory cervical lesions.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
All authors declare no financial support.

Ethical approval
Before beginning the study, permission was granted by the Clinical Research Ethics Committee dated 23/05/2016 and numbered 2016/48

References

1. Xing Y, Wang C, Wu J. Expression of geminin, p16, and Ki67 in cervical intraepithelial neoplasm and normal tissues.Medicine (Baltimore). 2017;96:7302.
2. Nayar R, Wibur DC. The Bethesda System for reporting cervical cytology: a historical perspective. Acta Cytol. 2017;61:359-72.
3. Darragh TM, Colgan TJ, Cox JT, et al. The lower anogenital squamous terminology standardization project for HPV-associated lesions: background and consensus recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology. Arch Pathol Lab Med. 2012;136:1266-97.
4. Martin CM, O'Leary JJ, Phil D. Histology of cervical intraepithelial neoplasia and the role of biomarkers. Best Pract Res Clin Obstet gynaecol. 2011;25:605–15.
5. Heatley MK.How should we grade CIN? Histopathology. 2002;40:377–80.
6. Alshenawy HA. Evaluation of p16, human papillomavirus capsid protein L1 and Ki-67 in cervical intraepithelial lesions: potential utility in diagnosis and prognosis. Pathol Res Pract. 2004;210:916–21.
7. Rouzier R. Management of CIN1. J Gynecol Obstet Biol R. 2008;1:114–20.
8. Baak JP, Kruse AJ, Robboy SJ, et al. Dynamic behavioural interpretation of cervical intraepithelial neoplasia with molecular biomarkers. J Clin Pathol. 2006;59:1017–28.
9. Prendiville W, Sankaranarayanan R. Colposcopy and treatment of cervical precancer. Lyon: IARC Technical Publication. 2017;131:28-32.
10. Rosa M, Mohammadi A. Cervical cytology and human papillomavirus testing in adolescent women: implications in management of a positive HPV test. Patholog Res Int. 2014;2014:165690.
11. Keating JT, Cviko A, Riethdorf S, et al. Ki-67, cyclin E, and p16INK4 are complimentary surrogate biomarkers for humanpapillomavirus-related cervical neoplasia. Am J Surg Pathol. 2001;25:884–91.
12. Herrington CS. The terminology of pre-invasive cervical lesions in the UK cervical screening programme. Cytopathology. 2015;26:346–50.
13. Vesco KK, Whitlock EP, Eder M, et al. Risk factors and other epidemiological considerations for cervical cancer screening: a narrative review for the US. Preventive Services Task Force. Ann Intern Med. 2011;155:698-705.
14. Mishra GA, Pimple SA, Shastri SS. An overview of prevention and early detection of cervical cancer. Indian J Med Paediatr Oncol. 2011;32:125-32.
15. Liverani CA, Dig J, Clemente N, et al.Length but not transverse diameter of the excision specimen for high-grade cervical intraepithelial neoplasia (CIN 2–3) is a predictor of pregnancy outcome. Eur J Cancer Prev. 2016;25:416-22.
16. Hawkes AP, Kronenberger CB, Mackenzie TD, et al. Cervical cancer screening: American college of preventive medicine practice policy statement. Am J Prev Med. 2016;12:342-4.
17. Liu Y, Lu Z, Xu R, et al. Comprehensive mapping of the human papilloma virus (HPV) DNA integration sites in cervical carcinomas by HPV capture technology. Oncotarget. CV. 2016;7:5852-64.
18. Chen Z, Wang Y, Mi X, et al. Application of van-clear and xylenein the detection of cervical hTERC gene by fluorescence in situ hybridization. Zhong Nan Da Xue Xue Bao Yi Xue Ban. 2016;41:367-73.
19. Nogueira MC, Guedes Neto Ede P, Rosa MW et al. Immunohistochemical expression of p16 and p53 in vulvar intraepithelial neoplasia and squamous cell carcinoma of the vulva. Pathol Oncol Res. 2006;12:153–7.
20. Léonard B, Kridelka F, Delbecque K, et al. A clinical and pathological overview of vulvar condyloma acuminatum, intraepithelial neoplasia, and squamous cell carcinoma. Biomed Res Int. 2014;2014:480573.
21. Lambert AF, Anshau F, Schmitt. p16 expression in cervical premalignant and malignant lesions. Exp Mol Pathol. 2006;80:192-6.
22. Klaes R, Friedrich T, Spitkovsky D, et al. Over expression of p16INK4a as a specific marker for dysplastic and neoplastic epithelial cells of the cervix uteri. Int J Cancer. 2001;92:276–84.
23. Kalof AN, Evans MF, Simmons-Arnold L, et al. p16 INK4A immunoexpression and HPV in situ hybridization signal patterns: potential markers of high-grade cervical intraepithelial neoplasia. Am J Surg Pathol. 2005;29:674–9.
24. Volgareva G, Zavalishina L, Andreeva Y, et al. Protein p16 as a marker of dysplastic and neoplastic alterations in cervical epithelial cells. BMC Cancer. 2004;4:58.
25. Lewis JS Jr. p16 Immunohisto chemistry as a standalone test for risk stratification in oropharyngeal squamous cell carcinoma. Head Neck Pathol.

2012;6:75–82.

26. Lorenzato M, Caudroy S, Bronner C, et al. Cell cycle and/or proliferation markers: what is the best method to discriminate cervical high-grade lesions? Hum Pathol. 2005;36:1101–7.

27. U Sarma, Ira B, Alakananda D, et al. p16INK4a Expression in Cervical Lesions Correlates with Histologic Grading- a Tertiary Level Medical Facility Based Retrospective Study. Asian Pac J Cancer Prev. 2017;18:2643–8.

28. Fitzmaurice C, Dicker D, Pain A, et al. The global burden of cancer 2013. JAMA Oncol. 2015;1:505-27.

29. Mezei AK, Armstrong HL, Pedersen HN, et al. Cost-effectiveness of cervical cancer screening methods in low- and middle-income countries: a Systematic review. Int J Cancer. 2017;141:437-46.

30. Östör AG. Natural history of cervical intraepithelial neoplasia: a critical review. Int J Gynecol Pathol. 1993;12:186-92.

31. Vink MA, Bogaards JA, van Kemenade FJ, et al. Clinical progression of highgrade cervical intraepithelial neoplasia: estimating the time to preclinical cervical cancer from doubly censored national registry data. Am J Epidemiol. 2013;178:1161-9.

32. McCredie MR, Sharples KJ, Paul C, et al. Natural history of cervical neoplasia and risk of invasive cancer in women with cervical intraepithelial neoplasia 3: a retrospective cohort study. Lancet Oncol. 2008;9:425-34.

33. Negri G, Egarter-Vigl E, Kasal A, et al. P16INK4a is a useful marker for the diagnosis of adenocarcinoma of the cervix uteri and its precursors. Am J Surg Pathol. 2003;27:187–93.

34. Kurman RJ, Carcangiu ML, Herrington CS, et al. WHO Classification of Tumours of Female Reproductive Organs. Geneva, Switzerland: World Health Organization; 2014.

35. Kanjana K, Jakkapan K, Siriwan T, et al. Expression of the p16 and Ki67 in Cervical Squamous Intraepithelial Lesions and Cancer. Asian Pac J Cancer Prev.2016;17:3201-6.

36. Doeberitz MVK. New molecular tools for efficient screening of cervical cancer. Dis Markers. 2001;17:123-8.

37. Gondos B, Marshall D and Ostergard. Endocervical cells in cervical smears. Am. J. Obstet. Gynecol.1972;15:833–4.

38. Foote FW Jr, Stewart FW. The anatomical distribution of intraepithelial epidermoid carcinomas of the cervix. Cancer. 1948;1:431–40.

39. He G, Li H, Lin H, et al. Topographical distribution pattern of cervical intraepithelial neoplasia across the cervix. J Int Med Res. 2012;40:1897–903.

40. Zhao Y, Chang IJ, Zhao F, et al. Distribution of cervical intraepithelial neoplasia on the cervix in Chinese women: pooled analysis of 19 population based screening studies. BMC Cancer. 2015;15:485.

Available online at www.medicinescience.org

ORIGINAL ARTICLE

Medicine Science International Medical Journal

Medicine Science 2021;10(1):202-6

Evaluation of the patient with lymphadenopathy: Is it always easy to reach the correct diagnosis?

Adem Kose, Ahmet Dogan, Yasar Bayindir, Yasemin Ersoy, Mehmet Ozden, Funda Memisoglu, Sibel Altunisik Toplu, Yakup Gezer

Department of Infectious Diseases and Clinical Microbiology, Faculty of Medicine, Inonu University, Malatya, Turkey

Received 03 February 2021; Accepted 21 February 2021
Available online 22.12.2021 with doi: 10.5455/medscience.2021.02.031

Abstract

Lymphadenopathy (LAP) is a common clinical problem in adult patients and should be thoroughly evaluated in a tertiary hospital to investigate its reasons. In this study, we aimed to present the demographic characteristics, etiology, diagnosis and follow-up results of the patients who applied with LAP symptoms and findings. This study was designed to include adult patients with neck, armpit, or groin swelling accompanied by symptoms, such as fever, night sweats, weight loss, cough and sputum between January 2010 and August 2017, retrospectively. Patients' data were collected from electronic files. Patients were diagnosed using radiological, histopathological, bacteriological, serological and other microbiological methods. Two hundred-thirty patients were included in this study. The mean age was 43.12±17.06 SD in males and 45.74±16.64 in females. On admission, the most common symptoms were night sweats (31%), fever (23%), weight loss (17%) and cough and/or sputum (13%) in order of frequency. However, 16% of the patients were asymptomatic. In this study, 157 (68.26%) patients were diagnosed. Tuberculosis (n=76; 33%), malignancies (n=28, 12.1%) and tularemia (N=14; 6.1%) were the most common diseases causing LAP that was most commonly located in the bilateral cervical chain. Lymphadenopathy should be evaluated comprehensively concerning diagnosing or ruling out many diseases that must be treated necessarily. Knowledge and awareness of the diseases as a cause of LAP may contribute to the early and correct diagnosis. Therefore, undiagnosed patients should be followed, and the institutions should develop policies for this purpose, such as telemedicine applications.

Keywords: Lymphadenopathy in adults, infectious diseases, diagnosis

Introduction

Lymphadenopathy (LAP) is defined as lymph nodes becoming abnormal in number, size, and consistency; and their normal size is less than 1 cm, but they have different sizes at different ages [1]. In primary care practice, the annual incidence of unexplained LAP is 0.6%, only 1.1% of these cases are related to malignancy, but this percentage increases with advancing age [2]. LAP occurs in two patterns: generalized and localized. Localized adenopathy occurs in contiguous groupings of lymph nodes. Generalized LAP entails LAP in two or more non-contiguous locations. It is generally recognized that the majority of LAP, both localized and generalized, is of benign and self-limited etiology [3]. The most common causes in the etiology of lymphadenopathies are malignancies, infections, autoimmune diseases, iatrogenic reasons and various rare and unusual diseases [4]. Seventy-five percent of all lymphadenopathies are localized and more than 50% of them are located in the head and neck region. It is usually caused by a specific pathology located in the lymphatic drainage area and can be detected without an additional evaluation; the remaining 25% is generalized and may often be a sign of an underlying systemic disease [5].

The most critical step in evaluating lymphadenopathies is a careful history and a focused physical examination, the content of which should be determined according to the patient's clinic. The concomitant symptoms and the patient's epidemiology provide further clues to the diagnosis. A more comprehensive investigation of fever, chills, night sweats, weight loss and accompanying

***Corresponding Author:** Adem Kose, Department of Infectious Diseases and Clinical Microbiology, Faculty of Medicine, Inonu University, Malatya, Turkey
E-mail: adem.kose@inonu.edu.tr

symptoms may contribute to the exhibition of the etiology. In addition, demographic characteristics, such as the patient's age, gender, exposure to infectious disease, toxins, drugs and habits, may also contribute more [6]. Since the cause is apparent in most cases (such as infection), no further studies of etiology are needed in primary evaluation. In cases where the cause cannot be explained, laboratory tests, imaging studies and tissue biopsy are recommended. Imaging can determine the size and distribution of the lymph node more accurately than a physical exam. Ultrasound is a non-invasive method to evaluate lymph nodes in superficial areas, such as the neck. On ultrasound (US) imaging, the cortex is usually hypoechoic or even imperceptible, and the medulla is hyperechoic. Computed tomography (CT) is useful for detecting LAP in the thorax or abdominopelvic space. Tissue diagnosis by fine-needle aspiration biopsy or excisional biopsy is the gold standard assessment for LAP [7]. The underlying etiology in acute, soft and painful neck masses are usually localized or systemic viral and bacterial infections, subacute malignancies and chronic thyroid pathologies [8]. Systemic lymph nodes are more common in restricted viral infections. In lymphomas, the lymph nodes are usually elastic, conglomerate and painless. Metastatic lymph nodes are often painless, rigid and attached to the surrounding tissue [9]. Fine needle aspiration biopsy is useful to investigate benign/malignant differentiation in the etiology of LAP, but the state of inadequacy for diagnosis is often encountered. In addition, an excisional biopsy is required to diagnose lymphoma. Excisional biopsy is a diagnostic method that can be safely applied with minimal morbidity and mortality. An incisional biopsy is not recommended because it may lead to the formation of fistulas, especially in cases of tuberculosis (TB) [10]. Pathophysiology, treatment and prognosis vary significantly from patient to patient, but it is necessary to reach the correct diagnosis. In addition, delays in reaching the correct diagnosis can harm the patient. Moreover, impatience may be observed in patients during the prolonged diagnosis process.

In the current literature, studies on the clinical and etiological spectrum of lymphadenopathies are limited, especially outpatients in developing countries, which has remained under-researched. Therefore, in this study, we aimed to present the demographic characteristics, etiology, diagnosis and follow-up results of the patients who applied with LAP symptoms and findings.

Materials and methods

Study design and inclusion criteria

Between 01 January 2010 and 30 August 2017, 230 adult patients with having swollen in the regions where neck, axilla or inguinal and accompanied by any one of the symptoms, such as fever, night sweats, weight loss, cough and sputum, were included in our study. Patients were diagnosed using radiological, histopathological, bacteriological, serological and other microbiological methods.

Exclusion criteria

Only patients with one application and/or without regular clinical follow-up and pediatric patients were excluded from our study.

Ethical approval

Ethical approval was obtained from the Inonu University Non-Interventional Ethics Committee (Approval No: 2018/15-26).

Invasive procedures

According to the outcomes of the physical examination and radiological studies, the lesions with a diameter of >1 cm were performed excisional or incisional biopsy for diagnostic purposes by otolaryngology or general surgery.

Statistical analysis

The demographic data and follow-up results of the diagnosed patients were retrospectively scanned from the patient registration system and all the data were recorded in the patient record forms. IBM SPSS Statistics 17.0 software program was used for all data analyses.

Results

Two hundred-thirty patients were included in this study. Sixty-six (28.7%) of our patients were male and 164 (71.3%) were female. The mean age was 43.12±17.06 SD in males and 45.74±16.64 in females. One hundred fifty-two (66%) patients lived in the city center, 58 (25%) in the district and nine (4%) in the rural area. On the first admission, the most common symptoms were night sweats (31%), fever (23%), weight loss (17%), cough and/or sputum (13%), in order of frequency. However, 16% of the patients were asymptomatic. One or more members of the relatives of 32 patients and 13 cases had previous TB diagnosis. 15% cases had a history of consuming unpasteurized milk and milk products and 5% cases had unhygienic water consumption. LAP was observed in the regions of bilateral cervical, submandibular, submental and parotid gland (78%), axillary zone (7.4%), inguinal area (7.4%), supraclavicular region (3%), preauricular region (2.2%) and abdominal region (1.3%). Skin fistula was observed in 3% of the patients with LAP in the neck. Five patients had LAP in both the neck and inguinal regions.

Biopsy was performed in 145 (63%) of the cases. In this study, 157 (68.26%) patients were diagnosed, and an exact diagnosis could not be made in 73 (31.74%) cases. Histopathological examination was made in only 16 of 73 undiagnosed patients. The three most common diagnoses were TB (33%), malignancies (12.1%) and tularemia (6.1%). Of these, five (8.7%) patients had their clinical findings who were healed with antimicrobial therapy, which was initiated empirically for 14 days, and five (8.7%) patients have been still being followed up in the Department of Hematology. The diagnostic results of all patients are summarized in Table 1. Lymphadenopathies were the most commonly detected in the bilateral cervical chain, submandibular region, submental region and inside the parotid gland. Localizations and frequency of LAP are indicated in Table 2. Different antimicrobial treatments were applied to 14 patients diagnosed with tularemia for varying periods and MAT titers were monitored.

Table 1. Diagnostic results of all patients

Biopsy performed	Number (n)	Rate (%)	Biopsy unperformed	Number (n)
Tuberculous lymphadenitis	66	28.7	Undiagnosed	57
Malignancy / metastasis	27	11.7	Tuberculous lymphadenitis	10
Undiagnosed	16	6.95	Suppurative lymphadenitis	7
Tularemia	8	3.47	Tularemia	6
Suppurative lymphadenitis	7	3.04	Multiple Myeloma	1
Toxoplasmosis	6	2.6	Melkerson Rosenthal Syndrome	1
Chronic inflammation	5	2.17	HIV infection	1
Sarcoidosis	2	0.8	Toxoplasmosis	1
HSV type-1 infection	1	0.4	Rosai Dorfman disease	1
Reactive lymphadenitis	1	0.4		
Fibroadipose tissue	1	0.4		
Spirochete infection	1	0.4		
Lymphocytic sialadenitis	1	0.4		
Castleman Disease	1	0.4		
Granulomatous mastitis	1	0.4		
Pleomorphic adenoma	1	0.4		
Total	145	63	Total	85

Table 2. Lymphadenopathy localization and frequency

Localisation	Number (n)	Ratio (%)
Bilateral cervical, submandibular, submental and parotid gland	181	78.7
Axillary zone	17	7.4
Inguinal area	17	7.4
Supraclavicular region	7	3
Preauricular area	5	2.2
Intraabdominal area	3	1.3
TOTAL	230	100

Discussion

Lymph node enlargement should be evaluated comprehensively in terms of diagnosing or ruling out many diseases that must be treated necessarily. However, especially in first and second-line health services, LAPs are either overlooked or not given the necessary attention [11]. Awareness and knowledge of the etiologies causing the disease in patients with LAP are the main keys in the diagnosis and management of these patients. However, the diagnostic procedures can be time-consuming in patients who have LAP with unknown etiology. Following carefully of these patients may contribute to correct diagnosis in the tertiary hospitals providing health care to the undiagnosed cases [12]. In the current study, we aimed to retrospectively analyze the patients admitted to our center with LAP that had not been diagnosed in other centers.

In a retrospective study evaluating 925 patients who underwent lymph node biopsies from 1973 to 1977, 60% of the lymph nodes had benign lesions, 28% had carcinomas and 12% had lymphomas. For peripheral nodal biopsies (cervical, axillary, inguinal), 56% were related to benign lesions, 29% to carcinomas, and 15% to lymphomas [13]. In a study conducted by Gul et al., which included the five-year follow-up of 67 patients who applied for peripheral LAP and underwent excisional biopsy, the most common causes

were malignancies (n = 23; 34.3%) and TB (n = 20; 29.9%) [10]. In our study, we found that the three most common causes of lymphadenopathy were TB (33%), malignancies (12.1%) and tularemia (6.1%).

Tuberculous lymphadenitis is the most common form of extrapulmonary TB. In the diagnosis, demographic features, radiological imaging of LAP, physical examination findings, purified protein derivative (PPD) skin test, acid-resistant bacilli (ARB), molecular tests, TB culture and histopathological examination are the components that should be evaluated together for correct diagnosis [14]. The definite diagnosis is made with culture positivity, but culture negativity does not rule out the diagnosis. Because the agent can be isolated only in 10-69% of the cases, initiating treatment late is an important disadvantage because the culture result is expected for 6-8 weeks. Ziehl-Neelsen staining and microscopic evaluation is an easy, cheap and fast method, and it is a diagnostic method with 46-78% sensitivity and 100% specificity [15]. One of the most important diagnostic methods is the histopathological method characterized by Langerhans cells, caseous necrosis, granulomatous inflammation or calcifications [16]. In our study, among the patients diagnosed with tuberculous lymphadenitis, ARB was detected in 13 cases, polymerase chain reaction (PCR) positivity in 29 cases, and culture positivity in 40 cases. In twelve cases that received antituberculosis treatment, treatment was initiated according to the history, biopsy, PPD and Interferon Gamma Release Assay (IGRA). It was observed that culture, PCR and ARB tests were negative in these patients. Only nine of our cases had caseous necrosis. Extrapulmonary TB mostly involves the lymph nodes in the cervical chain with diffuse, multiple, fixed and painless character [17]. In our study, LAP was most often found in bilateral cervical, submandibular, submental and parotid gland in accordance with the literature.

In adult patients, LAP may develop largely due to metastatic carcinomas [18]. Biopsy of peripheral lymph nodes (cervical, supraclavicular, axillary) in the upper part of the body is more preferred, while biopsy of lymph nodes in the lower parts of the body (popliteal, inguinal, femoral) is usually less useful [19]. Ultrasonography, fine needle aspiration, CT and MRI are the most useful methods for diagnosis. In USG, round-shaped, homogeneous structure, extracapsular involvement is significant concerning irregular limited, central necrosis and non-hilum lap malignancy, but a lymph node or bone marrow biopsy is needed for a definite diagnosis [20]. In the study conducted by Rahman et al. [16], including 191 cases, 11 cases (5.7%) had Hodgkin lymphoma, 22 cases (11.5%) non-Hodgkin lymphoma, and 24 cases (12.5%) metastatic neoplasms. In the study of Gul et al. [10] mentioned above, it was Non-Hodgkin lymphoma (n = 11; 16.4%), Hodgkin lymphoma (n = 7; 10.4%) and metastasis (n = 5; 7.5%). Saraswat et al. [21] reported a 63% specific diagnosis rate, excluding patients with known malignancies, systemic diseases, or abnormal chest radiographs. The most critical aspect in the clinical approach to adenopathy is determining which cases are associated with benign lesions and which are associated with malignant disorders. Then, it is important to distinguish carcinoma from lymphoma [22]. In our study, we achieved the rate of being able to make a definite diagnosis at the level of 68.26%, whether a biopsy is performed or not. We can say that the rate of undiagnosed patients is higher than previous similar studies, and this can be explained by that our number of patients is less. However, in the diagnostic process that requires time, our patients may prefer not to come or go to another clinic or hospital because of their outpatient follow-up due to their expectation of rapid diagnosis or their mild symptoms. In this study, we realized that these outpatients should be followed up until the correct diagnosis, even if they do not come to the clinic.

Especially in endemic regions, one of the important causes of LAP is tularemia, a zoonotic infection caused by Francisella tularensis [23]. Transmission to humans occurs through direct contact with infected animals, through vectors (ticks and mosquitoes), contaminated water and inhalation of infected aerosols. The findings showed that the most common symptoms and findings in cases were fever and lymphadenopathy, and the most frequent form of oropharyngeal tularemia was observed [24]. In a retrospective study conducted by Erdem et al. [25], including 1034 patients from 41 centers, 713 cases received monotherapy, 299 cases received combined therapy, 11 cases received sequential treatment, and 11 cases were lacking data. Recurrence was observed in our 12 cases who received monotherapy, 10 cases who received combined therapy and one patient who received consecutive treatment among patients who received treatment for at least two weeks or more. In our study, it was observed that 14 of 15 cases were administered treatment in our center, and a case was diagnosed and treated at an external center and applied to our center for control. One case presented with recurrence one year later despite receiving ciprofloxacin treatment for two weeks in an external center, and it was observed that this patient was administered combined doxycycline + ciprofloxacin therapy for three weeks. In our study, a diagnosis of tularemia was made in six cases that were not administered a biopsy and were examined serologically. The findings showed that tularemia treatment was administered to these patients for two or three weeks, as the micro-agglutination test (MAT) titer was reported as ≥1/160 in 11 of 68 patients who were suspected of tularemia with the history and physical examination findings and micro-agglutination test was studied. One case treated for tularemia was diagnosed in another center. In addition, serological data of two cases who received treatment could not be reached.

The most common causes of axillary LAP are carcinomas, lymphomas, benign reactive hyperplasia, tuberculosis, atypical mycobacterial infections, cat-scratch disease and granulomatous infections, such as HIV, syphilis, toxoplasmosis and hepatitis, non-infectious granulomatous diseases, such as sarcoidosis and autoimmune diseases, such as lupus, rheumatoid arthritis and scleroderma [26]. Infectious reasons were detected in all of our 17 cases who were admitted to our clinic with signs of axillary lymphadenopathy. In the etiology of lymphadenopathy, some diseases, such as Castleman's disease and Melkerssons-Rosenthal syndrome, which are rarely seen and not considered among preliminary diagnoses, should also be considered. Castleman's disease, also known as giant angiofolicular lymphoid hyperplasia, is a benign self-limiting and systemic disorder involving lymph nodes with unknown etiology. It can be clinically classified as localized (single center) or systemic (multicenter) [27]. Melkerssons-Rosenthal syndrome is a clinical entity identified by the presence of the triad of recurrent facial paralysis, recurrent often permanent (labial) oedema, and to a lesser extent, the placation of the tongue [28]. In our study, we identified a few cases that

were initially diagnosed with histopathological features but which we did not consider in pre-diagnosis. This situation shows how important histopathological diagnosis is in revealing the etiology of lymphadenopathies.

Conclusion

Lymphadenopathy is a clinical condition whose etiology must necessarily be investigated in adult patients; it is important to support histopathology along with a detailed history, a careful physical examination for its definite diagnosis. While the patients with LAP evaluate, endemic infectious diseases should be kept in mind, such as TB and tularemia, which may have recurrent characteristics. Finally, undiagnosed patients should be followed until the final diagnosis, and the institutions should develop policies for this purpose, such as telemedicine applications.

Acknowledgements
The authors warmly thank all laboratory staff working in Molecular Microbiology, Pathology, Biochemistry Departments and the hospital pharmacy responsible for helping us access to daily drug outputs of pharmacy.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
The financial support no have.

Ethical approval
This study was obtained from the Inonu University Non-Interventional Ethics Committee (Approval No: 2018/15-26).

References

1. Morland B. Lymphadenopathy. Arch Dis Child. 1995;73:476-9.
2. Fijten GH, Blijham GH. Unexplained lymphadenopathy in family practice. An evaluation of the probability of malignant causes and the effectiveness of physicians' workup. J Fam Pract. 1988;27:373-6.
3. Gaddey HL, Riegel AM. Unexplained Lymphadenopathy: Evaluation and Differential Diagnosis Am Fam Physician. 2016:1;94:896-903.
4. Habermann TM, Steensma DP. Lymphadenopathy. Mayo Clin Proc. 2000;75:723-32.
5. Viiala N, Gibson J [Internet]. An approach to the assessment of lymphadenopathy. [cited 2007 Jan 10]. Available from: http://www.medicalobserver.com.au/news/an-approachto-the-assessment-of-lymphadenopathy.
6. Bazemore AW, Smucker DR. Lymphadenopathy and malignancy. Am Fam Physician. 2002;66:2103-10.
7. Chau I, Kelleher MT, Cunningham D, et al. Rapid access multidisciplinary lymph node diagnostic clinic: analysis of 550 patients. Br J Cancer. 2003;88:354-61.
8. Haynes J, Arnold KR, Oskıns CA, et al. Evaluation of neck masses in adults. Am Fam Physician. 2015;91:698-706.
9. Richner S, Laifer G. Peripheral lymphadenopathy in immunocompetent adults. Swiss Med Wkly 2010;140:98-104.
10. Gul M, Aliosmanoglu I, Turkoglu A, et al. Erişkin çağı periferik lenfadenopatileri. Dicle Tıp Dergisi 2013;40:245-9.
11. Bosch X, Coloma E, Donate C, et al. Evaluation of unexplained peripheral lymphadenopathy and suspected malignancy using a distinct quick diagnostic delivery model: prospective study of 372 patients. Medicine (Baltimore). 2014;93:e95.
12. Mbata GC, Nweke IG, Egejuru RO, et al. South eastern histologic pattern of lymph node biopsies in a tertiary hospital in Nigeria. J AIDS Clin Res. 2015;6:6:475-8.
13. Lee Y, Terry R, Lukes RJ. Lymph node biopsy for diagnosis: a statistical study. J Surg Oncol. 1980;14:53-60.
14. Deveci HS, Kule M, Kule ZA, et al. Diagnostic challenges in cervical tuberculous lymphadenitis: A review. North Clin Istanb. 2016;3:150–5.
15. Albayrak N, Celebi B, Kavas S, et al. Investigation of the presence of Mycobacterium tuberculosis in the lymph node aspirates of the suspected tularemia lymphadenitis cases. Mikrobiyol Bul. 2014;48:129-34.
16. Rahman A, Biswas MA, Siddika TS, Sikder AM. Histopathological Evaluation of Lymph Node Biopsies: A Hospital Based Study. J Enam Med Col. 2012;2(1):8-14.
17. Shah KK, Pritt BS, Alexandera MP. Histopathologic review of granulomatous inflammation. J Clin Tuberc Other Mycobact Dis. 2017;7:1–12.
18. Mohseni S, Shojaiefard A, Khorgami Z, et al. Peripheral lymphadenopathy: approach and diagnostic tools. Iran J Med Sci. 2014;39:158–70.
19. Ochicha O, Edino ST, Mohammed AZ, et al. Pathology of peripheral lymph node biopsies in Kano, Northern Nigeria. Ann Afr Med. 2007;6:104-8.
20. Pangalis GA, Vassilakopoulos TP, Boussiotis VA, et al. Clinical approach to lymphadenopathy. Semin Oncol. 1993;20:570-82.
21. Kartal O, Ataş E, Gürsel O. Differentiation of benign from malignant cervical lymphadenopathy by ultrasonography in children. Arch Argent Pediatr. 2020;118:11-7.
22. Saraswat A, Rajender A, Purohit K, et al. Lymph node biopsy: Spectrum and clinical significance as diagnostic tool at tertiary care centre. J Evolution of Med Dental Sci. 2015;4:1008-15.
23. Penn RL. Francisella tularensis (tularemia). In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 8th ed. Philadelphia, PA: Elsevier Saunders, 2015:2590-602.
24. Kılıç UA, Kılıç S, Sencan I, et al. A water borne tuleremia outbreak caused by Francisella tularensis subspecies holarctica in Central Anatolia region. Mikrobiyol Bul. 2011;45:234-47.
25. Erdem et al. Evaluation of tularaemia courses: a multicentre study from Turkey. Clin Microbiol Infect 2014;20:1042–51.
26. Clarke P, Valadares CN, Balabram D, Pires DM. Bilateral axillary lymphadenopathy: differential diagnosis and management. Mastology 2020;30:e20200036.
27. Medina RP, Guio JI, Correa PL. Localized Castleman's Disease in the Breast in a Young Woman. Case Rep Pathol. 2016;2016:8413987.
28. Talabi OA. Melkerssons-Rosenthal syndrome: a case report and review of the literatüre. Niger J Clin Pract. 2011;14:477-8.

Available online at www.medicinescience.org

ORIGINAL ARTICLE

Medicine Science International Medical Journal

Medicine Science 2021;10(1):207-11

Management of subaxial cervical spine trauma: Clinical results of early surgical decompression

Serhat Yildizhan, Adem Aslan, Mehmet Gazi Boyaci, Usame Rakip, Kamil Anil Kilinc

Afyonkarahisar Health Sciences University, Department of Neurosurgery, Afyonkarahisar, Turkey

Received 22 December 2020; Accepted 01 February 2021
Available online 22.02.2021 with doi: 10.5455/medscience.2020.12.260

Abstract

Traumatic injuries of the subaxial cervical spine (C3-7); considered among the most common and most damaging injuries to the axial skeleton. Decompression of the spine is standard approach after cervical spinal cord injury.In this study, 72 patients who underwent early decompression with the decision of surgery according to the classification system with the Subaxial Injury Classification and Severity Scale (SLICS) among 212 patients who developed spine fractures as a result of acute traumatic subaxial cervical trauma were examined.ASIA scoring system was used for neurological examination evaluation.Patients were included in the rehabilitation program, which lasted at least six months after the operation.Neurological recovery results were evaluated with ASIA scores obtained after the rehabilitation program.It has been shown that early surgery for subaxial cervical spine fractures contributes significantly to the patient's neurological recovery.

Keywords: Cervical trauma, spinal cord injury, early decompression

Introduction

The lower cervical region (C3-C7) is called the subaxial cervical region.1/3 of all spine injuries occur in the cervical region [1]. 70% of all cervical traumas are subaxial traumas [2]. This region is responsible for 50% of cervical flexion, extension and rotation [3].The cervical region is vulnerable to injury due to this range of motion.Trauma-induced injuries of the subaxial region (C3–7) are currently among the most common and most mortal injuries of the spine [3,4]. It occurs mostly at younger ages and is associated with high-energy motor vehicle accidents in this age group [5]. It can also occur in older age groups with lower-energy traumas such as falls [6]. The cervical spine is one of the anatomical regions that should be evaluated first in patients with multiple trauma because it causes mortality [7,8]. Many classification methods have been proposed for these injuries from past to present [9]. Currently the most ideal is the Subaxial Cervical Spine Injury Classification (SLICS) scoring system [9].

***Corresponding Author:** Serhat Yildizhan, Afyonkarahisar Health Sciences University, Department of Neurosurgery, Afyonkarahisar, Turkey
E-mail: serhatyildizhan07@gmail.com

Computed tomography (CT) is the best imaging method for showing subaxial cervical fractures and dislocations because it shows the bone structure well. After subaxial cervical injuries, clinical conditions ranging from minor ligamentous injuries to very severe burst fractures can be encountered. Emergency management of such injuries is based on an accurate clinical history, careful physical examination and detailed radiological evaluation. Although decompression of the cervical spine is a standard treatment approach, a universally accepted protocol could not be established [10]. Debates continue about the preoperative application of traction, the appropriate surgical approach, and the ideal timing for decompression [11–13]. In this study, we reported the results of neurological recovery after long-term follow-up in patients who underwent early surgery (<24 hours) (anterior, posterior or both methods) after subaxial cervical spine injury in our clinic.

Materials and Methods

The study was conducted with the approval of the Afyonkarahisar Health Science University Clinical Research Ethics Committee on 03.07.2020 and protocol number 2020/289.With this study, 212 patients who were admitted to our clinic with subaxial (C3-7) traumatic injuries between January 2012 and December 2019, who were followed up and treated were retrospectively analyzed.

During this examination, patient files were accessed by using the information processing system of the hospital.Patients with subaxial cervical spine injuries who were operated due to spinal tumors, rheumatologic diseases and similar non-traumatic reasons were not included in the study.All patients were performed cervical computed tomography (CT) and cervical magnetic resonance imaging (MRI) to examine bone and ligament damage. Radiological and clinical findings of the patients were evaluated with the internationally accepted "Subaxial Injury Classification System" (SLIC). American Spine Injury Association (ASIA) scoring system was used for neurological examination evaluation. Control cervical CT was performed in patients who underwent surgery, and the positions of the stabilization materials were checked.Patients with post-operative neurological deficits were included in a physical therapy and rehabilitation program for at least 6 months. ASIA scores were re-evaluated after 6 months.

Results

72 patients out of 212 patients with subaxial cervical trauma were operated. The age range of these patients was between 15 and 79 (mean: 45.58). 53 of the patients were male and 19 were female. When etiologically examined, the most common 40 patients were found to be an in-vehicle traffic accident, and at least four patients with sports injuries. While 28 patients were neurologically in ASIA E class before the operation, 20 patients were in ASIA D and 10 patients were in ASIA A category. 52 patients were taken to surgery within the first 24 hours. Of these patients, 20 patients were ASIA E and neurologically stable, while 32 patients had neurological loss. Among the patients who underwent early surgery, 22 patients had ASIA E after the first 24 hours, while a total of 32 patients were found to have ASIA E at the sixth month after rehabilitation (Table 1). Among the patients who underwent late surgery, preoperative eight patients were ASIA E, nine patients were evaluated as ASIA E at the first 24-hour examination after the operation, and 10 patients as ASIA E at the sixth month after rehabilitation (Table 2). Of the 72 patients operated, 40 had compression or burst fractures, and the most common were C5 with 12 patients and C7 with 11 patients. Fracture-dislocation was present in 32 patients and it was most frequently observed at the C6-7 level with 13 patients.When SLIC classification was examined, it was determined that 32 patients got five points, 22 patients received four points, 12 patients received six points, and six patients received seven points and the decision of surgery was made.40 patients underwent only anterior surgery (figure 1). Surgery was performed in 14 patients with a posterior intervention (figure 2).Eighteen patients underwent both anterior and posterior surgery (figure 3).Ten of 44 patients with neurological deficits preoperation were evaluated as ASIA E in the first 24 hours postoperatively. Twenty-two out of 32 patients with continuing neurological loss received a rehabilitation program. Six months later, 10 of these patients showed neurological complete recovery, while 12 patients had an improvement of at least one point in ASIA scores.Multiple level cervical fracture was observed in 11.1% of the patients, while thoracic or lumbar fracture was associated with 16%. Only one level of cervical fracture was detected in 72%. In addition, 22% of the patients had postoperative pneumonia and medical treatment was applied. Ten patients (13.8%) died in the intensive care unit due to complications.

Table 1. Neurological evaluation of 52 patients who underwent early surgery (first 24 hours) after follow-up (Note: 3 patients died during follow-up)

ASIA	Pre-operation	Post-operation (24h)	Post-operation (6.month)
A	5	2	1
B	7	4	3
C	6	6	3
D	14	18	10
E	20	22	32
Total patient	52	52	49

Table 2. Neurological evaluation of 20 patients who underwent late surgery (after first 24 hours) after follow-up (Note: 7 patients died during follow-up)

ASIA	Pre-operation	Post-operation (24h)	Post-operation (6.month)
A	6	4	-
B	2	1	-
C	2	3	1
D	2	3	2
E	8	9	10
Total patient	20	20	13

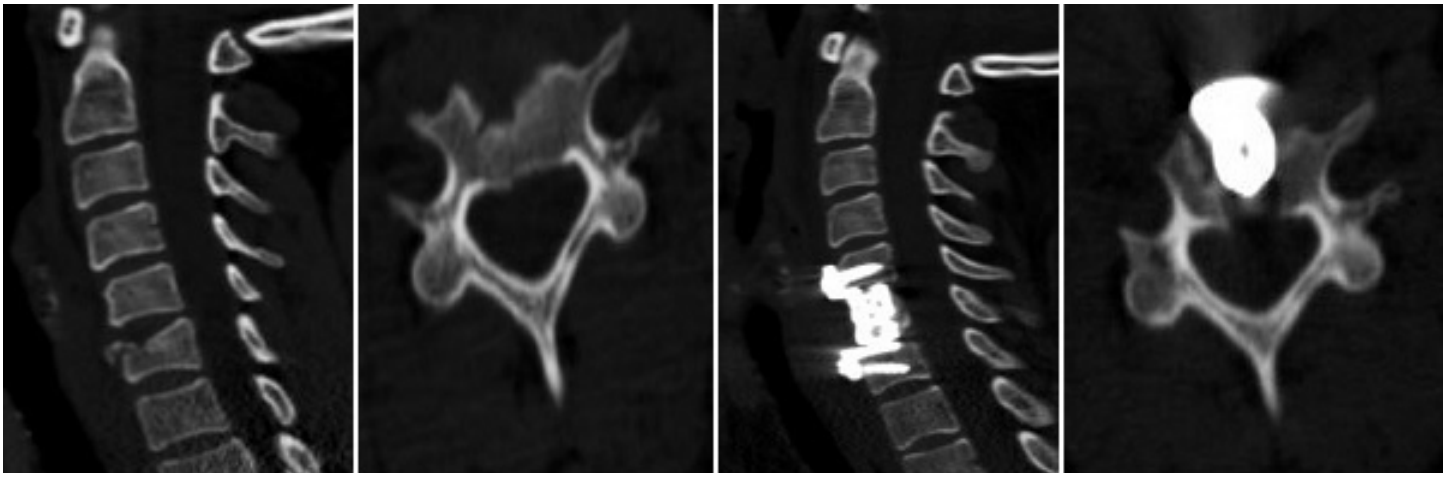


Figure 1. 33-year-old female patient AITK, C6 burst fracture, CT image after C6 corpectomy + Anterior cage application.

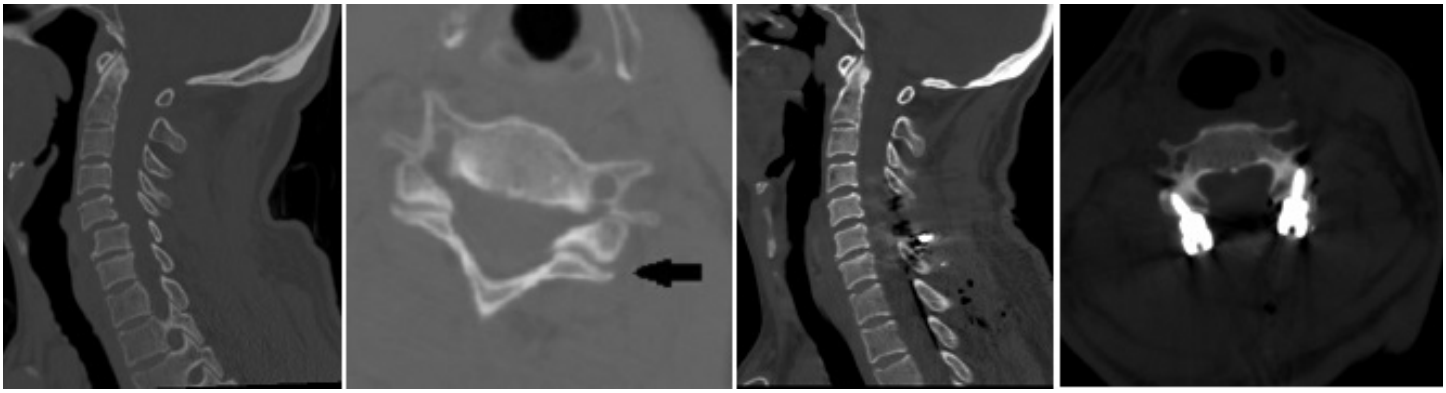


Figure 2. 58-year-old male patient C5-6 listesis and facet locking after a fall. CT image after posterior fixation and C5-C6 total laminectomy with C4-5-6-7 lateral mass.

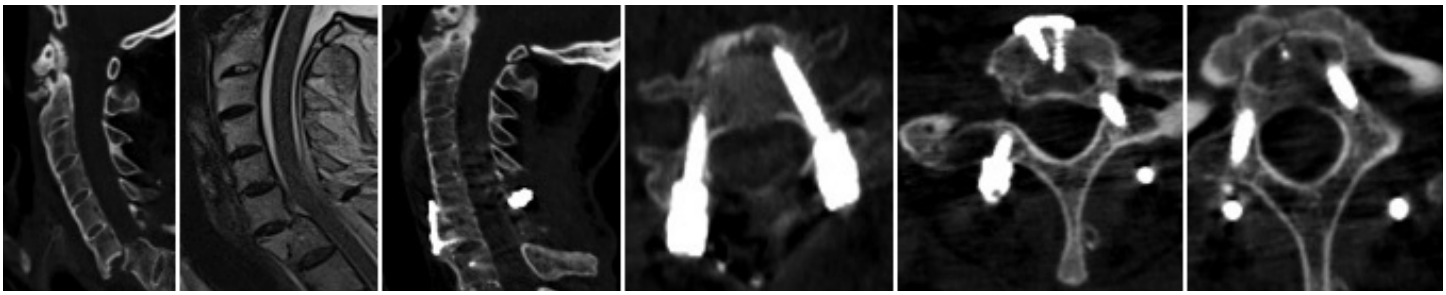


Figure 3. 57-year-old male patient after falling from height, C6-7 fracture dislocation, Posterior C5-6-7 instrumentation, C5-C6 laminectomy after anterior C6-C7 plate-screw fixation.

Discussion

The worldwide annual incidence of acute spinal cord injury is known to be 15–40 per million [14]. In our country, this number is reported as 1600-2000 annually [15]. Spinal cord injury is often seen in healthy 15-35 year olds and the clinical consequences are more dramatic.Male / female ratio is 5/1. In our study, the mean age of the patients was 45.58 (between 15-79 years) and the male / female ratio was 2.78.The most common causes of spinal cord injury are motor vehicle accidents (50%), falls and work accidents (30%), violent crimes (11%) and sports injuries (9%) [16]. In our study, 66% of the cases were motor vehicle accidents.

Approximately 35% of spinal traumas occur in the cervical region. Neurological deficits are observed in more than half of these patients.This is because this region has a thinner pedicle structure and narrower spinal canal transverse and sagittal diameter compared to the thoracic and lumbar region [17]. In addition, the fact that this region is very flexible and mobile, and that it does not have bone support around it as in the abdominal or chest wall [18-20]. These anatomical features lead to both severe clinical results and difficulties in surgical planning after trauma.Therefore, the clinical and radiological findings of this region trauma should be evaluated meticulously [11,21]. Of the 72 operated patients, 40 had compression or burst fractures, and the most common were C5 with 12 patients and C7 with 11 patients.Fracture-dislocation was present in 32 patients, and it was most frequently observed at the C6-7 level with 13 patients.In terms of surgical decision making, it is important to use a classification system that surgeons can rely on.In this way, it is important in terms of allowing studies to be conducted between different clinics in which clinical care and education can be compared [22,23]. For this purpose, the Subaxial Injury Classification System (SLIC) has been proposed by the Spinal Trauma Study Group and has been widely accepted [4,9,23-25]. Therefore, in our study, we used the SLIC scoring system.In this scoring system, patients with a score of three or less were considered stable and were followed up with conservative

treatment. On the other hand, 72 patients with SLIC scores of four and above were deemed to be unstable and the operation decision was made.

The system recommended by ASIA was used for degrees of spinal cord injury.In our study, while 28 patients were ASIA E in the preoperative classification, 44 patients had neurological loss. Out of 52 patients who underwent early surgery, 10 patients had ASIA E, while 42 patients had neurological deficits.After the postoperative follow-up and at least 6 months of rehabilitation, a significant increase was observed in ASIA scores (Table 1). No significant change was observed in ASIA scores in 20 patients who underwent late surgery (Table 2). Although decompression of the cervical spine is a standard treatment approach for subaxial cervical trauma, a universally accepted protocol has not been established [10]. Some surgeons believe that in patients currently undergoing delayed surgery (> 72 h), improvement is equal to or greater than patients undergoing early surgery [26,27]. Today, the vast majority agree that decompression and stabilization operations should be performed within the first 24 hours if the general condition of the patient is appropriate [11,24]. For example, Fehlings et al. found in a systematic review and prospective research study that 80.0% to 96.4% of spine surgeons generally prefer decompression within the first 24 hours, and the majority want to decompress within six hours [28]. This is consistent with the notion that the benefits of decompression are greater when the compression time in the spinal cord is shorter and that secondary neurological impairment is reduced [10,29]. In another study, after six months of follow-up, 20% of patients who underwent early surgery had an improvement of at least two points in ASIA, while this rate was only 9% in patients who underwent late surgery [30]. In another study, it was reported that 70% of the patients who were operated within six hours had at least one point improvement in ASIA scores, while those who were operated after the sixth hour had a recovery rate of 12% [24]. In our study, 52 patients (72.2%) were operated within the first 24 hours. 20 patients (27.7%) with multiple trauma and additional pathologies were operated late. Anterior decompression and stabilization were performed in 40 patients, posterior decompression and stabilization in 14 patients, and decompression and stabilization with a combined approach in 18 patients.When all spine traumas were examined, it was reported that two or more vertebral segments were damaged in at least 20% of the patients, and the cervical region was damaged in 80% of these patients [24,30]. Multilevel cervical fracture was observed in 11.1% of the patients operated in our clinic, while thoracic or lumbar fracture was associated with 16%. Only one level of cervical fracture was detected in 72%.

In addition, pneumonia was observed in 22% of the patients in the postoperative period. Ten patients (13.8%) died due to metabolic problems.

Subaxial cervical traumas are among the most important causes of morbidity and mortality in the world in terms of their consequences. Serious morbidity and labor losses are seen as a result of neurological damage, especially in the young age population.Early decompression and stabilization should be applied to patients with suitable general conditions and the immobile time should be kept as short as possible.In our study, a significant improvement was observed in the ASIA scores and neurological conditions of the patients after early decompression and subsequent rehabilitation treatments.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
All authors declare no financial support.

Ethical approval
The study was conducted with the approval of the XXX University Clinical Research Ethics Committee on 03.07.2020 and protocol number 2020/289.

References

1. Wilson JR, Grossman RG, Frankowski RF, et al. A clinical prediction model for long-term functional outcome after traumatic spinal cord injury based on acute clinical and imaging factors. J Neurotrauma. 2012;29:2263–71.
2. Klein GR, Vaccaro AR: Cervical spine trauma: upper and lower. Vaccaro AR, Betz RR, Zeidman SM (eds), Principles and practice of spine surgery, Philadelphia: Mosby, 2003;441-62.
3. Kwon BK, Vaccaro AR, Grauer JN, et al. Subaxial cervical spine trauma. J Am Acad Orthop Surg. 2006;14:78-89.
4. Vaccaro AR, Hulsert RJ, Patel AA, et al.The subaxial cervical spine injury classification system: a novel approach to recognize the importance of morphology, neurology, and integrity of the disco-ligamentous complex. Spine (Phila Pa 1976). 2007;32:2365-74.
5. Uhrenholt L, Charles AV, Hauge E, et al. Pathoanatomy of the ower cervical spine facet joints in motor vehicle crash fatalities. J Forensic Leg Med. 2009;16:253-60.
6. Lowery DW, Wald MM, Browne BJ, et al. Epidemiology of cervical spine injury victims. Ann Emerg Med. 2001;38:12-6.
7. Hadley MN, Walters BC, Aarabi B, et al. Clinical assessment following acute cervical spinal cord injury. Neurosurgery. 2013;72:40-53.
8. Hoffman JR, Mower WR, Wolfson AB, et al. Validity of a set of clinical criteria to rule out injury to the cervical spine in patients with blunt trauma. National Emergency X-Radiography Utilization Study Group. N Eng J Med. 2000;343:94-9.
9. Aarabi B, Walters BC, Dhall SS, et al. Subaxial cervical spine injury classification systems. Neurosurgery. 2013;72:170-86.
10. Carlson GD, Gorden CD, Oliff HS, et al. Sustained spinal cord compression: Part I: Time-dependent effect on long-term pathophysiology. J Bone Joint Surg Am. 2003;85:86–94.
11. Feuchtbaum E, Buchowski J, Zebala L. Subaxial cervical spine trauma. Curr Rev Musculoskelet Med. 2016;9:496–504.
12. Koller H, Reynolds J, Zenner J, et al. Mid to long-term outcome of instrumented anterior cervical fusion for subaxial injuries. Eur Spine J. 2009;18:630–53.
13. Park JH, Roh SW, Rhim SC. A single-stage posterior approach with open reduction and pedicle screw fixation in subaxial cervical facet dislocations. J Neurosurg Spine. 2015;23:35–41.
14. Sekhon LH, Fehlins MG. Epidemiyology, demographics and pathophysiology of acute spinal cord injury. Spine. 2001;26:2-12.
15. Karamehmetoglu SS, Unal S, Karacan I, et al. Traumatic spinal cord injuries in Istanbul, Turkey. An epidemiological study. Paraplegia. 1995;33:469-71.
16. Ho CH, Wuermser LA, Priebe MM, et al. Spinal cord injury medicine. 1. Epidemiology and classification. Arch Phys Med Rehabil 2007;88:49-54.
17. Canbek I, Korkmaz S, Rakip U, et al. Morphometric measurements performed by computed tomography on lower cervical vertebra pedicles. Bozok Med J. 2019;9:77-83.
18. Ciftdemir M. Cervical spine injuries. J Turk Spinal Surg. 2007;18:43-50.
19. Eubanks JD, Gilmore A, Bess S, et al. Clearing the pediatric cervical spine following injury. J Am Acad Orthop Surg. 2006;14:552-64.
20. Mirza SK, Bellabarba C, Chapman JR. Princeple of spine trauma care. In: Bucholz RW, Heckman JD, Court-Brown C. (Eds.). Rockwood and Green's

Fracture in Adults. 6th ed. Philadelphia: Lippincolt Williams & Wilkins Co. 2006;1402-21.

21. Joaquim AF, Patel AA. Subaxial cervical spine trauma: evaluation and surgical decision-making. Global Spine J. 2014;4:63-70.

22. Magerl F, Aebi M, Gertzbein SD, et al. A comprehensive classification of thoracic and lumbar injuries. Eur Spine J. 1994;3:184–201.

23. Allen BL, Ferguson RL, Lehmann TR, et al. A mechanistic classification of closed, indirect fractures and dislocations of the lower cervical spine. Spine. 1982;7:1–27.

24. O'Dowd JK. Basic principles of management for cervical spine trauma. Eur Spine J. 2010;19:18-22.

25. Marino RJ, Barros T, Biering-Sorensen F, et al. International standards for neurological classification of spinal cord injury. J Spinal Cord Med. 2003;26:50–6.

26. Fehlings MG, Tetreault LA, Wilson JR, et al. A clinical practice guideline for the management of patients with acute spinal cord injury and central cord syndrome: Recommendations on the timing (≤24 hours versus>24 hours) of decompressive surgery. Global Spine J. 2017;7:195–202.

27. Wilson JR, Tetreault LA, Kwon BK, et al. Timing of decompression in patients with acute spinal cord injury: A systematic review. Global Spine J. 2017;7:95–115.

28. Fehlings MG, Rabin D, Sears W, et al. Current practice in the timing of surgical intervention in spinal cord injury. Spine. (Phila Pa 1976) 2010;35:166–73.

29. Fehlings MG, Wilson JR. Timing of surgical intervention in spinal trauma: What does the evidence indicate? Spine. (Phila Pa 1976) 2010;35:159–60.

30. Fehlings MG, Vaccaro A, Wilson JR, et al. Early versus delayed decompression for traumatic cervical spinal cord injury: results of the Surgical Timing in Acute Spinal Cord Injury Study (STASCIS). PLoS One. 2012;7:32037.

Available online at www.medicinescience.org

ORIGINAL ARTICLE

Medicine Science International Medical Journal

Medicine Science 2021;10(1):212-7

Determining the perceived stress levels of nurses during COVID 19 infection in Turkey

Kubra Kayaoglu[1], Eren Aslanoglu[2]

[1]Firat University, Kovancilar Vocational School, Department of Medical Services and Techniques, Elazig, Turkey
[2]Firat University, Kovancilar Vocational School, Department of Opticianry, Elazig, Turkey

Received 18 November 2020; Accepted 26 January 2021
Available online 22.02.2021 with doi: 10.5455/medscience.2020.11.241

Abstract

This study was conducted to determine the stress levels of nurses working during COVID-19 infection. This descriptive study was conducted with 233 nurses. "Nurse Information Form" and "Perceived Stress Scale" were used to collect the data. Percentage, frequency, independent samples t-test, analysis of variance, and Shapiro-Wilk test were used to evaluate the data. It was determined that PSS total score of the participants was 26.22±6.14 (high level). PSS total mean scores of the female nurses working during COVID-19 infection were significantly higher than the scores of the male nurses ($p<0.05$). The nurses, who believed that they had enough knowledge about COVID-19 infection, had significantly a lower PSS total mean score when compared to the others ($p<0.05$). It was determined that the stress levels of the nurses working during COVID-19 infection were high.

Keywords: Coronavirus, nurses, pandemic, stress

Introduction

Coronavirus (CoV) are enveloped, single- stranded zoonotic RNA viruses with a 40-60 nm diameter from the family Coronaviridae [1]. CoV emerged with outbreak of severe acute respiratory syndrome coronavirus (SARS-CoV) type transmitted from bats in China in 2002 and Middle East respiratory syndrome coronavirus (MERS-CoV) type transmitted from camels to human beings in Saudi Arabia in 2012 [2]. Today, the COVID-19 infection which was first reported in Wuhan city, Hubei province in China on December 31, 2019 and is caused by the SARS-CoV-2 virus, has quickly spread to 6 continents and hundreds of countries and has gone down in history as the first pandemic induced by coronavirus [3]. While SARS-CoV and SARS-CoV-2 are similar to each other at the rate of 79%, MERS-CoV is similar to SARS-CoV-2 at the rate of 59% and less associated with it [4]. According to WHO data, confirmed cases of 3.090.445 and deaths of 217.769 were detected worldwide on 30.04.2020 [5].

Healthcare professionals work on the frontline of pandemics [6]. Healthcare professionals are exposed to psychological problems related to the pandemic both during the pandemic period and in the long term period [7,8]. Some studies, investigating the mental health, stress, anxiety, and coping styles of healthcare professionals providing treatment and care services in infectious diseases such as "Middle East Respiratory Syndrome" (MERS) and "Severe Acute Respiratory Syndrome" (SARS) seen in the past period, reported that healthcare professionals had high levels of stress, anxiety, and concern [9–12]. In the study conducted by Khee et al., to examine the psychological effect of SARS on healthcare professionals, they stated that the professionals had the fear, anxiety, fear of death, and sense of worthlessness [13].

The aim of this study is to determine the perceived stress levels of the nurses, working during COVID-19 infection which has similar characteristics with SARS and MERS, as well as their views on COVID-19.

The hypotheses of the study were below.

H0. COVID-19 infection is effective in reducing the perceived stress level of nurses.

H1. The nurses' views on COVID-19 affect their level of stress.

***Corresponding Author:** Kubra Kayaoglu, Firat University, Kovancilar Vocational School, Department of Medical Services and Techniques, Elazig, Turkey
E-mail: kkayaoglu@firat.edu.tr

Materials and Methods

Design

This study was conducted to find out the stress levels of nurses working during COVID-19 infection and determine their views on COVID-19 infection.

Sample and setting

The population of this study was composed of 550 nurses working in a pandemic hospital in Turkey. The sample of the study consisted of 233 nurses who agreed to participate in the study. Sample selection method was not used.

Inclusion criteria of the study were determined as follows; being during the pandemic, working in a pandemic hospital, being open to cooperation, and having no physical problems that would prevent participants from completing the data collection forms.

Exclusion criteria of the study were determined as follows; being on leave during the pandemic.

Measures

The data of the study were collected by applying Perceived Stress Scale [PSS] and Nurse Information Form, prepared by the researchers in line with the literature.

Nurse information form

The nurse information form, prepared by the researcher in accordance with the literature, consists of two parts. The first part consists of questions about the sociodemographic characteristics of nurses such as gender, age, marital status, education level, having children and having a chronic disease.

The second part consists of questions about the nurses' views on COVID-19 infection such as finding COVID-19 infection dangerous, finding their knowledge about COVID-19 infection adequate, and finding the individual and hospital measures against COVID-19 infection sufficient.

Perceived Stress Scale (PSS)

The Perceived Stress Scale (PSS) was developed by Cohen et al., (1983) [14]. Turkish adaptation and reliability and validity study of the scale were conducted by Eskin et al., (2013) in 2013 [15]. It has a total of 10 items. The participants rate each item on a 5-point Likert scale ranging from "Never (0)" to "Very often (4)". The lowest score of the scale is 0 point and its highest score is 40 points. High scores signify high stress perception. 4 of the items containing positive statements are scored reversely. In addition to this ten-item version, PSS has two other versions with 14 and 4 items. The internal consistency coefficients of PSS-14, PSS-10 and PSS-4 are calculated as 0.84, 0.82 and 0.66, respectively; on the other hand, test-retest reliability coefficients are calculated as 0.87, 0.88 and 0.72, respectively. In this study, Cronbach's alpha coefficient of PSS was determined as 0.82.

Measurements

The data were collected by the researchers using an online data collection system. The forms were sent to the nurses online and they were asked to send them back upon completion of the forms. The nurses were informed about the aim and benefits of the study. They (n=233) carefully read the questions and filled out all the questions in the data collection forms. The results were considered as statistically significant at $p < 0.05$.

Ethical Considerations

This study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval for this study was obtained from Fırat University Non-Interventional Research Ethics Committee (Date: 28.05.2020, Issue: 393456). The researchers informed the participants about the design of the study, its benefits, roles of participants, and their right to withdraw at any time.

Data Analysis

The data of the study were analyzed using SPSS for Windows 25.0 software. The compatibility of the data for normal distribution was analyzed with the Shapiro-Wilk test and the distribution was determined to comply the normality assumptions. Frequency and percentage were used as descriptive analysis. Independent samples t-test was used to compare two groups and the analysis of variance was used to compare three groups. The data were analyzed at confidence interval of 95% and significance level of $p<0.05$.

Results

Table 1 shows the sociodemographic characteristics of the participants and their views on COVID-19 infection. Their mean age was 34.73±8.69 years. It was determined that 78.5% of the nurses were female, 69.1% were married, 64.4% had children, and 80.7% had a bachelor's degree.

It was determined that 10.3% of the nurses had a patient diagnosed with COVID-19 in their environment and 59.3% were friends of the nurses. 96.6% of the nurses perceived COVID-19 infection as dangerous and 63.5% of them found the measures of the hospital management against the COVID-19 infection as insufficient. 44.6% of the nurses reported that they had insufficient knowledge about COVID-19 infection. In addition, 92.3% of the nurses believed that they may be infected even though all the measures [individual, social, and public] were taken.

Table 2 shows PSS mean scores of the nurses. In the study, their PSS total mean score was determined to be 26.22±6.14 (high level).

Table 3 shows the comparison of PSS total mean scores in terms of the descriptive characteristics of the nurses and their views on COVID-19 infection. When PSS total mean scores were compared in terms of the nurses' descriptive characteristics, it was determined that while no statistically significant difference was found between the scale total mean score and marital status, status of having a child, education level, and having a chronic disease ($p>0.05$), the difference found between gender and the scale total mean score was statistically significant ($p<0.05$). PSS total mean scores of the female nurses were significantly higher than the scores of the male nurses ($p<0.05$).

When the nurses' views on COVID-19 infection were compared with PSS total mean score, no statistically significant difference was found between the scale total mean score and the presence of a patient diagnosed with COVID-19 in their environment ($p>0.05$).

Table 1. Nurse Information Form

Variables	n	%
Mean age	34.73±8.69	
Gender		
Female	183	78.5
Male	50	21.5
Marital status		
Married	161	69.1
Single	72	30.9
Status of having a child		
Yes	150	64.4
No	83	35.6
Education status		
High school	21	9.0
Undergraduate	188	80.7
Graduate	21	9.0
Doctorate	3	1.3
Status of having a chronic disease		
Yes	40	17.2
No	193	82.8
The status of having a patient diagnosed with COVID-19 in their environment		
Yes	24	10.3
No	209	89.7
Affinity of the patient diagnosed with COVID-19		
Family	6	22.2
Neighbor	5	18.5
Friend	16	59.3
Do you think COVID-19 is dangerous		
Yes	225	96.6
No	8	3.4
Is your knowledge about COVID-19 sufficient?		
Yes	129	55.4
No	104	44.6
Are your individual measures against COVID-19 sufficient?		
Yes	125	53.6
No	108	46.4
Are hospital measures sufficient against COVID-19?		
Yes	85	36.5
No	148	63.5
Do you think that you can be infected despite all the measures?		
Yes	215	92.3
No	18	7.7

Table 2. Minimum, Maximum and Mean Scores from PSS-10 Scale

Scale	Minimum	Maximum	Mean±S.D.
PSS -10	14	38	26.22±6.14

Table 3. Comparison of PSS-10 Total Scores According to Nurse Information Form

Variables	PSS-10 X±S.D t/F p
Gender *	
Female	27.03±6.01
Male	23.28±5.75
	3.946
	<0.001
Marital Status*	
Married	25.97±6.43
Single	26.79±5.43
	-.937
	0.35
Status of having children*	25.76±6.34
Yes	27.07±5.70
No	-1.566
	0.11
Education Status**	
High School	26.71±6.56
Undergraduate	26.15±6.01
Graduate (MS+PhD)	26.33±7.00
	0.08
	0.92
Status of having a chronic disease*	
Yes	26.25±6.33
No	26.22±6.12
	0.025
	0.98
Status of having a patient diagnosed with COVID-19 in their environment*	
Yes	27.00±6.11
No	26.13±6.15
	0.650
	0.51
Is your knowledge about COVID-19 sufficient*	
Yes	25.14±5.85
No	27.56±6.25
	-3.041
	0.03
Are your individual measures against COVID-19 sufficient? *	
Yes	24.48±5.34
No	28.25±6.40
	-4.896
	<0.001
Are hospital measures sufficient against COVID-19? *	
Yes	24.54±5.84
No	27.19±6.12
	-3.239
	<0.001
Do you think that you can be infected despite all the measures?*	
Yes	26.35±6.24
No	24.66±4.58
	1.123
	0.26

* Independent samples t test ** One Way ANOVA test ($p<0.05$).

The difference between PSS total mean score and the nurses' status of believing that they had adequate knowledge about COVID-19 was determined to be statistically significant ($p<0.05$). PSS total mean score of the nurses who believed that they had sufficient knowledge about COVID-19 infection was significantly lower compared to the others ($p<0.05$).

The difference between PSS total mean score of the nurses and their status of believing that the individual measures they took against the COVID-19 infection were sufficient was determined to be statistically significant ($p<0.05$). PSS total mean scores of the nurses, who believed that the individual measures they took against COVID-19 infection were sufficient, were significantly lower than the scores of the nurses, who believed that the individual measures they took against COVID-19 infection were insufficient ($p<0.05$).

The difference between the PSS total mean score of the nurses and their status of finding the hospital measures taken against COVID-19 infection insufficient was statistically significant ($p<0.05$). The nurses who believed that the hospital measures against COVID-19 infection were sufficient had significantly lower PSS total mean score compared to the others ($p<0.05$).

Discussion

TThe results of the study conducted to determine the nurses' stress levels during COVID-19 infection were discussed in accordance with the relevant literature. COVID-19 infection is an infectious disease that had been previously unknown in Turkey. Hospitals having at least two specialists in Infectious Diseases and Clinical Microbiology, Thoracic Diseases, Internal Medicine and Hospitals having level 3 adult intensive care unit under the body of the Ministry of Health are accepted as Pandemic Hospitals [16]. Nurses working in these hospitals provide care to patients with COVID-19 infection.

Based on Table 2, PSS mean scores of the nurses were determined to be at high level. According to WHO data, the total case-death rate of COVID-19 infection was 7% on 30.04.2020 [5]. The same data showed that the SARS epidemic affected 29 countries. 8096 people were diagnosed and 774 people died. The total case-death rate of SARS was 9.6%. Also MERS infected 2494 people in 27 countries and caused 858 deaths. The case-death rate of MERS was 34.4%. Although SARS and MERS have a very high case-death rate, COVID-19 has infected a greater number of people and has caused their deaths [17]. Besides, COVID-19 pandemic is more infectious compared to the SARS epidemic and MERS pandemic [17].

Some studies, investigating the mental health, stress, anxiety, coping styles of healthcare professionals providing treatment and care services during MERS and SARS seen in the past, reported that their stress, anxiety, and anxiety levels were high [9–12]. In this study, stress levels of the nurses working during COVID-19 infection were also found to be high, which is compatible with the previous studies on SARS epidemic and MERS pandemic. Zhang et al. In the study in which they examined the stress and burnout levels of nurses working during the COVID-19 infection in China, it was reported that nurses experienced high levels of stress and burnout [18]. In a multinational and multicenter study conducted during the COVID-19 infection, 906 healthcare workers were included in the study and high levels of stress, depression, and anxiety were found in healthcare workers [19]. Que et al. In the study where they examined the effect of the COVID-19 infection on the mental state of healthcare workers, they found that healthcare workers experienced anxiety at a rate of 46.04% (high) and that among healthcare workers, nurses experienced the highest anxiety rate with a rate of 51.44% [20]. Chekole et al. In their study in Ethiopia, they reported that more than half of the healthcare workers working during the COVID-19 infection experienced high levels of stress [21]. Our study result is in line with the results of other studies in the literature. The increase in nurses' working hours, intense workload, dealing with serious cases, lack of information about the COVID-19 infection, stigma and feelings of uncertainty about the COVID-19 infection are thought to be effective in increasing the stress levels of nurses. Considering the scale score, it was observed that the hypothesis that "COVID-19 infection is effective in reducing the perceived stress level of nurses" was confirmed.

When Table 3 was examined, it was found that PSS total mean scores of the female nurses were significantly higher than the scores of the male nurses. In their study conducted to investigate the psychosocial effects of SARS on hospital staff, Nickell et al., determined that gender did not have any effect on increasing anxiety [12]. The present study is not compatible with their study. Again, based on Table 3, no significant difference was observed between the status of having a child and stress. Nickell et al., found that the anxiety level of healthcare professionals living with their children during the SARS was higher [12].

No statistically significant difference was found between the nurses' status of having a patient diagnosed with COVID-19 in their environment and their scale total mean score. Stress levels of the nurses who believed that they had sufficient knowledge about COVID-19 infection and the nurses who found the hospital measures taken against COVID-19 sufficient were significantly lower the levels of the other nurses. Considering the data obtained from the study, the hypothesis "Nurses' views on COVID-19 affect their level of stress " was confirmed. It is believed that future studies should investigate these results not included in the literature.

Conclusion

Consequently, COVID-19 infection has caused mental distress on nurses. COVID-19 is a pandemic caused by coronaviruses and similar epidemics or pandemics are likely to outbreak in the future. It is recommended to develop comprehensive intervention plans for future pandemics. These plans should also include training nurses, who are one of the occupational groups working on the frontline during pandemics, about coronavirus infections and all other epidemics or pandemics and supporting them psychologically.

Implications for Further Research

While all healthcare professionals are involved in the treatment of the patient with COVID-19 infection, this study covers only nurses. Future studies on COVID-19 may include all health professionals. This study is a descriptive and cross-sectional study. It is recommended to conduct longitudinal prospective studies in the future.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
All authors declare no financial support.

Ethical approval
Ethical approval for this study was obtained from Fırat University Non-Interventional Research Ethics Committee (Date: 28.05.2020, Issue: 393456

References

1. Lu Q, Shi Y. Coronavirus disease (COVID-19) and neonate: What neonatologist need to know. J Med Virol. 2020;92:564-67.
2. Özdemir Ö, Pala A. Treatment and prevention of covid-19 infection in children. J Biotechnol Strateg Heal Res. 2020;1:14–21.
3. Dikmen AU, Kına HM, Özkan S. Epidemiology of COVID-19: What we learn from pandemic. J Biotechnol Strateg Heal Res. 2020;4:29–36.
4. Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet. 2020;395:565–74.
5. WHO COVID-19 Dashboard [Internet]. [cited 2020 Apr 30]. Available from: https://covid19.who.int/
6. Simonds AK, Sokol DK. Lives on the line? Ethics and practicalities of duty of care in pandemics and disasters. European Respiratory Journal. 2008;34:303–9.
7. Lehmann M, Bruenahl CA, Löwe B, et al. Ebola and psychological stress of health care professionals. Emerg Infect Dis. 2015;21:913–4.
8. Lin CY, Peng YC, Wu YH, et al. The psychological effect of severe acute respiratory syndrome on emergency department staff. Emerg Med J. 2007;24:12–7.
9. Chen WK, Cheng YC, Chung YT, et al. The impact of the SARS outbreak on an urban emergency department in Taiwan. Med Care. 2005;43:168–72.
10. Khalid I, Khalid TJ, Qabajah MR, et al. Healthcare workers emotions, perceived stressors and coping strategies during a MERS-CoV outbreak. Clin Med Res. 2016;14:7–14.
11. Park JS, Lee EH, Park NR, et al. Mental health of nurses working at a government-designated hospital during a MERS-CoV outbreak: A cross-sectional study. Arch Psychiatr Nurs. 2018;32:2–6.
12. Nickell LA, Crighton EJ, Tracy CS, et al. Psychosocial effects of SARS on hospital staff: Survey of a large tertiary care institution. Cmaj. 2004;170:793–8.
13. Khee KS, Lee LB, Chai OT, et al. The psychological impact of SARS on health care providers. Crit Care Shock. 2004;7:99–106.
14. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav. 1983;24:385–96
15. Eskin M, Harlak H, Demirkıran F, et al. Algılanan stres ölçeğinin türkçeye uyarlanması: güvenirlik ve geçerlik analizi. Yeni Symp. 2013;51:132–40.
16. Sağlık Hizmetleri Genel Müdürlüğü-Hasta Hakları ve Tıbbi Sosyal Hizmetler Dairesi Başkanlığı Bilgi İçin T, ASLAN Bilkent yerleşkesi A, Mah Dumlupınar Ü. SAĞLIK BAKANLIĞI Sağlık Hizmetleri Genel Müdürlüğü.
17. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 [COVID-19] outbreak in China: summary of a report of 72314 cases from the chinese center for disease control and prevention. JAMA. 2020;323:1239–42.
18. Zhang Y, Wang C, Pan W, et al. Stress, burnout, and coping strategies of frontline nurses during the COVID-19 epidemic in Wuhan and Shanghai, China. Frontiers in Psychiatry. 2020;11:565520
19. Chew NWS, Lee GKH, Tan BYQ, et al. A multinational, multicentre study on the psychological outcomes and associated physical symptoms amongst healthcare workers during COVID-19 outbreak. Brain, Behavior, and Immunity. 2020;88:559-65.
20. Que J, Shi L, Deng J, et al. Psychological impact of the covid-19 pandemic on healthcare workers: A cross-sectional study in China. General Psychiatry. 2020;33:1–12.
21. Ali Chekole Y, Yimer Minaye S, Abate Mekonnen S, et al. Perceived stress and its associated factors during COVID-19 among healthcare providers in Ethiopia: A cross-sectional study. Advances in Public Health. 2020;5036861:1-7.

Available online at www.medicinescience.org

ORIGINAL ARTICLE

Medicine Science International Medical Journal

Medicine Science 2021;10(1):218-21

Characteristics of orthopedic research originating from Turkey

Ismail Guzel, Serkan Akpancar

Malatya Training and Research Hospital, Department of Orthopeics Surgery, Malatya, Turkey

Received 16 April 2020; Accepted 13 Jun 2020
Available online 17.08.2020 with doi: 10.5455/medscience.2020.04.057

Abstract

The present study aimed to highlight the quantity, research type, subject, evidence level, and publication patterns of scientific articles published in Turkey in the last 10 years. All scientific articles related to orthopedics and traumatology in the PubMed database from Turkey during the period from 01.01.2010 to 31.12.2019 were searched. Distribution of the articles based on subjects, journals, publication year, and yearly numbers was organized in tables and illustrated as graphics. The articles were categorized under six main groups: clinical studies, experimental studies, review articles, epidemiological studies, letters to the editor, and technical notes. The quality of the articles was evaluated based on the Oxford Centre for Evidence-Based Medicine System (Centre for evidence-Based Medicine, Oxford University Levels of evidence and grades of recommendation). The impact factor, scope, and indexing of the journals were evaluated using the data in the Journal Citation Report, Thompson Scientific Journal Citation Reports, and National Library of Medicine Report. The study covered 1,873 articles. There were 1,251 clinical studies (250 prospective, 629 retrospective, and 366 case study/case series), 293 were experimental studies (160 animal, 68 biomechanical, 34 cadaver and 31 cell cultures), 140 were review articles, 40 were epidemiological studies and 54 were letters to the editor. The most common subjects of the articles were trauma (n = 411, 23.5%), miscellaneous (basic science, practice management, osteoarthritis and rehabilitation medicine) (n = 331, 17.6%) and sports medicine-arthroscopy (n = 184, 9.8%). Based on the quality, most of the clinical studies were in Level IV (n = 768, 61.3%), followed by Level III (n = 233, 18.6%,), Level II (n = 204, 16.3%,) and Level I (n = 46, 3.7%). The highest number of articles were published in Acta Orthopaedica et Traumatologica Turcica journal (n = 376, 20%), followed by Joint Diseases and Related Surgery (n = 310, 16.6%) and Knee Surgery, Sports Traumatology, Arthroscopy (n = 48, 2.6%). Although there have been significant scientific advances in the field of orthopedics and traumatology and an increase in the number of relevant scientific publications in Turkey in recent years, the quality of publications seems to be minimal. Turkey is on track to reach the level of countries considered to be advanced in the world of science, and Turkish scientists should make efforts to improve the quality of publications. Science-based investments could foster such an aim.

Keywords: Orthopedics, publication, publication trend, scientific article.

Introduction

Countries need to develop policies that maximize scientific activities to secure their future and provide comfort for their citizens. That's why countries invest in science and train scientists in parallel with their level of development. The quantity and characteristics of scientific articles in a country are directly proportional to the scientific activities of that specific country [1].

Turkish scientists have been successful in the field of Orthopedics and Traumatology, and many scientific papers they published successfully represented Turkey in the international arena. In this context, the journals Acta Orthopaedica et Traumatologica Turcica (AOTT) and Joint Diseases and Related Surgery originating from Turkey are two important journals that have managed to enter the SCI-E index with articles published in the field of Orthopedics and Traumatology.

This study aimed to present the quantity, type of study, subject, evidence level, publication types, and characteristics of scientific articles published in Turkey in the last 10 years.

Materils and Methods

Scientific articles involving orthopedics and traumatology from Turkey in the PubMed database during 01.01.2010-31.12.2019 period were searched. Articles were grouped based on subjects, journals, publication year, and yearly numbers were organized in tables and illustrated as graphics. Subjects of the articles were classified in ten main categories: trauma, pediatric, sports injuries and arthroscopy, adult reconstruction (knee, hip, ankle), vertebrae, tumor (tumor, metabolic diseases, AVN, infection), hand-wrist, foot-ankle, shoulder-elbow and unclassified (basic sciences, osteoarthritis, and other subjects). The article types were classified into six main groups: clinical research articles, experimental research articles, review articles, epidemiological

***Coresponding Author:** Ismail Guzel, Malatya Training and Research Hospital, Department of Orthopeics Surgery, Malatya, Turkey
E-mail: dr.ismailguzel@gmail.com

research articles, letters to the editor, and technical notes. Clinical research articles were separated into three main groups of prospective and retrospective studies and case studies/case series. Experimental research articles were of four groups: animal, biomechanical, cadaver, and cell culture studies. The quality of the articles was analyzed using the Oxford Centre for Evidence-Based Medicine System (Centre for evidence-Based Medicine, Oxford University Levels of evidence and grades of recommendation)[2]. In this system, good quality, randomized studies with controls were classified Level 1, low quality, randomized studies with controls were Level II, case-control, and retrospectively compared studies were Level III, and case series without a control group or comparison were Level 4. The impact factor, scope, and indexing of the journals were analyzed based on the data in the Journal Citation Report, Thompson Scientific Journal Citation Reports, and National Library of Medicine Report[3,4]. The articles were evaluated by two independent investigators. Conflicting evaluations were resolved by discussion or by taking the opinion of a third researcher. SPSS for Windows software (ver. 15.0) was used for statistical analyses of the data.

Results

Of 1,911 scientific articles evaluated in 01.01.2010-31.12.2019 period, 38 were eliminated since they were not related to orthopedics and traumatology, and a total of 1,873 articles were examined. The number of published articles was low in the 2010-2013 period, but starting with 2014 a major increase was observed. The highest number of articles were published in 2014 (n = 257) and the lowest in 2011 (n = 81) (Figure 1). During the study period, 1,251 clinical research articles were published, and 629 of them were retrospective, 366 were case study/case series and 250 were prospective. The number of experimental research articles in the surveyed period was 293, and 160 of them were animal studies while 68 were biomechanics, 34 were cadaver and 31 were cell culture studies. There were also 140 review articles, 40 epidemiological research articles, and 54 letters to the editor. In terms of subjects, articles involving trauma were most common (n = 411, 23.5%), followed by miscellaneous (basic science, practice management, osteoarthritis and rehabilitation medicine) (n = 331, 17.6%) and sports medicine-arthroscopy (n = 184, 9.8%) (Figure 2).

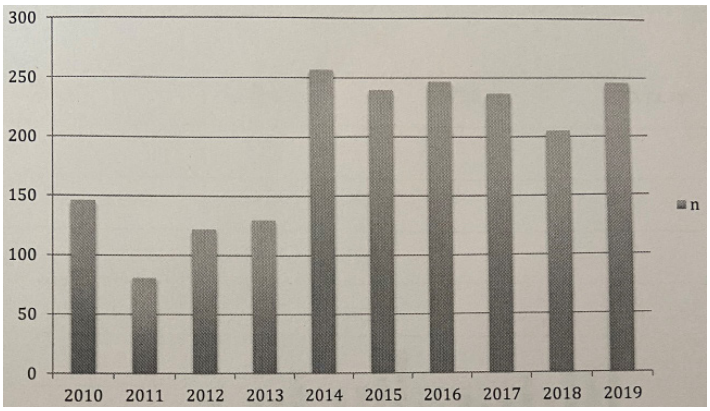


Figure 1. Number of publications per year

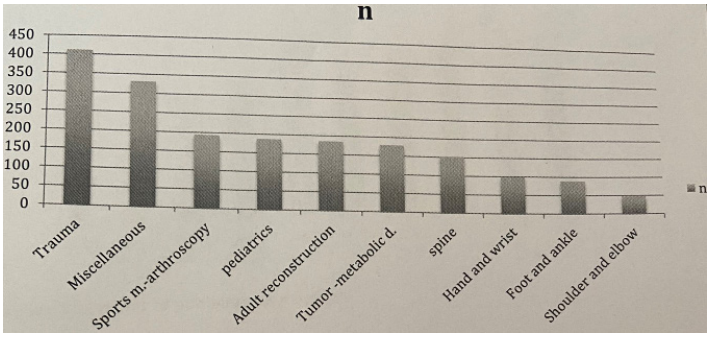


Figure 2. Distribution of article based on subjects

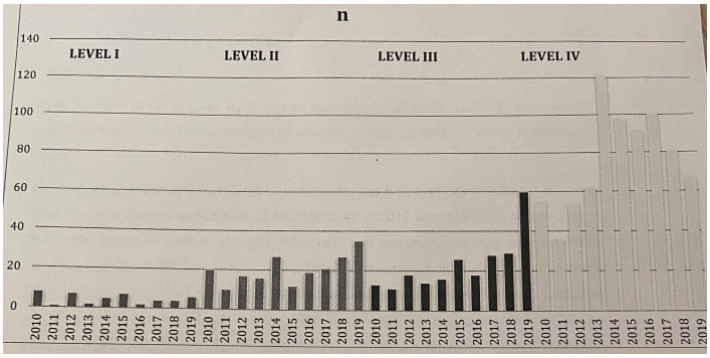


Figure 3. Quality of study designs according to the Oxford Centre for Evidence-Based Medicine System

When it comes to the quality classification of the scientific articles, most of the published clinical studies were Level IV (n = 768, 61.3%), followed by Level III (n = 233, 18.6%,), Level II (n = 204, 16.3%,) and Level I (n = 46, 3.7%). The number of Levels I studies, which represent the best quality, was highest in 2010 (n = 8), 2012, and 2015 years (n = 7 each) (Figure 3). The journals in which the highest number of articles were published were Acta Orthopaedica et Traumatologica Turcica (n = 376, 20%), followed by Joint Diseases and Related Surgery (n = 310, 16.6%) and Knee Surgery, Sports Traumatology, Arthroscopy (n = 48, 2.6%).

Discussion

In the present study, orthopedics and traumatology scientific articles published in PubMed in the last 10 years were analyzed, and their impacts on international scientific literature were evaluated. Our results showed that the number of publications in the field of Orthopedics and Traumatology has increased successfully. However, the ratio of experimental and Level I and II clinical trials in all publications was very low.

The number of scientific articles in the field of Orthopedics and Traumatology was low in the 2010-2013 period, and a considerable increase occurred after 2013. The highest number was observed in 2014 (257 articles) while the lowest was in 2011 (81 articles) (Figure 1). In a similar study performed in Turkey, Demirtaş et al.[5]surveyed the scientific articles in Acta Orthopaedica et Traumatologica Turcica (AOTT) journal in the 2006-2015 period. They observed an increase until the year 2009, followed by a considerable decrease until 2013, and an increase

Table 1. Distribution of articles according to the journals

Journal	n	%	Impact Fsctor*	Scope **, ***
Acta Orthopaedica et Traumatologica Turcica	376	20.0	0.896	Index Medicus MEDLINE PubMed SCI-E Essential Science Indicators
Joint Diseases and Related Surgery	310	16.6	1.058	Index Medicus MEDLINE PubMed SCI-E Essential Science Indicators
Knee Surgery, Sports Traumatology, Arthroscopy	48	2.6	3.210	Index Medicus MEDLINE PubMed SCI-E Current Contents- Clinical Medicine Essential Science Indicators
Ulus Trauma Emergency Surgery	44	2.3	0.643	Index Medicus MEDLINE PubMed SCI-E Essential Science Indicators
Journal of Pediatric Orthopaedics	29	1.5	2.046	Index Medicus MEDLINE PubMed SCI-E Current Contents-Clinical Medicine Essential Science Indicators
Archives of Orthopaedic and Trauma Surgery	27	1.4	1.973	Index Medicus MEDLINE PubMed SCI-E Biological Abstracts BIOSIS-Previews Current Contents-Clinical Medicine Essential Science Indicators
European Journal of Orthopaedic Surgery & Traumatology	26	1.4	0.180	Index Medicus MEDLINE PubMed
International Journal of Surgery Case Reports	22	1.2	0.620	Index Medicus MEDLINE PubMed DOAJ
Orthopedics	21	1.1	1.608	Index Medicus MEDLINE PubMed SCI-E Current Contents- Clinical Medicine Essential Science Indicators
Case Reports in Orthopedics	21	1.1	-	Index Medicus MEDLINE PubMed PMC DOAJ
Others (< 20)	**949**	**50.6**		
TOTAL	**1873**	**100**		

* Journal Citation Report ** Thompson Scientific Journal Citation Reports *** National Library of Medicine Report

again until the end of 2015. We surveyed all journals published in Turkey and indexed in Pubmed. Our findings were similar to those of Demirtaş et al until the year 2015. The increase after the year 2013 indicated that scientific activities increased considerably in Turkey. The number of scientific articles remained similar until the end of 2019, and a major decrease was not observed.

Prospective studies thatare considered to be better quality compared to other studies constituted about 20% of all clinical studies, while 15.6% of them were experimental studies. The number of retrospective studies increased in the last ten years during which prospective studies did not have a considerable increase. In a similar study, Demirtaş et al. found that 2.5% of the studies originating from Turkey were published in the AOTT journal and that percentage increased to 7.4 in the 2011-2015 period[5]. In the same study, it was mentioned that a statistical increase was not observed in the number of prospective studies until the year 2015.Koca et al.[6]surveyed Orthopedics and Traumatology theses and publication patterns in Turkey. They revealed that 8.6% of the theses were Level I prospective studies, 5.8% were Level II prospective studies and 25.6% were experimental studies. They also found that only 16% of the theses were published and made a better contribution to science. The journals have impact value based on the citations they received.Yalçınkaya et al.[7] evaluated studies that originated in Turkey. They observed that most study types were retrospective, observational, and case reports. Obremskey et al. mentioned that Level 1 and 2 publications receive more citations, and consequently, they guide other scientific studies[8]. Reich et al. mentioned that Level I, Level II, and III publications could be published (in decreasing order) in journals that guide the scientific studies while publication chance of Level IV publications is very low [9]. Because the journals with high impact value which guide the science attach more importance to experimental, Level 1, and 2 clinical studies, Turkey should promote scientists and implement scientific policies to produce this kind of research.

The most commonly studied subject was trauma (23.5%), followed by miscellaneous (basic science, practice management, osteoarthritis, and rehabilitation medicine) (17.6%) and sports medicine-arthroscopy (9.8%) (Figure 2). Such a distribution of topics is in line with other studies carried out in Turkey. However, there are some discrepancies compared to international studies in the literature. In a study conducted in Brazil, the most common studies involved shoulder/elbow (13.8%), followed by the knee (12.6%) and trauma (10.7%)[10].The frequency differencescould have been caused by the method used for the classification of articles. A relatively low number of studies in the shoulder/elbow area points to the need for studies in this field in Turkey.

More than one-third of the Orthopedics and Traumatology studies originating in Turkey was published inActa Orthopaedica et Traumatologica Turcica and Joint Diseases and Related Surgery, two Turkish journals indexed in Science Citation Index-Expanded (SCI-E). These two journals host a considerable number of successful scientific articles. Knee Surgery, Sports Traumatology, Arthroscopy ranks third with a share of 2.6%. This journal boasts with an impact value of 3.21 and hosts the most successful studies originating in Turkey, but the number of these studies is limited. Increasing the number of good quality publications in Turkey could allow these high-impact journals to publish more of them.

Although there have been considerable scientific advances and increased publications in the field of orthopedics and traumatology in Turkey during the recent years, the quality of publications (a journal where they were published, the number of citations they received, whether they had patent output, etc.) is still minimal. Turkey, on her track to reach the level of countries considered advanced in the scientific world, needs to make efforts to improve the quality of publication of her scientists and to make science-centered investments.

Conflict of interests
The authors have no conflicts of interest to declare.

Financial Disclosure
All authors declare no financial support.

Ethical approval
Ethical approval for this study was obtained from Inonu University Clinical Research Ethics Committee (Date: 23.12.2020, protocol number: 2020/209).

References

1. Bordons M, Zulueta MA. Evaluation of the scientific activity through bibliometric indices. Revista Espanola de Cardiologia. 1999;52:790–80.
2. American academy of orthopaedic surgeons. Levels of evidence and grades of recommendations. http://www2.aaos.org/bulletin/apr05/fline9.asp accessed date January 21, 2020
3. Thompson Scientific. J Citation Reports. http://science.thomsonreuters.com/cgi-bin/jrnlst/jlresults.cgi accessed date January 21, 2020
4. National Library of Medicine Report. http://locatorplus.gov/cgibin/Pwebrecon.cgi?PAGE=sbSearch&SEQ=20160106161608&PID=-jITHFzwEZHyelEI7_sk3TMF4NlrR accessed date January 21, 2020
5. Demirtaş A, Tutak Y, Duymus TM, et al. Change in the impact of Turkish Orthopedics and Traumatology on international scientific literature. Medeniyet Med J. 2018;33:75-81.
6. Koca K, Ekinci S, Akpancar S, Gemci MH, Erşen Ö, Akyıldız F. An analysis of orthopaedic theses in Turkey: Evidence levels and publication rates. Acta Orthop Traumatol Turc. 2016;50:562-6.
7. Yalcinkaya M, Bagatur AE. Articles published in acta orthopaedica et traumatologica turcica between 2003-2012: content, characteristics and publication trends. Acta Orthop Traumatol Turc. 2014;48:576-83.
8. Obremskey WT, Pappas N, Attallah-Wasif E, et al. Level of evidence in orthopaedic journals. J Bone Joint Surg Am. 2005;87:2632-8.
9. Reich MS, Shaw J, Barrett I, et al. Level of evidence trends in the J Bone and Joint Surgery, 1980-2010. Iowa Orthop J. 2014;34:197-203.
10. Ejnisman L, Gomes GS, de Oliveira RG, et al. Publication rates of papers presented at the Brazilian Orthopedic Meeting. Acta ortopedicabrasileira. 2013;21:285.

Available online at www.medicinescience.org

ORIGINAL ARTICLE

Medicine Science International Medical Journal

Medicine Science 2021;10(1):222-5

Investigation of the relationship between eye involvement and systemic diseases in patients with COVID-19

Abdulgani Kaymaz, Rukiye Kilic Ucgul

Bolu Abant Izzet Baysal University, Faculty of Medicine, Department of Ophthalmology, Bolu, Turkey

Received 31 December 2020; Accepted 01 February 2021
Available online 22.02.2021 with doi: 10.5455/medscience.2020.12.266

Abstract

Investigation of whether there is a relationship between eye involvement and systemic diseases in patients diagnosed with Coronavirus Disease-2019 (COVID-19). One hundred and tenpatients who admitted to our hospital and were diagnosed with COVID-19 by Polymerase Chain Reaction (PCR) and chest computed tomography (CT) were included in the study. The demographic characteristics and existing systemic diseases of the patients were questioned. Whether the patients had ocular involvement associated with COVID-19 was investigated. The patients with eye involvement were examined in terms of systemic diseases and the drugs they used. Sixty oneof the patients were male and 49 were female. Eight (7.3%) of the 110 patients had ocular involvement. Six of these 8 patients had no comorbid diseases. Two patients with additional systemic disease had a common diagnosis of chronic kidney disease. The mean age of those with ocular involvement (44.88 ± 21.97 years) was lower than the average age of the total group (52.29 ± 22.93 years). The most common additional systemic disease in patients with COVID-19 was hypertension (26.4%).All patients had conjunctival hyperemia. Five of the patients had epiphora, 5 had secretion, 4 had burning-stinging and 2 had ocular pain.3 of the patients were smokers.In 2 patients, the first finding of COVID-19 started with eye complaints.One of the patients with ocular involvement had a history of previous Fuchs uveitis. Although eye involvement in COVID-19 patients is not common, it may appear as the first finding. Detection of patients with eye involvement may be beneficial in terms of early diagnosis, treatment and prevent transmission. In addition, the relationship between comorbid diseases and eye involvement may be important in terms of prognosis.

Keywords: Comorbid diseases, conjunctival hyperemia, coronavirus disease-2019 (COVID-19), epiphora, eye involvement, fuchs uveitis

Introduction

Coronavirus Disease-2019 (COVID-19) has been on the agenda of the whole world for more than 1 year. Although the main target of COVID-19 is the respiratory system, the virus also targets many other systems and organs. [1-3] People with underlying uncontrolled medical conditions have been found to have a higher risk of contracting COVID-19 (Such as diabetes mellitus (DM), hypertension (HT), cardiovascular diseases (CVD), chronic respiratory (CRD) and kidney disease (CKD), cancer patients receiving chemotherapy, smokers, organ transplant patients and chronically steroid users.). [4,5] It was also observed that the prognosis was worse and the mortality rate was higher in this patient group. [6-8] In addition, it has been determined that the virus can cause serious illness not only in the elderly but also in children. [2,9]

***Corresponding Author:** Abdulgani Kaymaz, Bolu Abant Izzet Baysal University, Faculty of Medicine, Department of Ophthalmology, Bolu, Turkey
E-mail: kaymaz9@hotmail.com

In COVID-19, direct contact with mucous membranes is an important transmission route for the disease. [10] It has been shown that COVID-19 can involve the anterior and posterior segments of the eye. [11-13] The most commonly reported ocular sign of COVID-19 is conjunctivitis. [14] Conjunctival infection can occur through droplets or contact of infected structures with the eyes. [15] It is known that ocular findings are rare and usually mild. [10] However, it should be borne in mind that the eye can be a way of both getting infected and transmitting the infection to other people. [16]

Although PCR from nasopharyngeal swabs has an important role in the diagnosis of COVID-19, false negativity rates of tests performed from conjunctival swabs are quite high. [17] Eye involvement in COVID-19 can sometimes occur as the first sign of the disease, and sometimes during the disease. Although there are many studies in the literature on the ocular findings of COVID-19, [14,15,18] the number of studies revealing the relationship between eye involvement and systemic diseases is quite limited. Determining the relationship between eye involvement and

systemic diseases will provide important information about the prognosis and transmission of the disease. Therefore, such a study has been planned.

Materials and Methods

The study included 110 patients who were diagnosed with COVID-19 by PCR test and chest CT, hospitalized in the coronavirus (CoV) infection services of Bolu Abant Izzet Baysal University Training and Research Hospital. Ethics committee approval was obtained from the same university. Informed consent was obtained from the patients and the principles of the Declaration of Helsinki were followed.

The patients with COVID-19 included in the study were asked about their systemic diseases, medications they used, smoking cigarettes, existing eye conditions, wearing glasses, or contact lenses. The symptoms of those with eye complaints that may be associated with COVID-19 and the relationship of these symptoms with systemic diseases were investigated. The form prepared for the study was filled in by the physicians included in the study, with questions asked to patients and/or their relatives. Patients with confusion, shortness of breath, and speech difficulties, and patients who needed intensive care and had a poor general condition were not included in the study. The doctors participating in the study complied with all the necessary conditions at the maximum level to protect from CoV and prevent the spread of the disease outside the service.

Statistical analysis of all data used in the study was done with SPSS version 25.0 for Windows. Parametric data were calculated as mean ± standard deviation, nonparametric data were calculated as percentages.

Results

The demographic characteristics and findings of existing systemic diseases of the 110 patients included in the study are summarized in Table 1. Sixty oneof the patients were male (55.5%), 49 were female (44.5%) and their mean age was 52.29 ± 22.93 years (min-max: 7-90 y). While 38.2% of the patients did not have any comorbid diseases, 27.3% had 1, 16.4% had 2, 12.7% had 3, 4.5% had 4 and 0.9% had 5 additional systemic diseases.

The most common systemic disease accompanying COVID-19 was HT (26.4%). Other accompanying diseases were DM, CVD, CKD, CRD, central nervous system disease (CNSD), thyroid disease, and malignity (respectively) (Table 1). The number of patients with CNDS (n=13) was equal to the number of patients with CRD (n=13). All 6 patients with thyroid disease had a diagnosis of hypothyroidism. Of the 4 patients in the other systemic diseases group, 2 had rheumatoid arthritis, 1 had ankylosing spondylitis, and 1 had chronic hepatitis B. One of the 2 patients with malignancy had colon cancer and the other had pancreatic cancer. Forty seven of all patients (42.7%) were not using any medication.

Eight (7.3%) of the 110 patients included in the study had ocular involvement associated with COVID-19. The characteristics of these patients are shown in Table 2. Of the patients with ocular involvement, 4 were male and 4 were female, and their mean age was 44.88 ± 21.97 years (min-max: 25-90 y). Eight of the patients had conjunctival hyperemia, 5 had epiphora, 5 had secretion, 4 had burning-stinging and 2 had ocular pain. Remarkably in the study, only 2 (25%) of 8 patients with ocular involvement had comorbid disease and their mean age was lower than the mean age of the whole group. Two patients with ocular involvement and comorbid disease also had a diagnosis of CKD. One of the patients with ocular involvement had a history of Fuchs uveitis.

Tablo 1. Characteristics and comorbid diseases of patients diagnosed with COVID-19.

	Yes (n, %)	No (n, %)
Comorbid disease(s) (at least one)	68 (% 61.8)	42 (% 38.2)
Hypertension	29 (% 26.4)	81 (% 73.6)
Diabetes mellitus	25 (% 22.7)	85 (% 77.3)
Cardiovascular disease	21 (% 19.1)	89 (% 80.9)
Chronic kidney disease	15 (% 13.6)	95 (% 86.4)
Chronic respiratory disease	13 (% 11.8)	97 (% 88.2)
Central nervous system disease	13 (% 11.8)	97 (% 88.2)
Thyroid disease	6 (% 5.5)	104 (% 94.5)
Malignity	2 (% 1.8)	108 (% 98.2)
Other systemic diseases	4 (% 3.6)	106 (% 96.4)
Fever	45 (% 40.9)	65 (% 59.1)

Tablo 2. Characteristics of the patients with COVID-19 with eye involvement.

Gender/ age,y	Fever	Ocular symptoms	Systemic diseases	Jop	EG	Contact lens	Smoker
Case 1 F/38	No	Epiphora Burning-stinging Secretion Conjunctival hyperemia	No	Worker	No	No	No
Case 2 F/90	No	Burning-stinging Conjunctival hyperemia	DM HF CKD	Retired	No	No	No
Case 3 M/37	No	Secretion Epiphora Ocular pain Conjunctival hyperemia	No	Official	Yes	No	Yes
Case 4 M/30	Yes	Conjunctival hyperemia Ocular pain Secretion	No	Worker	No	No	Yes
Case 5 M/64	No	Burning-stinging Conjunctival hyperemia	CKD	Retired	Yes	No	Yes
Case 6 F/46	No	Conjunctival hyperemia Epiphora Secretion	No	Worker	No	No	No
Case 7 M/29	Yes	Secretion Epiphora Burning-stinging Conjunctival hyperemia	No	Official	No	No	No
Case 8 F/25	No	Conjunctival hyperemia Epiphora Secretion	No	Student	Yes	No	No

CKD: Chronic kidney disease, DM: diabetes mellitus, EG: eyeglasses, F: Female, HF: Heart failure, M: Male

Discussion

In this study we conducted to determine the relationship between ocular involvement and systemic disease, it was found that at least

one comorbid disease was present in 68 of 110 patients and ocular involvement was present in 8 patients. Only 2 of the patients with ocular involvement had comorbid diseases.

Studies have shown that the rate of ocular involvement in patients with CoV varies between 4.5-31.6%. [15,18,19]. Ocular involvement rate was found to be 7.3% in our study. Although this value is within the specified range in studies, it only expresses the rate of the inpatients. Similar to our study, Chen et al.[13] found ocular involvement in 8 patients in their study of 121 patients.In addition, they found positive conjunctival PCR of 2 patients without eye complaints and 1 patient with ocular involvement. As a matter of fact, it has been observed that even symptomatic patients with ocular involvement may have negative PCR test results. [14,15, 19]. Since eye findings are not sufficiently questioned or reported in the inpatient clinics, this rate can be detected lower than normal. In our study, the mean age of patients with ocular involvement was lower, but the limited number of patients makes it difficult to comment on the situation. In order to elucidate the unknown aspects of the disease, there is a need for large-scale studies that include outpatients, asymptomatic patients and intensive care patients.

While COVID-19 can cause simple anterior segment pathologies such as conjunctivitis and anterior uveitis, it can also lead to severe vision-threatening ocular symptoms such as retinitis and optic neuritis. [10-12,20] In our study, all 8 patients with ocular involvement had symptoms associated with the anterior segment. Detailed ophthalmologic examinations of the posterior segment could not be performed because the patients were hospitalized in the CoV clinics. Due to the difficulty in examining patients with COVID-19, establishing a special examination room for COVID-19 patients in ophthalmology clinics will enable more information about the eye involvement of the disease. Although eye involvement is not a common finding, it is important that it occurs as the first symptom of COVID-19 in two patients. Therefore, care should be taken to use preventative measures such as goggles or face shields, even when looking at patients with or without COVID-19 symptoms.

In the first studies on CoV, while lung involvement was at the forefront, it was later seen that the virus could involve and damage other organs. [1,3,21] The ability of the virus to infect many organs is particularly associated with angiotensin-converting enzyme (ACE)-2 receptors. [1] Because the CoV attaches to target cells through ACE-2 expressed by epithelial cells of the lungs, blood vessels, kidneys, and intestines. [3,22] Despite this, it is still not clear why the disease has different prognosis in different ages and groups. [23-25] It is known that patients with comorbid diseases are more affected by multisystem organ involvement. [26,27] In a meta-analysis of 34 studies, the most common comorbid diseases accompanying COVID-19 were found as HT, CVD, DM, and CKD, respectively. [26] In another study in which a meta-analysis of 24 studies was made, this ranking was found as HT, DM, CVD, and CRD, respectively. [4] In our study, 61.8% of the patients had at least one systemic disease and the most common comorbid disease was HT (26.4%). DM, CVD, CKD, CRD, and CNSD diseases followed HT, respectively. Our findings were similar to other studies.

Since there is no study investigating the relationship between ocular involvement and systemic disease in the literature, 2 patients were identified in this study, one of whom was diagnosed with CKD, the other with CKD, DM, and HF. Although the number of patients with this relationship is small (only 2 patients), three questions come to mind. 1) I wonder if the rate of comorbid diseases is low in patients with eye involvement? 2) Do those with comorbid diseases have lower eye involvement rates? 3) Other receptors other than ACE-2 accompany this process? Of course, more research is needed to identify possible COVID-19 receptors on ocular surface cells and to determine the relationship of these receptors with other organs/tissues.

There were some limitations in our article. Only patients hospitalized in the CoVclinic were included in the study. Outpatients, intensive care patients, and undiagnosed asymptomatic patients were excluded from the study. In addition, since the patients were evaluated in the CoV clinics, the anterior and posterior segment findings of the patients could not be revealed in detail. Although not performing the conjunctival swab PCR test is another limitation of the article, Gue et al. reported that the viral load in the conjunctival sac may be insufficient for PCR positivity. [17] Despite all these limitations, it is important for the prognosis and transmission of the disease that patients with ocular involvement have a lower mean age, less comorbid disease association, and the first symptom of the disease can start with eye complaints.

Performing a detailed eye examination of all COVID-19 patients with and without eye involvement will further contribute to the literature on the ocular findings of the diseas. In addition, early diagnosis of patients with eye involvement will minimize transmission of the virus to both healthcare professionals and other people through eye fluids.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
All authors declare no financial support.

Ethical approval
This study was performed in adherence with the tenets of the Declaration of Helsinki and was approved by local ethical committee (no: 2020/315).

References

1. Gavriatopoulou M, Korompoki E, Fotiou D, et al. Organ-specific manifestations of COVID-19 infection. Clin Experimental Med. 2020:1-14.
2. Son M,Friedman K. Coronavirus disease 2019 (COVID-19): Multisystem inflammatory syndrome in children. Up to Date. 2020.
3. Temgoua MN, Endomba FT, Nkeck JR, et al. Coronavirus disease 2019 (COVID-19) as a multi-systemic disease and its impact in low-and middle-income countries (LMICs). SN Comprehensive Clin Med. 2020:1-11.
4. Liu H, Chen S, Liu M, et al. Comorbid chronic diseases are strongly correlated with disease severity among COVID-19 patients: a systematic review and meta-analysis. Aging Disease. 2020;11:668.
5. Sanyaolu A, Okorie C, Marinkovic A, et al. Comorbidity and its Impact on Patients with COVID-19. SN Comprehensive Clin Med. 2020:1-8.
6. Garg S. Hospitalization rates and characteristics of patients hospitalized with laboratory-confirmed coronavirus disease 2019—COVID-NET, 14 States, March 1–30, 2020. MMWR. Morbidity Mortality Weekly Report. 2020;69.
7. Singh AK, Gupta R, Ghosh A, et al. Diabetes in COVID-19: Prevalence, pathophysiology, prognosis and practical considerations. Diabetes & Metabolic Syndrome: Clin Res Rev. 2020.

8. Zhao Q, Meng M, Kumar R, et al. The impact of COPD and smoking history on the severity of COVID-19: a systemic review and meta-analysis. J Medical Virolog. 2020.

9. Yoldas MA,Yoldas H. Pediatric COVID-19 disease: a review of the recent literature. Pediatric Annals. 2020;49:319-25.

10. Seah I,Agrawal R. Can the coronavirus disease 2019 (COVID-19) affect the eyes? A review of coronaviruses and ocular implications in humans and animals. Ocular Immunol Inflammation. 2020;28:391-5.

11. Bettach E, Zadok D, Weill Y, et al. Bilateral anterior uveitis as a part of a multisystem inflammatory syndrome secondary to COVID-19 infection. J Med virolog. 2020.

12. Zago Filho LA, Lima LH, Melo GB, et al. Vitritis and outer retinal abnormalities in a patient with COVID-19. Ocular Immunol Inflammation. 2020;28:1298-300.

13. Zhou Y, Duan C, Zeng Y, et al. Ocular findings and proportion with conjunctival SARS-COV-2 in COVID-19 patients. Ophthalmology. 2020;127:982-3.

14. Shemer A, Einan-Lifshitz A, Itah A, et al. Ocular involvement in coronavirus disease 2019 (COVID-19): a clinical and molecular analysis. Intern Ophthalmol. 2020:1-8.

15. Wu P, Duan F, Luo C, et al. Characteristics of ocular findings of patients with coronavirus disease 2019 (COVID-19) in Hubei Province, China. JAMA ophthalmology. 2020;138:575-8.

16. Loon S, Teoh S, Oon L, et al. The severe acute respiratory syndrome coronavirus in tears. British journal of ophthalmology. 2004;88:861-3.

17. Guo D, Xia J, Shen Y, et al. SARS-CoV-2 may be related to conjunctivitis but not necessarily spread through the conjunctiva SARS-CoV-2 and conjunctiva. J Medical Virology. 2020.

18. Öncül H, Öncül FY, Alakus MF, et al. Ocular findings in patients with coronavirus disease 2019 (COVID-19) in an outbreak hospital. J Medical Virolog. 2020.

19. Atum M, Boz AAE, Çakır B, et al. Evaluation of conjunctival swab PCR results in patients with SARS-CoV-2 infection. Ocular Immunol Inflammation. 2020;28:745-8.

20. Shaigany S, Gnirke M, Guttmann A, et al. An adult with Kawasaki-like multisystem inflammatory syndrome associated with COVID-19. Lancet. 2020;396:8-10.

21. Zheng Y-Y, Ma Y-T, Zhang J-Y, et al. COVID-19 and the cardiovascular system. Nature Reviews Cardiol. 2020;17:259-60.

22. Mi J, Zhong W, Huang C, et al. Gender, age and comorbidities as the main prognostic factors in patients with COVID-19 pneumonia. Am J Translational Res. 2020;12:6537.

23. Cure E,Cure MC. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may be harmful in patients with diabetes during COVID-19 pandemic. Diabetes & Metabolic Syndrome: Clin Res Reviews. 2020.

24. Yang L, Liu S, Liu J, et al. COVID-19: immunopathogenesis and Immunotherapeutics. Signal Transduction and Targeted Therapy. 2020;5:1-8.

25. Cao X. COVID-19: immunopathology and its implications for therapy. Nature Reviews Immunol. 2020;20:269-70.

26. Wang X, Fang X, Cai Z, et al. Comorbid chronic diseases and acute organ injuries are strongly correlated with disease severity and mortality among COVID-19 patients: a systemic review and meta-analysis. Research. 2020;2020:2402961.

27. Fang X, Li S, Yu H, et al. Epidemiological, comorbidity factors with severity and prognosis of COVID-19: a systematic review and meta-analysis. Aging (Albany NY). 2020;12:12493.

Available online at www.medicinescience.org

ORIGINAL ARTICLE

Medicine Science International Medical Journal

Medicine Science 2021;10(1):262-7

Outcomes of diaphyseal femur fractures treated by long- and short-term traction methods in pre-school children

Savas Camur[1], Haluk Celik[1], Bekir Eray Kilinc[2], Yunus Oc[3], Muhammed Sefa Ozcan[2], Adnan Kara[4]

[1]Health Science University, Umraniye Training and Research Hospital, Department of Orthopaedics and Traumatology, Istanbul, Turkey
[2]Health Science University, Fatih Sultan Mehmet Training and Research Hospital, Department of Orthopaedics and Traumatology, Istanbul, Turkey
[3]Medilife Bağcılar Hospital, Clinic of Orthopaedics and Traumatology Istanbul, Turkey
[4]Medipol Mega University Hospital, Department of Orthopaedics and Traumatology, Istanbul, Turkey

Received 30 November 2020; Accepted 18 January 2020
Available online 18.03.2021 with doi: 10.5455/medscience.2020.11.246

Abstract

This study aimed to compare the effects of the traditional short- and long-term traction methods on the union and angulation of femoral fractures in pre-school children. Thirty-six patients aged 0–6 years, with diaphyseal femur fractures, who had undergone a conservative treatment, were included in the study. The patients were divided into two groups according to their traction times before the application of the hip spica cast: 0–10 days of traction (Group A) and 11–21 days of traction (Group B). After the completion of the union and the removal of the casts, bone scans were performed and the angulations in the coronal and sagittal planes were comparatively evaluated, as well as the lengths of the lower extremities. The mean age of the patients was 4.2 ± 1.94 years. Hip spica casts were applied to 17 patients after short-term traction and 19 patients after long-term traction. The mean length of hospital stays of the patients who were applied the hip spica casts after short-term and long-term tractions were 8.4 and 19.3 days, respectively. A statistically significant difference was observed between groups A and B regarding hospital stay ($p < 0.001$). After the removal of the casts, the angulation values of groups A and B were 13.5 ± 5.28° and 13.69 ± 8.84° in the coronal plane and 14.75 ± 6.66° and 14.46 ± 10.95° in the sagittal plane, respectively. The shortness value of the groups was 1.67 ± 0.75 and 1.56 ± 0.95 cm, respectively. There was no statistically significant difference between both groups in terms of angulation and shortness ($p > 0.05$). Hip spica casting after short-term traction can be used as a safe alternative method in the treatment of diaphyseal femur fractures in preschool children due to its adequate stability and shorter length of hospital stay.

Keywords: Pediatric femur fractures, hip spica cast, traditional method, traction

Introduction

Diaphyseal femur fractures constitute approximately 2% of all childhood fractures, and it is 2.6 times more common in boys than in girls [1]. In school-age children and adolescents, surgical methods such as flexible/rigid intramedullary nails, submuscular plates and fixation with external fixators that allow early mobilisation are preferred in the treatment of isolated diaphyseal femur fractures, while non-surgical methods are more commonly used in pre-school children [2].

Unlike in adults, fractures in pre-school children have a high remodelling capacity due to their developing bone structure, the presence of an open physis and a thick periosteal layer and the fact that they have different biomechanical responses to mechanical pressure. Thus, the conservative treatment has increased success due to this high remodelling capacity [2,3].

Factors such as the patient's age and weight, location of the fracture, degree of angulation and shortness, whether it is an open or a closed fracture and the existence of accompanying fractures and injuries are vital when choosing the treatment method. Several methods such as pavlik harness, closed reduction with immediate spica casting and spica casting after skin and skeletal traction have been described in the conservative treatment of diaphyseal femoral fractures. Recently, closed reduction with immediate casting was preferred over the traditional post-traction spica casting methods

***Coresponding Author:** Savas Camur, Health Science University, Umraniye Training and Research Hospital, Department of Orthopaedics and Traumatology, Istanbul, Turkey . E-mail: savascamur@yahoo.com

due to shorter hospital stay and better outcomes [4]. In the traditional method, traction is performed until the solid callus is formed in the third week, which can also be seen radiologically, and this treatment extends the hospital stay. There is only a limited number of studies on the efficacy of short-term traction application in terms of its shortening of the length of hospital stay [5].

In this study, the treatment outcomes of diaphyseal femur fractures in preschool children using a hip spica cast after a traditional long-term traction versus short-term traction methods were compared in terms of coronal and sagittal plan angulation, leg length inequality and hospital stay. We hypothesised that hip spica casting after short-term traction would yield comparable results as with traditional long term traction, with adequate stability and a shorter length of hospital stay.

Materials and Methods

Ethical approval for the study (with a file number of 06/25/2019-2454) was obtained from our institutional ethics committee, and informed consent could not be obtained from the patients due to the retrospective design of the study.

Ninety-six patients were treated with conservative methods in our hospital between 2001 and 2013. Of the 96 patients, 36 patients with 36 diaphyseal femur fractures who were present for their last follow-up visit were included in the study.

Patients under one year of age and over 6 years, those who underwent immediate reduction with hip spica casting and those with open fractures were excluded from the study.

Hip spica casts were applied under anaesthesia in the operating room after 0–10 days of traction in patients with a shortness of < 2–3 cm in the coronal-sagittal plane and an angulation of < 20 degrees (Figure 1). Traction was conducted for 11–23 days in patients with a shortness of > 3 cm and an angulation of > 20 degrees. Patients who presented a radiological callus in their weekly radiographies, loss of fracture sensitivity and pathological movements were applied the hip spica casts in their own patient wards.

The appropriate traction type was applied according to the fracture line location, patient's age and weight and presence of accompanying injury. Skeletal, split Russell's and Bohler Braun splint tractions were applied to 2, 14 and 20 patients, respectively (Figure 2). Tractions with minimum and maximum weights of 1.5 and 3 kg, respectively, were applied. During the traction treatment, skin and pin base checks were performed at regular intervals.

The main cast position consisted of hip spica casting at approximately 60 to 90 degrees of hip and knee flexion, at 30 degrees of leg abduction and 15 degrees of external leg rotation (Figure 3).

Patients were observed for 24 hours after the hip spica cast application for the evaluation of compartment syndrome and neurovascular complications.

The first radiographs after cast application and radiographs after the cast removal were evaluated. Valgus-varus angulation (coronal angulation) was measured in the anterior-posterior femur radiographs, and anterior-posterior angulations (sagittal angulation) were measured in the lateral radiographs (Figure 4).

Figure 1. Hip spica cast aplication under anestesia

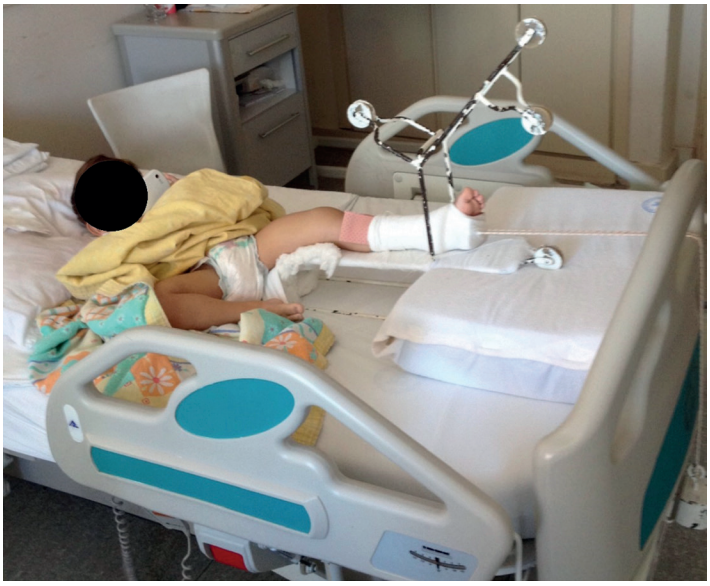


Figure 2. Bohler Braun splint traction

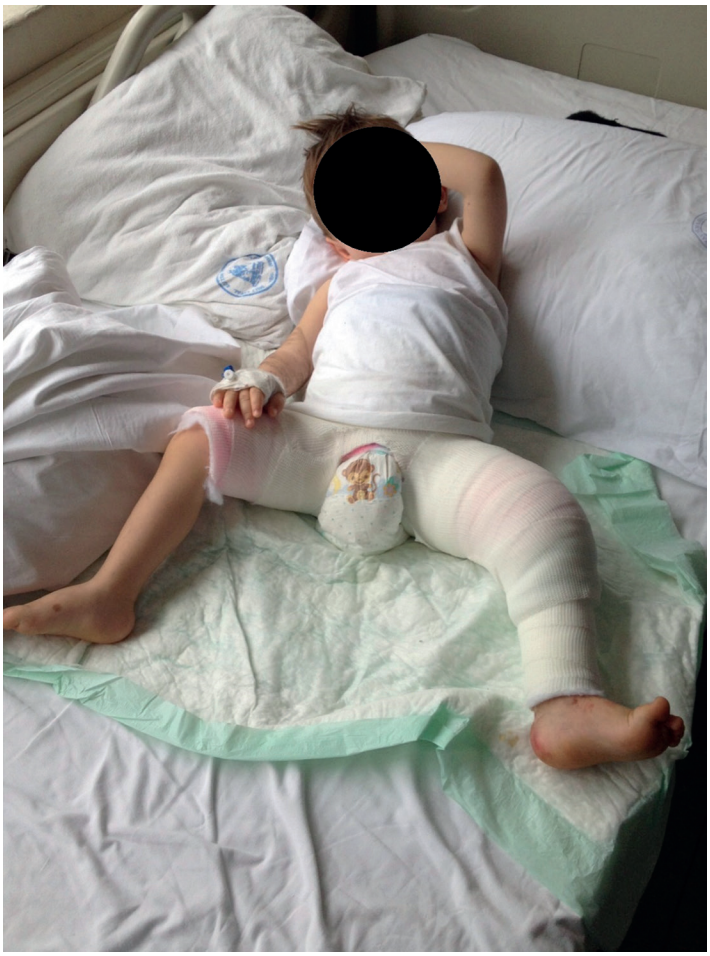


Figure 3. Hip spica cast

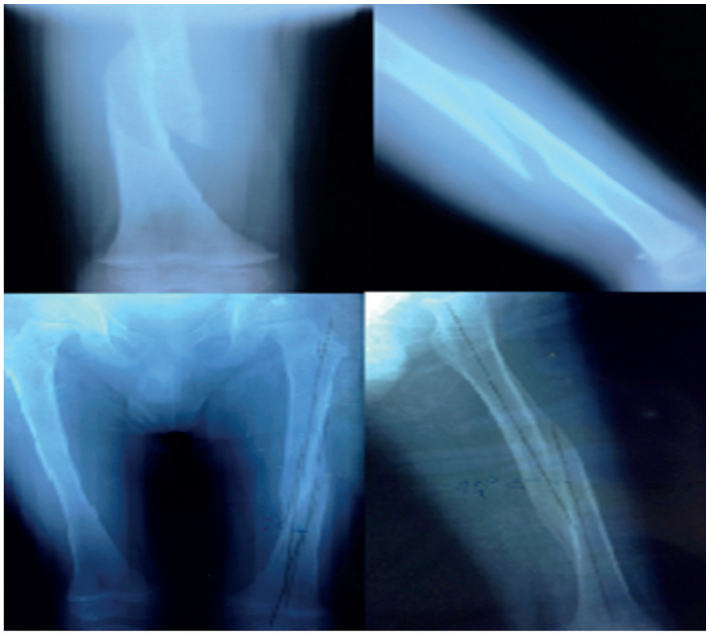


Figure 4. Fracture and the last follow up x- rays

Limp-length inequality was determined through the bilateral measurements and the comparison of the distance between the anterior superior iliac spine and the medial malleolus. Patients were divided into two groups according to their traction time: 0–10 days (Group A) and 11–23 days (Group B). These two groups were compared in terms of limp-length inequality as well as coronal and sagittal angulation.

Statistical methods

All statistical analysis was performed with the statistical software named SPSS ver. 22.0 (IBM-SPSS Inc., Chicago, Illinois). The results were presented as mean ± standard deviation. The Mann-Whitney U Test was used in the measurement of the angulation in coronal and sagittal planes and the duration of hospital stays and cast. A p-value <0.05 was considered statistically significant.

Results

This study included 36 patients; 25 (69.4%) were males and 11 (30.6%) were females. The mean age of the 36 patients was 4.20 ± 1.74 years, and the mean age of the female and male patients was 4.7 and 4 (range, 1–6 years old in both sexes), respectively.

Regarding injury mechanisms among our patients, our findings were as follows: 15 fell at home (41.6%), two fell from stairs (5.5%), three fell from a height (8.3%), two fell in the playground (5.5%), five were injured in a traffic accident outside the car (13,8%), three were injured in a traffic accident inside the car (8.3%), four had a heavy object fall on them (11%) and two had pathological fractures (5.5%) (osteogenesis imperfecta and spina bifida).

Regarding the classification of diaphyseal femur fractures according to their locations, six (16.7%) were located in the proximal, 26 (72.3%) in the middle, and four (11%) in the distal one-third.

Of the 36 patients, 17 were applied closed repositioning and a hip spica cast after short-term (0–10 days) traction, and 19 were applied a hip spica cast following long-term (11–23 days) traction after a callus was observed in the radiograph, fracture sensitivity was noticed on physical examination and the pathological movements were lost.

Traction time was evaluated according to the condition of the fracture, degree of angulation and shortness and the general condition of the patient. The shortest traction time was 3 days as the longest traction time was 23 days.

There was no statistical difference in the angulation and shortness measurements between the cases with the short traction time (0–10 days) and long traction time (11–23 days) after the removal of the cast ($p > 0.05$) (Table 1).

The casts were checked during the routine follow-up visits of the patients, and the fracture line and fracture alignment were

examined using the radiographs. The mean casting time of the group A and B patients were 6.47 ± 1.00 (5–8) and 4.84 ± 0.68 (4–6) weeks, respectively. After the plaster was removed, patients were gradually allowed weight-bearing.

Table 1. Comparison of shortness an angulation of two groups

After the cast removal	Traction Time		*P**
	0-10 Days (n=17) Mean±SD (median)	11-23 Days (n=19) Mean±SD (median)	
Angulation AP	13.50±5.28 (13.00)	13.69±8.84 (10.00)	0.682
Angulation LAT	14.75±6.66 (12.50)	14.46±10.95 (10.00)	0.247
Shortness	1.67±0.75 (1.75)	1.56±0.95 (1.50)	0.561

* Mann-Whitney U Test

Discussion

There are many surgical and non-surgical treatment methods for paediatric femoral fractures, and none of them have a certain superiority over the other. There has been a tendency of using surgical methods for treating paediatric fractures that can be treated with conservative methods [6]. Among these treatment options, only the method of acute casting and delayed casting after traction have level 2 evidence in the guideline that was published by the American Academy of Orthopedic Surgeons (AAOS) for pre-school childhood period (from 6 months to 5 years old). Evidence levels of all other surgical and non-surgical methods are controversial and lower in all age groups [7,8].

Non-surgical methods include pavlik harness application, immediate casting and delayed casting. The treatment method depends on many factors such as age, weight, swelling condition of the extremity and the surgeon's experience.

In recent years, closed reduction with immediate hip spica casting has become increasingly common among the non-surgical treatment methods in preschool children instead of the delayed hip spica casting. The most important advantage of closed reduction with immediate hip spica casting is that it shortens the length of hospital stay. This is a more cost-effective method, which is more affordable in terms of hospitalisation expenses and has social advantages for the child and family [9]. Close follow-up is required after the procedure, especially in the first weeks until the formation of the soft callus (7-12 days), when adequate fracture stability has been achieved [10,11]. The disadvantage of immediate spica cast is the need for re-reductions and cast changes due to the loss of reduction and shortening in this period [12]. Illgen et al. and Thelogis reported a reduction loss of 21.7% and 27%, respectively, and that new surgical and non-surgical interventions were needed due to this loss [13]. This finding indicates that a loss of reduction occurs in one patient out of every 4–5 patients; however, in our study, none of our patients who were applied traction required any additional interventions due to a loss of reduction during the follow-ups.

Although the treatment protocol may be different in each case, post-traction casting in patients with high degrees of angulation and shortness is a successful and reliable method and is used as the primary treatment method for those who do not have any surgical indication. Several studies reported that traction and hip spica casting are safe treatment methods, having a low rate of complications such as limb-length inequality and angular deformity in paediatric closed diaphyseal femur fractures [14,15].

Diaphyseal femur fractures in preschool children can easily tolerate 15 degree of coronal and 20 degree of sagittal plane angulations and a shortness of up to 2 cm due to their high remodeling potential [16].

In our study, the coronal and sagittal plane angulations and shortness values, which were obtained after the cast removal, were reported to be within the acceptable limits. There was no statistical difference between the two methods regarding angular deformities and lower limb length inequalities. ($p > 0.05$).

In our study, the shortness in the group B patients was found to be > 2–3 cm and angulation was > 20 degrees, indicating decreased soft tissue support and increased fracture instability. However, we believe that a traction period of 7–12 days will provide sufficient reduction of the fracture, and the combination of the soft callus, which is formed during this period, and the hip spica cast can provide adequate stability as the solid callus, which is formed during long-term traction.

Long hospital stay is the disadvantage of post-traction spica cast treatment, and it also has negative psychosocial effects on children and families and increases treatment costs. In most studies, post-traction spica cast treatment was reported to have a higher cost than all other treatment methods [17,18]. Serin et al., in a series of 61 cases, found that the mean traction duration was 19.8 days (16–26 days) in 31 patients who underwent traction and were applied spica casts [19].

In our study, the mean hospitalisation time of the patients who were applied hip spica cast after short-term traction (group A) was 8.4 days, and the mean hospitalisation time of the patients who received the conventional long-term traction and were applied hip spica cast was 19.3 days ($p < 0.0001$). Spica cast treatment after short-term traction reduces the length of hospital stay, negative psychosocial effect on children, burden on the hospital management and expenses of the patient's family, similar to immediate spica casting application when compared to traditional casting after long-term traction.[20-22].

Simple complications such as plaster softening, soiling and superficial skin irritation are more frequent, especially in patients treated with early hip spica cast [23]. Rarely, hip spica casting has serious complications such as superior mesenteric artery syndrome, peroneal nerve damage and compartment syndrome [24]. In our study, no significant complications requiring a cast revision (wedging or removing and re–spica casting) were encountered, since the cast was applied after the swelling had resolved.

The retrospective nature of the study and the small number of patients in the two groups are among the limitations of the present study. Besides, the fact that we perform the casting process under sedation in the short-term traction method creates a disadvantage in terms of anaesthesia risks and costs compared to the long-term traction method [25].

Conclusion

Preschool childhood diaphyseal femur fractures can be successfully treated using many conservative treatment methods. Due to its sufficient stability and short length of hospital stay, hip spica cast application after short-term traction can be used as a safe alternative method to immediate hip spica casting and hip spica casting methods after traditional long-term traction.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
All authors declare no financial support.

Ethical approval
Ethical approval for this study (with a file number of 25/06/2019-2454) was obtained from Şişli Hamidiye Etfal Clinical Research Ethics Committee, and informed consent was obtained from all patients prior to the study.

References

1. Rewers A, Hedegaard H, Lezotte D, et al. Childhood femur fractures, associated injuries, and sociodemographic risk factors: a populationbased study. Pediatrics. 2005;115:543-52.

2. Khoriati, AA, et al. The management of paediatric diaphyseal femoral fractures: a modern approach . Strategies Trauma Limb Reconstr. 2016;11:87-97.

3. Harvey AR, Bowyer GW, Clarke NMP. The managementof paediatric femoral shaft fractures. Curr Orthop. 2002;16:293–9.

4. P. González-Herranz Et al Diaphyseal femur fractures in children. Treatment update. Rev Esp Cir Ortop Traumatol. 2011;55:54-66.

5. Aksoy B ,Ozturk K, Kara A N, Olcay E, Güven B, Şener B T. Çocuk femur cisim kırıklarının pelvi-pedalik alçı içinde cilt traksiyonu ile tedavisi ve erken sonuçları. Acta Orthop Traumatol Turc.1996;30:128-31.

6. Wilkins KE. Operative management of children's fractures: is it a sign of impetuousness or do the children really benefit? J Pediatr Orthop. 1998;18:1-3.

7. Kocher MS, Sink EL, Blasier RD, et al. American academy of orthopaedic surgeons- clinical practice guideline on treatment of pediatric diaphyseal femur fracture. J Am Acad Orthop Surg. 2009;17:718–25.

8. Khoriati AA, Jones A, Gelfer Y, Trompeter A. The management of paediatric diaphyseal femoral fractures: a modern approach. Strategies Trauma Limb Reconstr. 2016;11:87–97.

9. D'Ollonne T, Rubio A, Leroux J, Lusakisimo S, Hayek T, GriffetJ. Early reduction versus skin traction in the orthopaedic treatment of femoral shaf t fractures in children under 6 years old. J Child Orthop. 2009;3:209–15.

10. Serin S. Kılıçoğlu,Mikroskobi düzeyinde kırık iyileşmesi. Ankara Üniversitesi Tıp Fakültesi Mecmuası.2002;55:143-50.

11. Dokmeci MO, Kalender AM, Sevimli R, et al.The effect of ibandronate on fracture healing in rat tibia model .SM J Orthop. 2016;2:1041.

12. Podeszwa DA, Mooney JF III, Cramer KE, et al. Comparison of Pavlik harness application and immediate spica casting for femur fractures in infants. J Pediatr Orthop. 2004;24:460-2.

13. Illgen R 2nd, Rodgers WB, Hresko MT, et al. Femur fractures in children: Treatment with early sitting spica cast. J Pediatr Orthop. 1998;18:481–7.

14. Aranson DD, Singer RM, Higgins RF. Skeletal traction for fractures of the femoral shaft in children.a long term study. J Bone Joint Sug Am. 1987;69:1453-9.

15. Casas J,Gonzales-moran G, Albiana J.Femoral fractures in children from 4 years to 10 years: conservative treatment. J Pediatr Orthop B. 2001;10:56-62.

16. Wallace ME, Hoffman EB. Remodelling of angular deformity after femoral shaft fractures in children. J Bone Joint Surg Br. 1992;74:765–9.

17. Newton PO, Mubarak SJ. Financial aspects of femoral shaft fracture treatment in children and adolescents. J Pediatr Orthop. 1994; 14: 508-512.

18. Nork SE, Hoffinger SA. Skeletal traction versus external fixation for pediatric femoral shaft fractures. A comparison of hospital costs and charges. J Orthop Trauma .1998;12:563-8.

19. Serin E,Yılmaz E, Belhan O. Çocuk Femur Cisim Kırıklarının Tedavi Sonuçları. Hacettepe Ortopedi Dergisi .2001;11:65-70.

20. Ferguson J,Nicol RO. Early spica treatment of pediatric femoral shaft fractures.. J Pediatr Orthop. 2000;20:189-92 .

21. Sarkar S, Bandyopadhyay R, Mukherjee A. Titanium elastic nail - Complications in the treatment of paediatric diaphyseal fracture of femur. Open Orthop J. 2013;7:12-7.

22. Reeves RB, Ballard RI, Hughes JL. Internal fixation versus traction and casting of adolescent femoral shaft fractures. J Pediatr Orthop. 1990;10:592-5.

23. Younis MH, Mahmoud K, Kawas A, Ibrahim T. Early versus late hip spica casting for paediatric femoral shaft fractures. J Pediatr Orthop B. 2019;28:122–6.

24. Tisherman RT, Hoellwarth JS, Mendelson SA. Systematic review of spica casting for the treatment of paediatric diaphyseal femur fractures. J Child Orthop. 2018;12:136-44.

25. Rabattu P-Y, Courvoisier A, Bourgeus,E , Eid A, Durand C, Griffer J. Spica cast as an alternative to general anesthesia for lower limb MRI in young children. J Orthop Trauma. 2014 ;15:55–8.

Available online at www.medicinescience.org

CASE REPORT

Medicine Science International Medical Journal

Medicine Science 2021;10(1):226-9

Tuberculous tenosynovitis involving wrist and extensor compartment of the forearm: Case presentation

Ali Yuce[1], Bulent Karslioglu[2], Mustafa Yerli[2], Suleyman Semih Dedeoglu[2], Yunus Imren[2], Hakan Gurbuz[2]

[1]*Basaksehir Pine and Sakura City Hospital, Department of Orthopedic and Traumatology, Istanbul, Turkey*
[2]*Prof. Dr. Cemil Tascioglu City Hospital, Department of Orthopedic and Traumatology, Istanbul, Turkey*

Received 20 September 2020; Accepted 02 November 2020
Available online 17.01.2021 with doi: 10.5455/medscience.2020.09.192

Abstract

Musculoskeletal tuberculosis is a rare form of extrapulmonary tuberculosis, constituting <10% of cases even in developing countries. Diagnosis and treatment are usually delayed due to non-specific findings. In this case report, we presented a 55-year-old male butcher who had complaints of pain and tenosynovitis at the dorsal side of the right wrist after trauma, for which we performed surgery upon diagnosis of ganglion cyst secondary to steroid injection. The patient had developed a second lesion on the forearm of the same extremity while waiting for the initial report of the biopsy specimen, which showed positive Ziehl-Neelsen staining, necrotizing granulomatous inflammation, caseating necrosis. No growth was detected in the culture. The patient received anti-tuberculosis treatment for 12 months and no recurrence was observed at a 1-year follow-up. Since tuberculous tenosynovitis can be confused with other diseases, the diagnosis may be established late. Contraindicated procedures such as corticosteroid injection can be applied to the patient due to inaccurate pre-diagnosis, which may activate the disease. It may be important to suspect this disease considering the risk factors and occupational group. Performing ultrasonography and biopsy with a pre-diagnosis of tuberculosis can be a guide for early diagnosis and treatment.

Keywords: Extensor compartment, forearm, tuberculous, tenosynovitis, wrist

Introduction

Musculoskeletal tuberculosis is a rare form of extrapulmonary tuberculosis, constituting <10% of cases even in the developing countries [1,2]. This form typically involves flexor tendons while dorsal involvement might also be observed [1-3]. Diagnosis and treatment are usually delayed due to non-specific findings[4],which may result in unwanted complications[5,6].

Case Presentation

A 55-year-old male butcher was admitted to the outpatient clinic with a complaint of pain at the dorsal side of his right wrist persisting for 1 month after trauma. The pain was described to occur with wrist movements.Medical history showed diabetesmellitus and alcoholism. During the physical examination, there wastenderness on compression of the dorsum of the wrist and direct radiography revealed degenerative changes.

***Corresponding Author:** Mustafa Yerli, Prof. Dr. Cemil Tascioglu City Hospital, Department of Orthopedic and Traumatology, Istanbul, Turkey.
E-mail: mustafayerli199@gmail.com

The patient was initially prescribed nonsteroidal anti-inflammatory drugs with splinting and cold application. Upon presenting with persisting pain afterone month, blood parameters and ultrasound images were studied: WBC, 8.94 x 103/L (reference: 4-10); C-reactive protein, 4 mg/L; uric acid, 6.4 mg/dL, RF, 0;Rose-Bengal test, (-);and ESR: 18 mm/h, while ultrasonography (USG) was consistent with tenosynovitis.The patient received a corticosteroid injection for this diagnosis. The patient, whose complaints were relieved after a steroid injection, was applied to the outpatient clinic with swelling of the dorsum of the wrist after 2 months.A suspected diagnosis of ganglion cyst was confirmed on USG with additional diffuse tenosynovitis surrounding the cyst. The patient was scheduled for surgical intervention, which showedrice bodies within the cyst after vertical incision (Figure 1). Cyst and rice bodies were excised and tenosynovectomy was performed. Histocytologicalexamination revealed necrotizing granulomatous inflammation and caseating necrosis with histiocytesas well as PAS (-) and Ziehl-Neelsen (+) staining (Figure 2). The primary diagnosis was tuberculosis infection. The culture result was negative, andthe PPD test showed a diameter of 2mm. No lesion was detected in the chest X-ray. Meanwhile, a second lesion had

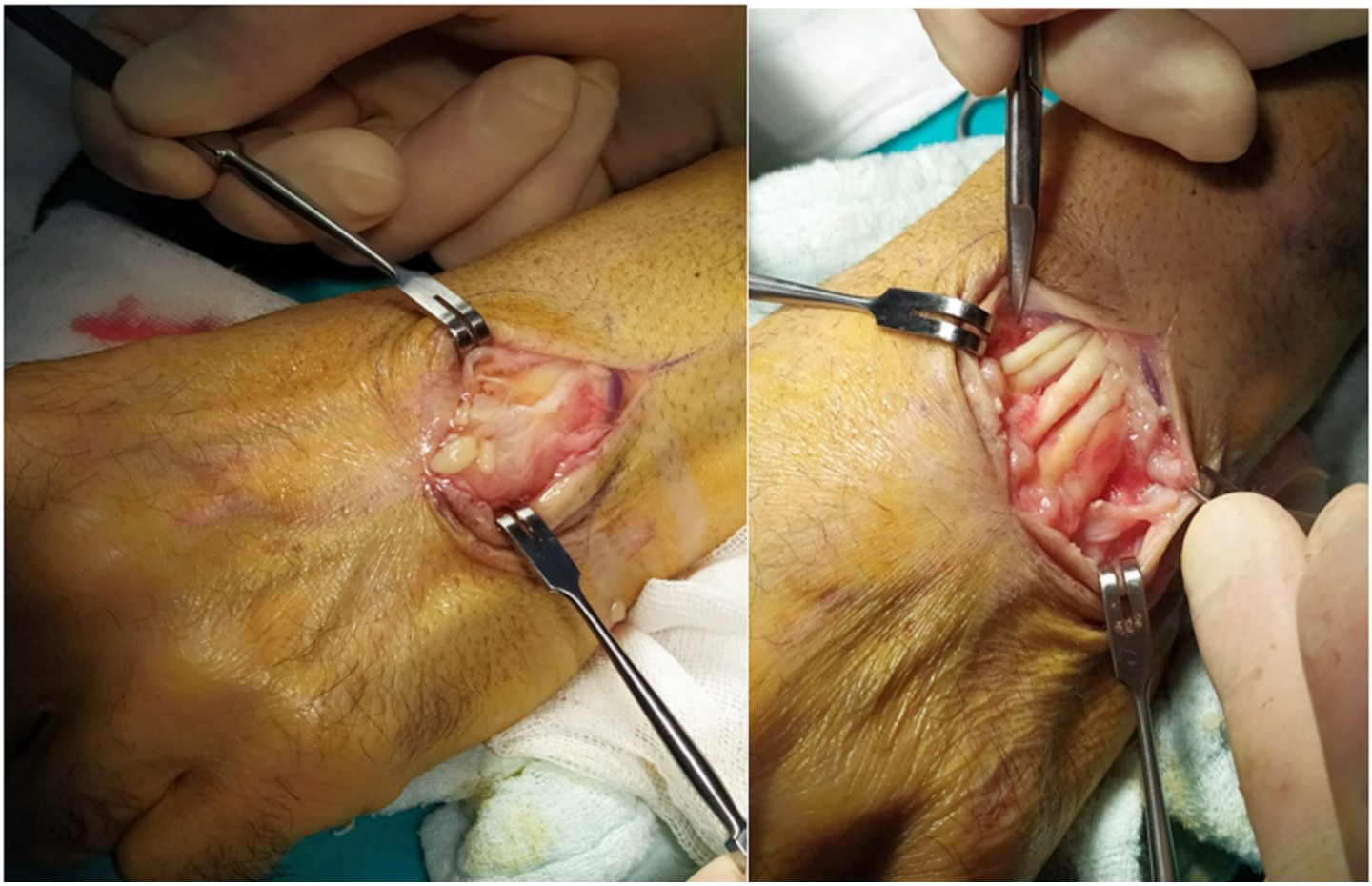


Figure 1. Rice bodies were observed after the opening of the extensor retinaculum (left). The appearance after total tenosynovectomy and debridement (right).

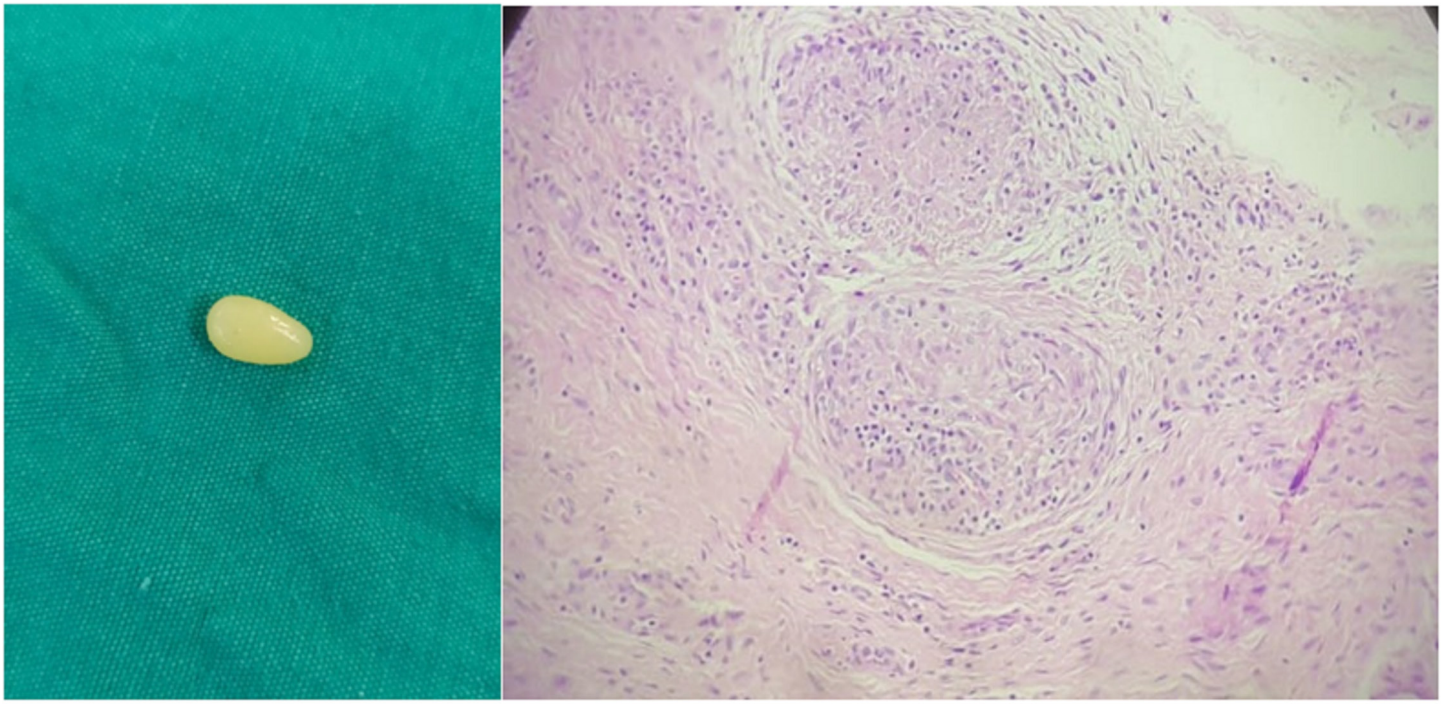


Figure 2. Macroscopic (left) and microscopic (right) appearance of the rice bodies.

occurred on the dorsal of the forearm along the axis of the extensor tendons. USG findings with suspected tuberculosis support the diagnosis. The patient was initiated on a 4-drug antituberculosis regimen (rifampicin, isoniazid, ethambutol, pyrazinamide), which was continued with dual therapy with rifampicin and isoniazid after the second month to continue till 12 months. The second lesion on the forearm disappeared in the third month of treatment. No recurrence was observed at 1-year follow-up.

Discussion

Tuberculous tenosynovitis, which usually affects the flexor tendons of the wrist, is an important public health problem, especially in developing countries [6]. Nevertheless, digital flexor sheaths, and the dorsal side of the wrist might also be involved [7]. The diagnosis of tuberculous tenosynovitis is often delayed due to a wide variety of differential diagnoses, including other atypical mycobacterial infections, tuberculosis, systemic lupus erythematosus, pyogenic infections, brucellosis, foreign body tenosynovitis, osteoarthritis, and rheumatoid arthritis [6]. Such delayed diagnosis eventually may lead to serious joint and tendon damage and the spread of mycobacteria to the surrounding bursa, muscle, and other soft tissues [8]. The typical risk factors for tuberculosis include >60 years of age, previous trauma, corticosteroid injections, low socioeconomic status, alcoholism, and immunosuppression [4,9]. While being a risk factor and contraindicated, corticosteroid injections could even be performed for other potential diagnoses as such administration is a nonspecific practice [9]. Our case was a diabetic patient with a history of alcoholism, and his complaints started after trauma. Also, corticosteroid injection was applied due to nonspecific findings, which resulted in wrist edema at the dorsal side. Corticosteroid injection may likely have accelerated the progression of tuberculosis involvement in this area.

Wrist tuberculosis may be associated with several occupations like butchery [9]. However, a dorsal lesion may mimic ganglion cysts. This is one of the situations that can cause a delay in diagnosis; where the initial step in workup is to perform USG. Rice bodies can be detected as a low-level internal echo but it is possible that USG may not distinguish rice bodies [1,4,10]. In our case, which was a butcher, USG was performed after edema development at the wrist and could not differentiate it from ganglion cyst. This differentiation was only revealed after the pre-diagnosis of tuberculous tenosynovitis in the forearm extensor side lesion which developed after the biopsy. Perhaps it is possible to suspect this disease early in the diagnostic work-up in at-risk populations and to inform radiologists before USG. This may yield more accurate reports and help surgeons for early diagnosis and consequent prompt initiation of the treatment.

MR has been reported to help in ruling out differential diagnoses and as a reliable tool for early diagnosis, especially if performed with gadolinium injection [5]. In our study, MR could not be performed due to the hospital protocol. It is possible that the diagnosis can be supported by contrast-enhanced MR in case of doubt and no differentiation by USG could be achieved.

In the early stages of the disease, the clinical and radiological findings may mimic those of arthritis; therefore, biopsy and culture specimens should be obtained from rice bodies for definitive diagnosis [3,11]. Tuberculosis is diagnosed based on histopathological and microbiological examinations. Caseous granulomas, tuberculosis bacilli, and multinucleated Langerhans giant cells may be seen in the histological evaluation of these fibrinous loose bodies. Microbiological studies are generally not sufficient to establish the diagnosis. Hand tuberculosis is a paucibacillary lesion. For this reason, smear, Ziehl-Neelsen staining, and tuberculosis cultures in Lowenstein and BACTEC media are often negative in extrapulmonary involvement [3]. We also detected similar findings in microscopic examination of our case, but with a positive Ziehl-Neelsen staining. However, there was no growth in culture. Considering the delays in diagnosis in our case and establishment of the definitive diagnosis only after biopsy, we suggest that suspicion of tuberculosis and immediate decision for a biopsy is critical in tenosynovitis cases with risk factors for tuberculosis and inaccurate radiological findings.

Simultaneous active pulmonary tuberculosis is present in less than half of patients with wrist tuberculosis [8]. If remain untreated, tuberculosis leads to severe joint and tendon damage and dissemination of the mycobacteria of the surrounding bursa, muscles, and other soft tissues [8]. Tendon tuberculosis may occur due to direct transmission of the infectious agent or via hematogenous spread [8]. Multifocal involvement was reported previously in a case presentation, where the underlying mechanism was suggested to be direct inoculation or inoculation from the culprit tuberculous lesion in the pulmonary/genitourinary system [5]. In our study, we did not detect pulmonary involvement in thorax computed tomography. Considering the job of the patient, the infection might have occurred via direct transmission. It is also possible that the second lesion might have developed after dissemination through the tendon sheath after being aggravated secondary to the corticosteroid injection.

Case reports are emphasizing the importance of surgical treatment as a biopsy tool for early diagnosis and early chemotherapy; while some advocated performing synovectomy, surgical lavage, curettage, and debridement as part of the treatment [1-4,11]. In our case, surgical debridement, lavage, synovectomy was applied to the lesion on the dorsal of the wrist, and no surgical intervention was performed on the forearm lesion. Three months of chemotherapy provided remission also in the forearm lesion where tenosynovectomy and debridement were not performed. The critical benefit of surgical intervention in tuberculous tenosynovitis maybe its contribution to early diagnosis and initiation of the treatment through the obtainment of biopsy, rather than its potential help to the disease management by tenosynovectomy and debridement. We think that surgery can contribute more to the treatment in selected cases accompanied by nerve entrapment, pain affecting the quality of life, functional impairment, or restricted range of motion.

Conclusion

The diagnosis of tuberculous tenosynovitis can be established late due to confusion with other diseases. Contraindicated procedures such as corticosteroid injection can be administered to the patient due to inaccurate pre-diagnoses, which may reactivate the infection. The most important factor in the treatment of tuberculous tenosynovitis may be to suspect this disease in patients with risk factors in endemic regions. Performing USG and biopsy with this pre-diagnosis could be a guide for early diagnosis and treatment.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
All authors declare no financial support.

Patient informed consent
Written informed consent was obtained from study participant.

References

1. Rampal K, Prajapati DK, Sharma M, et al. Tubercular tenosynovitis of extensor tendon of wrist mimickinga ganglion. Int J Intg Med Sci. 2016;3:318-20.
2. Sevimli R, Karakaplan M, Korkmaz MF, et al. Resection arthroplasty in shoulder joint tuberculosis: A Case Presentation. Ann Case Rep. 2016;1:1-3.
3. Kabakaş F, Uğurlar MD. Turan DB, et al. Flexor tenosynovitis due to tuberculosis in hand and wrist is tenosynovectomy imperative? Ann Plast Surg. 2016;77:169-72.
4. Miladi S, Dhahri R, Hamdi W, et al. Wrist synovectomy confirmed tuberculous tenosynovitis in 8 cases: A follow-up study. Egypt Rheumatol. 2016;38:257-61.
5. Amine B, Benbouazza K, Bahiri R, et al. Multifocal tuberculous tenosynovitis. Joint Bone Spine. 2006;73:474-5.
6. Shareef AJ, Sreehari CK, Subbaraya B, et al. Extensors tenosynovitis of wrist with rupture of extensor digitorum: rare presentation of tuberculosis. Int Surg J. 2015;2:398-401.
7. Baidoo PK, Baddoo D, Ocloo A, et al. Tuberculous tenosynovitis of the flexor tendons of the wrist: a case report. BMC Res Notes. 2018;11:238.
8. Freitas T, Couto A, Lopes M, et al. Tuberculous tenosynovitis of the wrist and hand- a case report. MOJ Orthop Rheumatol. 2016;6:222.
9. Guner MD, Bektas U, Akmese R, et al. Wrist tenosynovitis due to Mycobacterium bovis infection: case series and review of the literature. Plast Reconstr Surg Global Open. 2015;2:262.
10. Sbai MA, Benzarti S, Msek H, et al. Pseudotumoral form of soft-tissue tuberculosis of the wrist. Int J Mycobacteriol. 2016;5:99-101.
11. Lashkare D, Gaur TNS, Moolchandani D, et al. Chronic tenosynovitis of extensors of hand. PJSR. 2018;11:74-7.

Available online at www.medicinescience.org

CASE REPORT

Medicine Science International Medical Journal

Medicine Science 2021;10(1):230-2

Restricted diffusion of the corpus callosum in extensive neonatal hypoxic–ischemic encephalopathy

Gunay Rona[1], Meral Arifoglu[1], Hediye Pinar Gunbey[1], Ufuk Yukselmis[2]

[1]University of Health Sciences, Kartal Lutfi Kirdar Training and Research Hospital, Department of Radiology, Istanbul, Turkey
[2]University of Health Sciences, Kartal Lutfi Kirdar Training and Research Hospital, Department of Pediatrics, Istanbul, Turkey

Received 29 July 2020; Accepted 02 November 2020
Available online 17.01.2021 with doi: 10.5455/medscience.2020.07.152

Abstract

Hypoxic-ischemic encephalopathy (HIE) is a devastating brain injury that may result in death and severe neurologic deficits. Corpus callosum (CC) involvement, especially its entire involvement, is very rare in HIE. A 41-week-old male term neonate had a difficult delivery and developed cardiac arrest after birth. His Apgar scores were low in the first 10 minutes. The magnetic resonance imaging (MRI) showed high signal intensity in bilateral basal ganglia, bilateral thalami, temporofrontal cortex, subcortical white matter, perirolandic region, and the entire corpus callosum in T1 sequences. Restricted diffusion was noted on the diffusion-weighted imaging (DWI) images of all these regions. CC is affected in cases of severe and advanced brain injury, and especially splenial lesions have poor outcomes. Entire CC involvement may lead to worse clinical presentation and can serve as an early neuroradiologic marker.

Keywords: Hypoxic ischemic encephalopathy, corpus callosum, Magnetic Resonance Imaging(MRI), restricted diffusion

Introduction

Neonatal hypoxic-ischemic encephalopathy (HIE) is a serious condition that develops as a result of decreased cerebral blood flow and decreased blood oxygenation, resulting in death or deep neurological deficit.

In severe hypoxia, metabolically more active regions such as deep gray matter structures (basal ganglia and thalamus) are earlier and more severely affected by oxidative stress. In the case of partial hypoxia, where blood oxygenation is prolonged and partially decreased, blood flow is directed through shunting towards the brainstem, cerebellum, hippocampus, and deep gray matter, which are more vital structures of the brain, and these regions are protected. The cerebral cortex and white matter, which are metabolically less active, are affected, and the involvement is observed especially in more hypoperfused inter-vascular boundaries (watershed zone) [1,2]. The corpus callosum and particularly the splenium region are sensitive to hypoxia. Corpus callosum involvement is more common in severe and advanced HIE cases.

***Corresponding Author:** Gunay Rona, University of Health Sciences, Kartal Lutfi Kırdar Training and Research Hospital, Department of Radiology, Istanbul, Turkey. E-mail: gunayrona@gmail.com

The corpus callosum is the major pathway of association fibers between the two cerebral hemispheres. Various pathologies such as neonatal seizures, hemolytic-uremic syndrome with encephalopathy, neonatal hypoglycemia, an antiepileptic drug, therapy, epilepsy, viral encephalitis, demyelinating disorders, and many other conditions can affect the corpus callosum and cause restricted diffusion in the corpus callosum.[3,4].

In the literature, corpus callosum involvement has been rarely addressed in HIE cases. In most cases, some components of the corpus callosum, especially the splenium, are involved, whereas very few cases of its entire involvement have been reported in articles.

Case report

A 41-week-old term male neonate was referred to our clinic with suspicion of perinatal asphyxia and HIE after birth. It was learned from the patient's history that he had a difficult and prolonged vaginal delivery. His 1-min Apgar score was noted as 3, 5-min Apgar score as 4, and 10-min Apgar score as 7. His birth weight was 3635 g and his clinical examination was evaluated to be consistent with asphyxia. Immediately after birth, he was resuscitated and initiated on treatment in intensive care conditions.

His bedside cranial ultrasound (US) examination performed on a postpartum day 1 revealed obliterated sulci and cisternae consistent with diffuse cerebral edema, narrow CSF space, and ventricles, and disrupted gray-white matter junction. No intracranial hemorrhage was visualized. In addition to the US findings, the cranial computed tomography (CT) obtained after birth showed a pseudo sac and white cerebellum signs consistent with cerebral edema. No hemorrhage was noted on the CT examination (Figure 1).

The MRI examination performed on a postpartum day 6 showed a diffuse signal increase in bilateral basal ganglia, bilateral thalami, bilateral temporofrontal cortical and subcortical white matter, perirolandic region, and corpus callosum on the T1-weighted images (Figure 2). Again, in these regions, there was a signal increase consistent with diffusion restriction on the DWI images, and a signal decrease in the apparent diffusion coefficient (ADC) map (Figure 3). A large area of caput succedaneum was present in the fronto-parieto-occipital junction on the right. The clinical history, examination, and imaging findings of the patient were evaluated to be consistent with HIE.

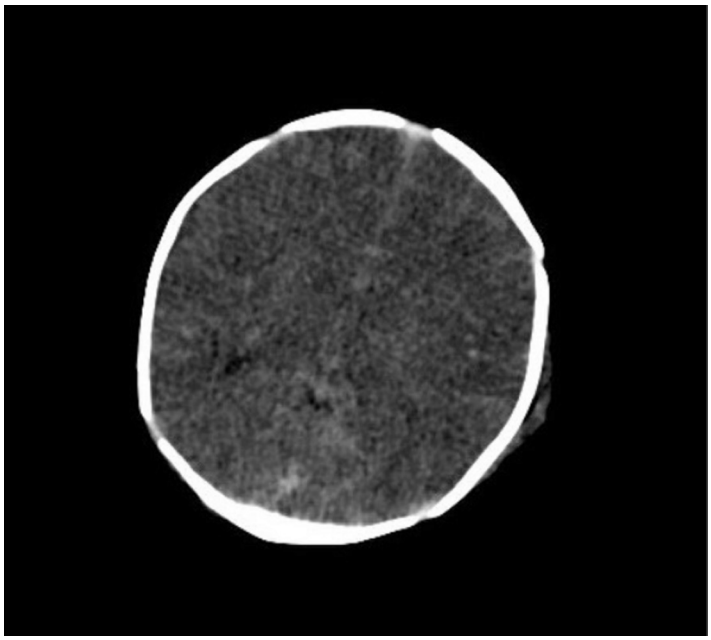


Figure 1. The CT findings demonstrated effacement of hemispheric cortical sulci, narrowing of lateral ventricles, disruption in the separation of White and gray matter compatible with CT brain edema, and pseudo sac appearance in the interhemispheric fissure.

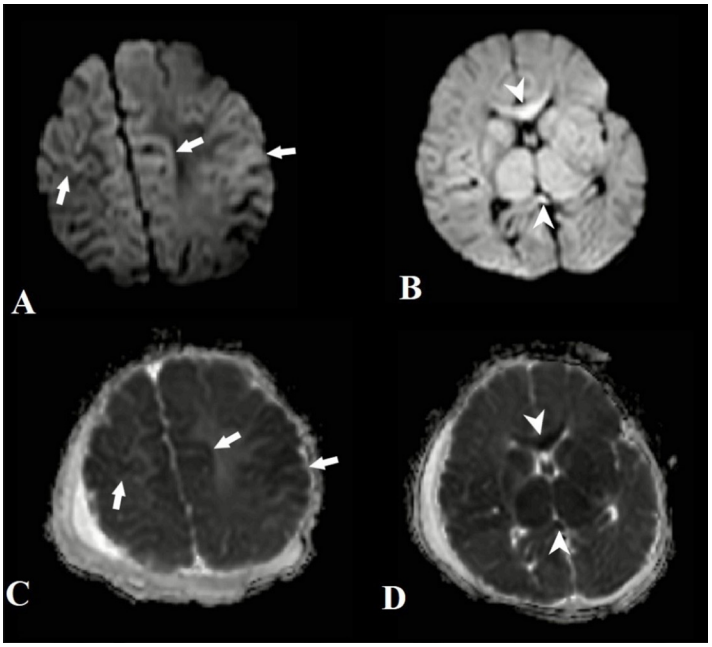


Figure 3. Diffusion restriction of perirolandic area (arrows, A, C) and corpus callosum (arrowheads, B, D) with DWI hyperintense and ADC hypointense signal changes.

Discussion

In HIE cases, corpus callosum involvement is an indicator of severe neurological deficit and death[5,6]. Takenouchi et al. found diffusion restriction in the splenium of the corpus callosum in 29% of the HIE patients in their study. They observed that these patients had a worse prognosis than those without diffusion restriction in the splenium [7]. In our case, diffuse brain injury was present and the corpus callosum was entirely affected. In cases where the corpus callosum is entirely affected, it may lead to a much more severe clinical presentation compared to partial involvement [7].

As neonates with suspicion of HIE mostly require treatment in intensive care conditions. The US a portable examination, is the first-line modality. However, its low sensitivity, practitioner-dependency, and the low probability of demonstrating the lesions in the cerebral convexity reduce success. CT involves ionizing radiation and is not sensitive in detecting non-hemorrhagic injury. MR is the most sensitive modality among the examinations. MRI

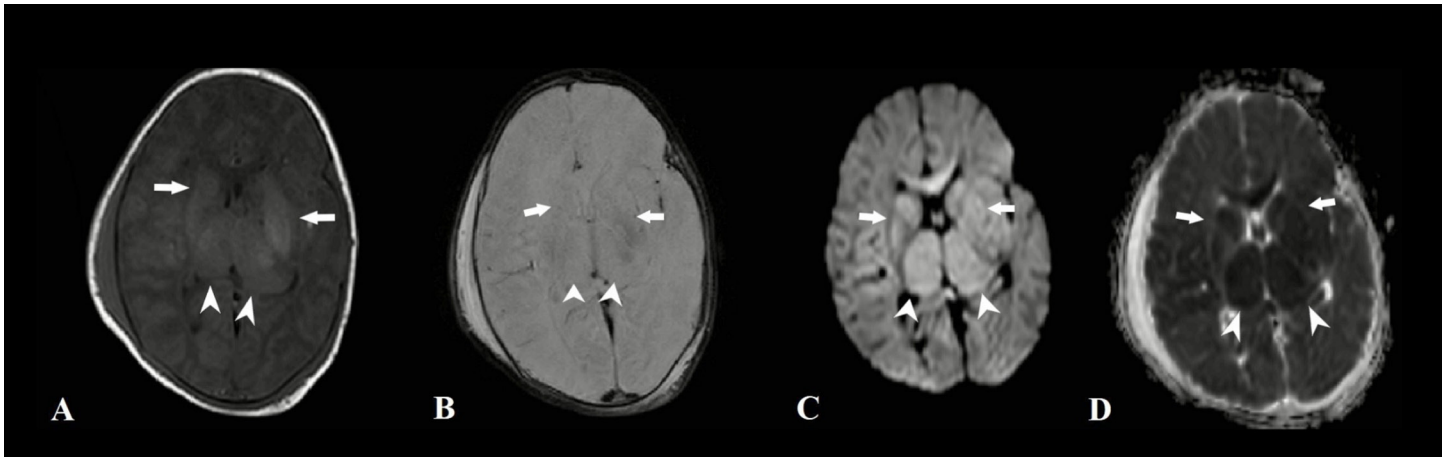


Figure 2. Bilateral basal ganglia (arrows) and thalamus (arrowheads) signal changes as hyperintense on T1W (A), iso-hypointense on T2W (B), hyperintense on DWI (C), and hypointense on ADC (D) images.

examination should include at least T1, T2, DWI sequences, and ADC map. In the affected parts, high signal intensity is visualized in T1-weighted sequences. Diffusion-weighted images show restriction due to cytotoxic edema. Among the MRI sequences, diffusion-weighted images show the findings at the earliest; however, they may be negative in some cases. On DWI sequences the findings reach the maximum level of significance in 3-5 days [8-11].

Diffusion-weighted MRI manifests early in hypoxic encephalopathy and can detect more detailed involvement of corpus callosum, which is a sign of poor prognosis.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
All authors declare no financial support.

Patient informed consent
We took oral consent from patient's parents.

References

1. Barkovich AJ. Brain and spine injuries in infancy and childhood. In: Barkovich AJ, ed. Pediatric neuroimaging. 4th ed. Philadelphia, Pa: Lippincott Williams & Wilkins, 2005;190-290.
2. Ashwal S, Majcher JS, Vain N, et al. Patterns of fetal lamb regional cerebral blood flow during and after prolonged hypoxia. Pediatr Res. 1980;14:1104-10.
3. Takanashi J, Barkovich AJ, Shiihara T, et al. Widening spectrum of a reversible splenial lesion with transiently reduced diffusion. AJNR Am J Neuroradiol. 2006;27:836-8.
4. Volpe J. Neurology of the Newborn. 5th ed. Philadelphia: Saunders; 2008
5. Kale A, Joshi P, Kelkar AB. Restricted diffusion in the corpus callosum: A neuroradiological marker in hypoxic-ischemic encephalopathy. Indian J Radiol Imaging. 2016;26:487-92.
6. Nagy Z, Lindström K, Westerberg H, et al. Diffusion tensor imaging on teenagers, born at term with moderate hypoxic-ischemic encephalopathy. Pediatr Res. 2005;58:936-40.
7. Takenouchi T, Heier LA, Engel M, et al. Restricted diffusion in the corpus callosum in hypoxic-ischemic encephalopathy. Pediatr Neurol. 2010;43:190-6.
8. Forbes KP, Pipe JG, Bird R. Neonatal hypoxic-ischemic encephalopathy: detection with diffusion-weighted MR imaging. AJNR Am J Neuroradiol. 2000;21:1490-6.
9. Huang BY, Castillo M. Hypoxic-ischemic brain injury: imaging findings from birth to adulthood. Radiographics. 2008;28:417-617.
10. Robertson RL, Ben-Sira L, Barnes PD, et al. MR line-scan diffusion-weighted imaging of term neonates with perinatal brain ischemia. AJNR Am J Neuroradiol. 1999;20:1658-70.
11. Heinz ER, Provenzale JM. Imaging findings in neonatal hypoxia: a practical review. AJR Am J Roentgenol. 2009;192:41-7.

Available online at www.medicinescience.org

CASE REPORT

Medicine Science International Medical Journal

Medicine Science 2021;10(1):233-5

Erosive adenoma of nipple treated with cryotherapy and dermatoscopic features

Dua Cebeci[1], Sirin Yasar[2], Pembegul Gunes[3]

[1] Famagusta State Hospital, Department of Dermatology and Venerology, Famagusta, Cyprus, Republic Of Turkish
[2]Haydarpasa Training and Research Hospital, Department of Dermatology and Venerology, Istanbul, Turkey
[3]Haydarpasa Training and Research Hospital, Department of Pathology, Istanbul, Turkey

Received 22 September 2020; Accepted 02 November 2020
Available online 17.01.2021 with doi: 10.5455/medscience.2020.09.195

Abstract

Erosive adenoma of the nipple (EAN) is a rare benign condition and originates from the lacteroseducts of the nipple. It mimics benign conditions such as contact dermatitis, psoriasis and cutanous infections, but Paget's diseaseits main differential diagnosis. Patients usually present with a serous discharge from the nipple and nipple erosion. While the histopathological evaluation is being the gold Standard for diagnosis, dermatoscopy is an easy, practical and versatile optical tool that helps in the diagnosis of EAN. In this article we present fortyfour years old female patient with clinical and dermoscopic features of EAN wich was referred to the Dermatology Service with a lesion on her left nipple.

Keywords: Erosive adenoma of the nipple, breast diseases, histopathology

Introduction

Erosive adenomatosis of the nipple (EAN) is a benign tumor that develops from the lactiferous ducts of the nipple. İt is generally seen 4-5.th decades,in woman [1]. Clinically, the lesion has a polymorphic structure and may appear in the form of nipple erosion, erythema, inflammation in the initial stages. İtching and pain are the main complaint . Symptoms can be aggravated in the premenstrual period [2-3]. This condititon, can easily be mistaken with psoriasis and eczema in the early stages and with the Paget's disease clinic at later stage [4]. The use of dermoscopy has increased significantly in recent years to help diagnose skin conditions other than melanocytic lesions / non-melanocytic tumors. EAN's dermoscopic features first were described by Takashima et al. as the regular and small, linear cherry-redstructures characteristically observed possibly reflect with luminal openings. However, withdermoscopy it is impossible to differentiate EAN from non-pigmented Paget's disease ,apigmented melanoma and squamous cell cancer.

***Corresponding Author:** Dua Cebeci, Famagusta State Hospital, Department of Dermatology and Venerology, Famagusta, Cyprus, Republic Of Turkish.
E-mail: perolidua@gmail.com

Therefore, the literature reports that careful dermoscopic observations and histopathological examinations, will be useful for the correct diagnosis of AN [5]. Histologically, EAN is characterized by intra-ductal proliferation invading well-circumscribed, non encapsulated stroma. The inner layer of the cubic epithelial cells that make the apocrine secretion and the outer layer of the myoepithelial cells form the main cell population [6]. Immunohistochemistry tests and immunoperoxidase markers can be useful in making differential diagnosis with malignant diseases [7]. In this article we present the case of a 42- year-old white woman with erosive adenomatosis of the nipple, with clinical and dermoskopic features.

Case Presentation

Forty -two -years old female patient had applied to outpatient clinic for more than a year with the complaint of swelling, bleeding and discharge in the left nipple. Biopsy was taken with preliminary diagnosis of nipple eczema, Paget's disease and EAN. After the incisional biopsy, she applied to us due to enlargement of the lesion and the increase of bleeding. Dermatological examination revealed rough and thickened with erosion that caused mild papillary prominence and bleeding in the left nipple (Figure 1abc).

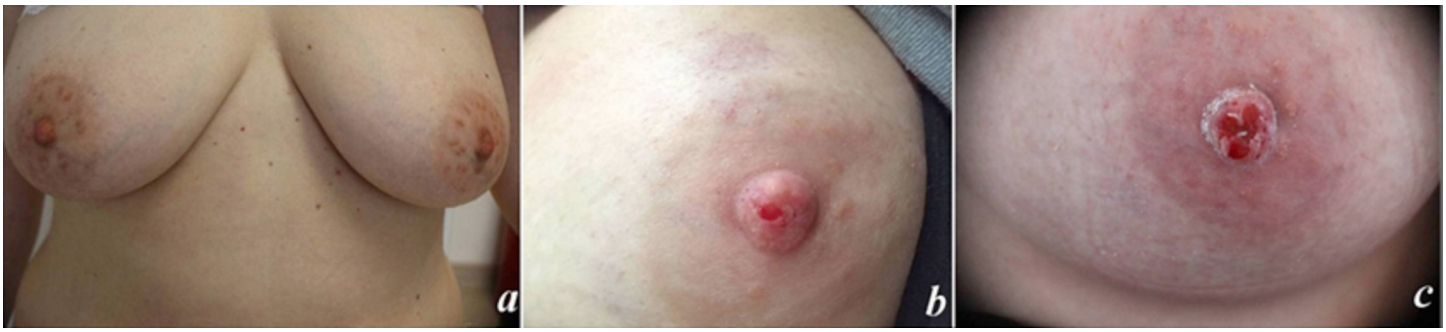


Figure 1. ab; Erosion and slight growth in the left nipple. c;lobular, hemorrhagic appearance after 1 month

Dermoscopic examination with immersion gel observed , partial hemorrhage and 1 linear vessel structure close to the center on the background of the homogeneous pink white area (Figure 2a).

Histologic findings showed ductal hyperplasia in the solid cribriform pattern with double-row epithelium-lined fluoride and apocrine cell metaplasia without nuclear pleomorphism. The lesion was evaluated as compatible with EAN in mixed-proliferative type pattern. (Figure 3abc).

In mammographic imaging, bilateral type 3 parenchymal structure fibrocystic changes were detected. The patient did not accept surgical treatment. She was defined as BIRADS category 2, as therapy was applied topical 10% sucralfate and zinc mixture and then 3 cycles of spray cryotherapy for 10 seconds. Two weeks after application, the bleeding areas disappeared and the lesion regressed. Therefore we decided to continue the cryotherapy treatment (Figure 2 d). She will be followed up regularly for recurrence if any.

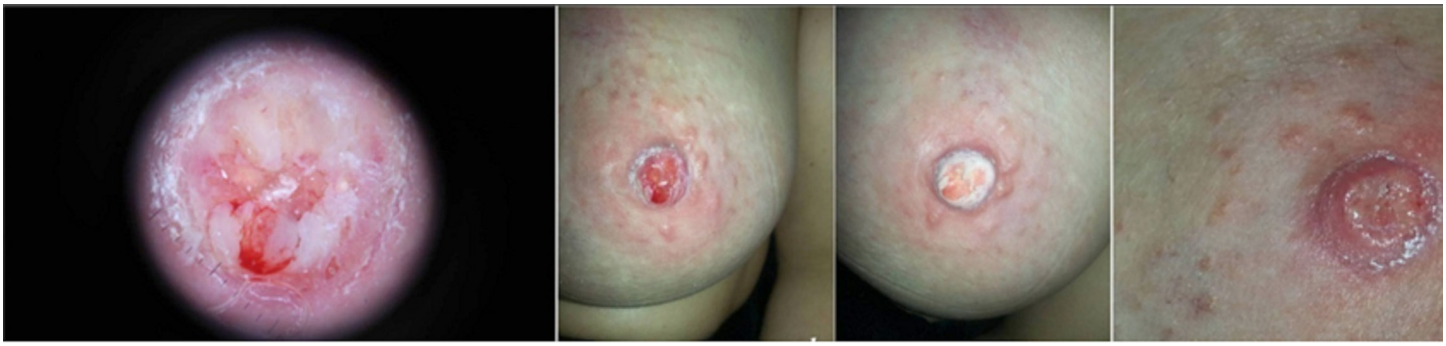


Figure 2. a; Eroded areas and 1 linear serpiginous vessels in dermatoscopic examination, b; 10 days after topical treatment, c; cryotherapy application, d; 15. days after the first session of cryotherapy.

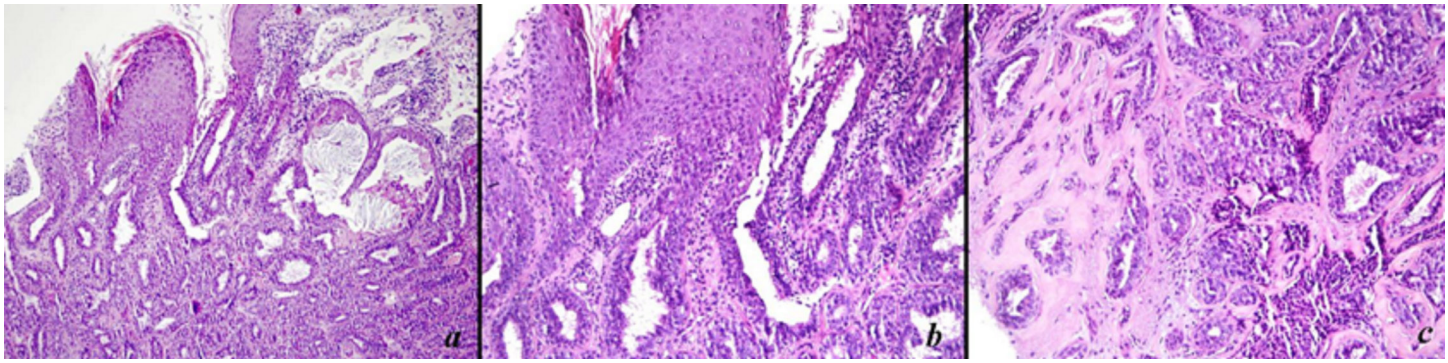


Figure 3. Hyperkeratosis , parakeratosis, adenosis that fills the entire dermis, and ductal hyperplasia that goes with double-row epithelium and fluoride and apocrine cell metaplasia (H & Ex 40,100,200)

Discussion

Erosive adenomatosis (EAN) of the nipple was first described by Jones in 1955 as fluoride papillomatosis or papillary adenoma of the nipple. Later, in 1959, LeGal et al. revealed the term “erosive adenomatosis” due to clinical and pathological findings. Other synonyms for EAN include nipple adenoma, subareolar papillomatosis, nipple papillary adenoma, and fluoride subareolar ductal papillomatosis [8].

Although the pathogenesis is not clear there are two hypothesis about the origin of hyperplasia of these channels; one thought argues that origin is the precursor of breast adenocarcinoma, while the other thought suppose that is a marker for fibrocystic breast

changes. However, more evidence is needed to determine the relationship with fibrocystic 83 breast changes [9].

The association of EAN with ipsilateral or contralateral breast cancer has been reported in the literature. In this context, a direct causal relationship between EAN and breast cancer cannot completely excluded. Therefore, some authors suggest that cases with histology compatible with the papillomatosis lesions of the breast should be evaluated in the "B3" category and they recommend breast mammography imaging once a year and total excision involving nipple, areola and subareolar tissue in some suspected condidition [10].

Skin biopsy is important histologically to distinguish EAN from intraductal carcinoma wich atypical large cells with hyperchromatic eccentric nuclei and abundant cytoplasm is the main findings [8]. In our case, the absence of cytological atypia and the dominance of two cell types covering the ducts removed from the possibility of mamarian paget's disease or intraductal carcinoma.

Dermoscopically, light brown diffuse pigmentation", "irregular black spots and small blue -gray structures" "irregular linear veins, bright white lines or chrysalis-like structures are more prominent in pigmented mamary Paget's disease. Some of the features above-mentioned can seen also in classical (clinically nonpigmented) paget's disease [11]. This condition can be explained by a concept that benign lesions generally have a regular vascular structure - while malignant lesions have atypical vessels, irregular structures [12].

Our case report with light pink regular structures and lumenial openings confirm the diagnosis of EAN. Therefore, more studies are needed on larger patient groups to support our observations.

Partial or complete nipple excision is the most recommended treatment option with the lowest recurrence rate. Mastectomy or extensive surgery should be avoided, especially in unmarried women [2].Since the relationship between EAN and breast cancer cannot be ignored, cryotherapy is a method that can be used to provide local bleeding / discharge control when the surgery is not possible. In a previous study, cryosurgery has been shown a successful treatment in a patient who has been followed for 7 years. Thus, cryosurgery that is used in the treatment of other benign conditions, can eliminate the tumor by local destruction [13].

In our case, who did not accept any surgical treatment, based on this successful literature, we chose the less invasive and traumatic treatment as cryotherapy.

We treated with the open-spray technique, with a double freeze-thaw cycle, 10-second spray, and reaching a tissue temperature of –50° C. After forming a freezing ring, application repeated in 3 cycles within 1 minute. The duration of cooling to achieve an optimal depth of freeze necessary for this lesion was 10 seconds.

After the disappearance of bleeding areas and regression of the lesion we decided to followe- up the patient and continue this treatment. The patient was satisfied with the results, as the nipple structure was preserved.

Conclusion

The erosive adenoma of nipple (EAN) is typically a benign breast tumor, manifested by erythema, erosion, and crusting. Due to its variable clinical features it must distinguish from inflammatory skin diseases such as Paget's disease, psoriasis, and eczema. Besides the clinical approach and histology , dermoscopy is helpful and effective tool that promise to be useful for the accurate diagnosis of EAN. Cryosurgery can be offered as an alternative option insome patients who refuse conservative treatments.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymitycannot be guaranteed.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
All authors declare no financial support.

Patient informed consent
Written informed consent was obtained from study participant.

References

1. Spohn GP, Trotter SC, Tozbikian G, et al. Nipple adenoma in a female patient presenting with persist entery thema of the right nipple skin: case report, review of the literature, clinical implications, and relevancy to health care providers who evaluate and treat patients with dermatologic conditions of the breast skin. BMC Dermatol. 2016;16:4.
2. Ward KA, Burton JL. Dermatologic diseases of the breast in young women. Clin Dermatol. 1997;15:45-52.
3. Gu X, Wang G, Wu R, et al. Erosive adenomatosis of the nipple in a man. Indian J Dermatol Venereol Leprol. 2015;81:68-70.
4. Takashima S, Fujita Y, Miyauchi T, et al. Dermoscopic observation in adenoma of the nipple. J Dermatol. 2015;42:341-2.
5. Alvarez-Veliz S, Majluf-Caceres P, Gonzalez-Bombardiere S. Erythematous eroded plaque on the left nipple in a 75-year-old woman. Indian J Dermatol Venereol Leprol. 2019;85:307-9.
6. Moulin G. Superficial papillary adenomatosis of the nipple. J Am Acad Dermatol. 1997;36:133.
7. Kumar PK, Thomas J. Erosive adenomatosis of the nipple masquerading as Paget's disease. Indian Dermatol Online J. 2013;4:239-40.
8. Albers SE, Barnard M, Thorner P, et al. Erosive adenomatosis of the nipple in an eight-year-old girl. J Am Acad Dermatol. 1999;40:834-7.
9. Rosen PP, Caicco JA. Florid papillomatosis of the nipple. A study of 51 patients, including nine with mammary carcinoma. Am J Surg Pathol. 1986;10:87-101.
10. Crignis GS, Abreu L, Bucard AM, et al. Polarized dermoscopy of mammary Paget disease. An Bras Dermatol. 2013;88:290-2.
11. Errichetti E, Avellini C, Pegolo E, et al. Dermoscopy as a supportive ınstrument in the early recognition of erosive adenomatosis of the nipple and mammary paget's disease. Ann Dermatol. 2017;29:365-7.
12. Kuflik EG. Erosive adenomatosis of the nipple treated with cryosurgery. J Am Acad Dermatol. 1998;38:270-1.

Available online at www.medicinescience.org

SHORT COMMUNICATION

Medicine Science International Medical Journal

Medicine Science 2021;10(1):236-7

Reopening of schools in the COVID-19 affected areas: Considerations and suggested recommendations

Saurabh RamBihariLal Shrivastava, Prateek Saurabh Shrivastava

Department of Community Medicine, Shri Sathya Sai Medical College and Research Institute, Sri Balaji Vidyapeeth – Deemed to be University, Ammapettai, Nellikuppam, Chengalpet District, Tamil Nadu, India

Received 24 September 2020; Accepted 13 October 2020
Available online 17.01.2021 with doi: 10.5455/medscience.2020.09.200

Abstract

The coronavirus disease-2019 (COVID-19) pandemic accounted for massive interruptions in the lives of all the age-groups of people and the same stands true for school-going children. Although, the decision of closure of schools was taken to ensure overall well-being and safety of children, but we have to acknowledge the fact that it has resulted in a negative impact on education, health status, development, family income and the economy of the nation at large. It has been advocated that educational facilities should be closed only when there are no other options available. In-fact, the policy makers have been advised to plan and implement a set of measures at different levels to negate the possibility of introduction and onward spread of the infection in schools as well as in the local community. In conclusion, the COVID-19 pandemic has significantly affected the lives of school children and it is high time that we take evidence-based decision to ensure schools are reopened. However, a lot of preparedness and risk mitigation efforts need to be taken to ensure the safety of children as well as the community.

Keywords: COVID-19 pandemic, Schools, Students

Introduction

The coronavirus disease-2019 (COVID-19) pandemic accounted for massive interruptions in the lives of all the age-groups of people and the same stands true for school-going children [1]. Even though, the infection has accounted for more than 30.6 million cases and death of 950000 people, the magnitude of the infection among children is significantly less [2]. The available estimates suggest that only 8.5% of the reported cases have been from the children age-group worldwide [3,4]. However, considering the mode of disease transmission and to ensure safety of the children, all educational institutions, including schools have been closed since the start of the pandemic in almost all the affected nations [1]. The current article has been written to understand the prerequisites which needs to be fulfilled so that schools can be re-opened and the responsibilities expected from different stakeholders in ensuring the safety of school personnel and the community at large.

***Corresponding Author:** Saurabh RamBihariLal Shrivastava, Department of Community Medicine, Shri Sathya Sai Medical College and Research Institute, Sri Balaji Vidyapeeth (SBV) – Deemed to be University, Tiruporur - Guduvancherry Main Road, Ammapettai, Nellikuppam, Chengalpet District - 603108, Tamil Nadu, India E-mail: drshrishri2008@gmail.com

Reopening of schools

Although, the decision of closure of schools was taken to ensure overall well-being and safety of children, but we have to acknowledge the fact that it has resulted in a negative impact on education, health status, development, family income and the economy of the nation at large [1,3]. Any decision regarding closure or re-opening of schools should be taken based on the comprehensive risk assessment in the region, which is determined by the level of transmission, clinical profile, the capacity of the schools to improve their preparedness, the anticipated rise in the number of cases after the re-opening of schools, and other public health measures implemented in the local area outside the school boundaries [4].

Suggested preparedness and risk mitigation

In general, it has been proposed that in regions with no or sporadic cases, all schools can be opened after the standard infection prevention and control measures are in place [4]. In regions with clusters transmission, most of the schools can be re-opened after implementation of necessary measures, while in regions with community transmission, a risk-based approach can be adopted

[4,5]. The primary principles which should be kept in mind includes maintaining social learning & development of children in a safe environment, reducing the risk of transmission among all stakeholders of schools, aversion of the possibility that schools act as an amplification site, and that school level public health measures are merged at community level [1,4,5].

Interventions at different level

It has been advocated that educational facilities should be closed only when there are no other options available. In-fact, the policy makers have been advised to plan and implement a set of measures at different levels to negate the possibility of introduction and onward spread of the infection in schools as well as in the local community [4]. In the areas wherein schools are reopening, at the community level measures pertaining to the detection of suspect cases, treatment of cases, contact tracing, and other measures pertaining to promotion of physical distancing and risk reduction strategies have to be intensified [4,5]. At school level, decisions have to be taken with regard to the policies supporting physical distancing, infrastructure support (viz. hand washing facilities, ventilation promotion, etc.), maintenance of a clean environment, school transportation services, etc, [1,3].

At classroom levels, physical distancing of at least 1 metre (if feasible), wearing masks (among children aged 12 years and above plus all staff), frequent handwashing, respiratory etiquette, cleaning and disinfection should be advocated. The decision to encourage the use of mask among children in the 6-11-year age-group should be taken depending on the intensity of transmission, sociocultural attributes, the impact on learning & development, etc [4]. It is very essential to enforce the policy that student or staff should stay at home, if they are not well. Further, the staff has to communicate with the parents and inform them about the measures taken by the school for the safety of their children, clarify rumors, and ask them to report any cases of COVID-19 that are reported in the household [4,6]. Moreover, the teachers have to keep a watch on the condition of the students an should immediately report to the school authorities, if they observe any suspect cases [4-6].

In case, a student or a school personnel becomes symptomatic, they should be isolated in a previously defined earmarked room and should be instructed to use face mask. All the surfaces touched by the suspected person should be disinfected and they should be asked to use a specific toilet which should not be used by others [3-6]. At the same time, arrangements should be made for their transit to the health care facilities for medical attention and collection of laboratory samples, if necessary. In situations, where students cannot attend school, arrangements should be made for remote learning and all steps should be taken to ensure constant monitoring of the school operations [3-5].

Conclusion

In conclusion, the COVID-19 pandemic has significantly affected the lives of school children and it is high time that we take evidence-based decision to ensure schools are reopened. However, a lot of preparedness and risk mitigation efforts need to be taken to ensure the safety of children as well as the community.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
The financial support no have.

References

1. Donohue JM, Miller E. COVID-19 and school closures. JAMA. 2020;324:845-7.
2. World Health Organization. Weekly Operational Update on COVID-19 - 21 September 2020; 2020. Available from: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200921-weekly-epi-update-6.pdf?sfvrsn=d9cf9496_6 [Last accessed on 2020 Sep 24].
3. Munro APS, Faust SN. Children are not COVID-19 super spreaders: time to go back to school. Arch Dis Child. 2020;105:618-9.
4. UNICEF, United Nations Educational, Scientific and Cultural Organization, World Health Organization. Considerations for school-related public health measures in the context of COVID-19 - Annex to Considerations in adjusting public health and social measures in the context of COVID-19 - 14 September 2020. Geneva: WHO press; 2020. p: 1-7.
5. Viner RM, Russell SJ, Croker H, et al. School closure and management practices during coronavirus outbreaks including COVID-19: a rapid systematic review. Lancet Child Adolesc Health. 2020;4:397-404.
6. Centers for Disease Control and Prevention. Operating schools during COVID-19: CDC's Considerations; 2020. Available from: https://www.cdc.gov/coronavirus/2019-ncov/community/schools-childcare/schools.html [Last accessed on 2020 Oct 12].

Available online at www.medicinescience.org

SHORT COMMUNICATION

Medicine Science International Medical Journal

Medicine Science 2021;10(1):238-40

Amit Jain's diabetic foot "PENTAGON" - a new model

Amit Kumar C Jain

Amit Jain's Diabetic Foot and Wound Research Unit, Amit Jain's Institute of Diabetic Foot and Wound Care, Brindhavvan Areion Hospital, Bengaluru, India
Department of Surgery, Raja Rajeswari Medical college, Bengaluru, India

Received 15 August 2020; Accepted 08 October 2020
Available online 17.01.2021 with doi: 10.5455/medscience.2020.08.164

Abstract

Teaching and training healthcare professionals like nurses and family physicians is essential in prevention of diabetic foot complications and subsequent amputation which can lead to poor quality of life. In a busy schedule and variety of conditions treated by them, simple and effective strategy that can be remembered with ease serves an efficient way to achieve the required goal. Amit Jain's diabetic foot Pentagon is a new concept that covers diabetic foot framework briefly and is an easy to remember acronym. This article discusses on this new concept which serves an important tool to understand diabetic foot in a simplified manner.

Keywords: Diabetic foot, acronym, pentagon, complication, amputation

Introduction

Diabetic foot complications and subsequent amputations due to it are preventable in more than 75% of the cases with screening and education [1]. Education should be both for patients and health care professionals. Nurses and family physicians are some of the healthcare professionals who play a very important role in early detection and prevention of complication in foot of diabetes patients [2].

Various novel strategies have been used in different parts of the world to address the above issues. The authors 'Amit Jain's project for diabetic foot' was one such effort to train healthcare professionals [3, 4].

Strategies to simplify the understanding of diabetic foot for primary health care professionals like nurses and general practitioners were employed by the author through Amit Jain's system of practice, the modern diabetic foot surgery, wherein the universal classification and a new screening tool were used to educate the health care professionals [5, 6]. The author later developed various new models for diabetic foot which serves excellent teaching tool [7, 8, 9].

Amit Jain's diabetic foot "PENTAGON" is one such new teaching model (Figure 1) which is an efficient education tool that covers briefly the framework (Figure 2) of diabetic foot [7]. The acronym "PENTAGON" is a simple and easy to remember tool and it serves to simplify diabetic foot for health care professionals including family physicians and nurses.

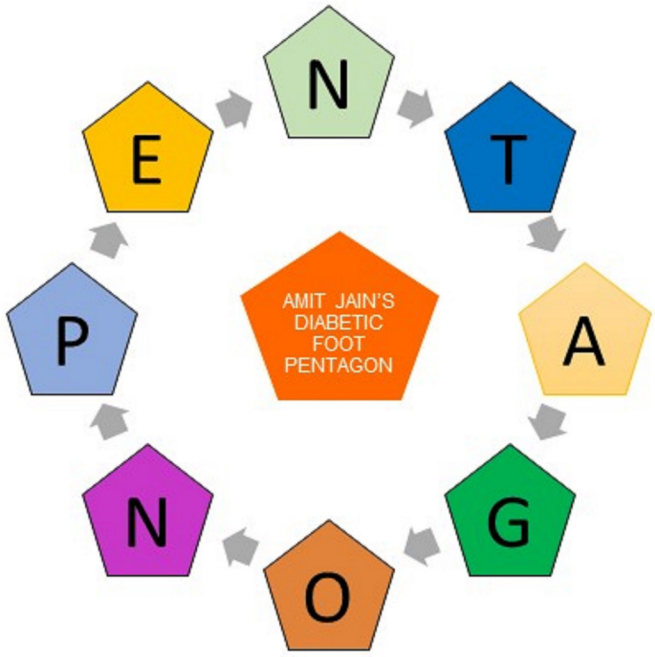


Figure 1. showing the Amit Jain's Diabetic foot Pentagon

***Corresponding Author:** Amit Kumar C Jain, Amit Jains Institute of Diabetic foot and Wound Care Brindhavvan Areion Hospital, Bengaluru, India
E-mail: dramitkumarcj@yahoo.in

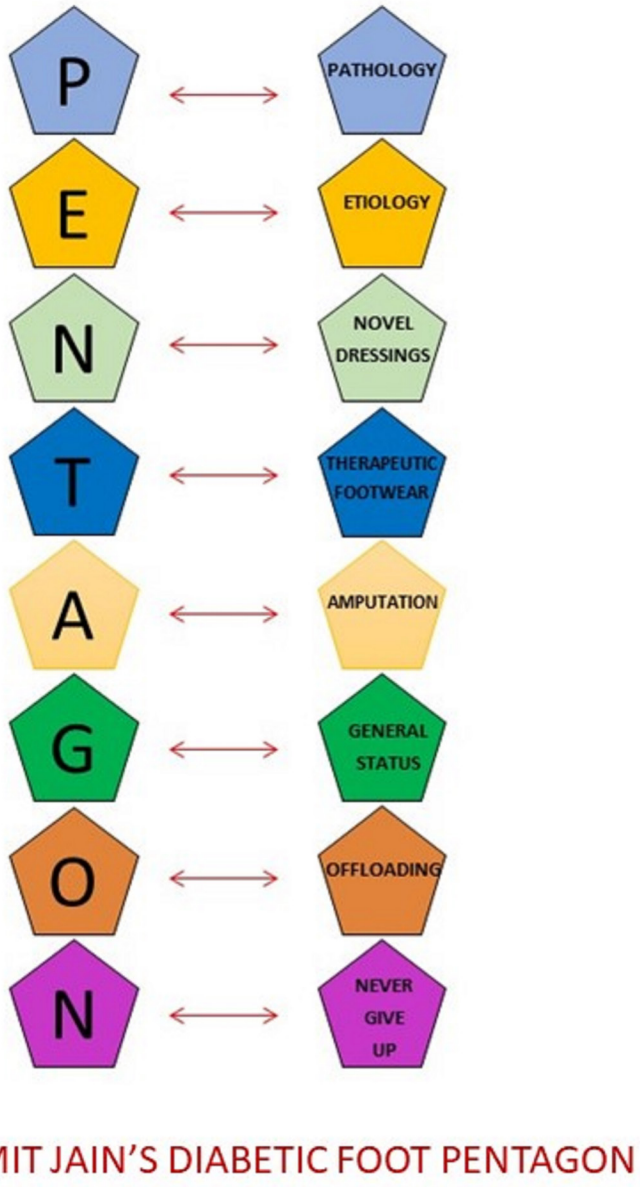


Figure 2. showing the acronym PENTAGON covering the brief framework of diabetic foot

The PENTAGON is as follows

Pathological lesions. Diabetic foot has various other pathological lesions apart from ulcers and they are abscess, cellulitis, Charcot foot, necrotizing fasciitis, etc. Amit Jain's universal classification is currently one of the only descriptive classifications from India that includes all these lesions [5]. In type 1 diabetic foot complications, infection lesions are included like abscess, cellulitis, wet gangrene, necrotizing fasciitis, etc whereas in type 2 diabetic foot complications, non-infective complications like trophic ulcers, callus, Charcot foot, dry gangrene, etc are included. When any of the type 2 diabetic foot lesions get infected secondarily, then they are categorized in type 3 complications [5]. For example, when a trophic ulcer is infected or a dry gangrene gets secondarily infected, then they are type 3 complications. Most of the infected complications like abscess, wet gangrene, necrotizing fasciitis are acute in nature and require immediate intervention to salvage the limb. Often, patients give history of some trauma after which these pathological lesions ensue in foot.

Etiology/Evaluation/Education. Diabetic foot is a triad of infection, ischemia and neuropathy [6, 10]. Patient often will have sensory, motor and autonomic neuropathy [10]. In an insensate foot, repeated trauma while walking can result in an ulcer or an injury with foreign bodies can result in acute infections like abscess or wet gangrene. Long standing diabetes, if uncontrolled, can lead to peripheral arterial disease which is aggravated if smoking habit is present. In diabetes, peripheral arterial disease is usually infrapopliteal [10]. Peripheral arterial disease is associated with higher risk of lower extremity amputation [11]. Amit Jain's evaluation tool addresses the above triad effectively and efficiently [6]. This screening tool can be used to educate health care professionals like doctors and nurses. Further, patients should also be educated and taught to inspect their feet frequently and take good footcare. Education is known to decrease the incidence of diabetic foot ulceration substantially [12].

Novel Dressings. There are various novel dressings available in market ranging from hydrogel, Foams, alginates, hydrocolloid, etc which can be used in diabetic foot wounds. Usages of these are often based on wounds characteristics [13]. These wound dressings can be divided into active, interactive and passive dressings [13]. These novel wound dressings enhance wound healing by providing moist environment apart from their antimicrobial properties, protection from trauma and by providing comfort [14]. Hydrogels are one of the popular choices of dressing among above [13].

Therapeutic footwear/ Team approach. One of the preventive strategies in diabetic foot is use of therapeutic footwear which is essential to protect the feet. Often therapeutic footwear is not used commonly in clinical practice and one can use the Amit Jain's footwear ladder to encourage the usage of footwear [15].
The lowest rung of ladder is barefoot walking and the highest rung is availability of complicated footwear's. Amit Jain's triangle of therapeutic footwear is a newly proposed teaching model that provides guidance to available diabetic footwear options [16]. Team approach is also needed when one encounters complex diabetic foot problems. There are studies which show that multidisciplinary team approach can improve outcomes in diabetic foot [17].

Amputation/Antibiotics/Adjunct therapy. Diabetic foot patients may require amputation surgeries or non-amputation surgeries like debridement. Amputations can be minor amputation or major amputations [18]. One can consider the use of Amit Jain's triangle of foot amputations (minor) to choose the best available option for successful foot salvage in case amputation becomes a necessity [15]. One may have to climb the Amit Jain's destructive/ amputation ladder when ever proximal amputation is needed [15]. Today, debridement is one of the most commonly performed procedures in diabetic foot [19]. Antibiotics are required in infections and must be used judiciously. One should always choose proper antibiotics to decrease the treatment cost, avoid antibiotic resistance and side effects. There are various adjunctive therapies that can help in healing wounds. Negative pressure wound therapy, oxygen therapy, hyperbaric oxygen therapy, etc are some of the available adjunctive therapies used in different parts of the world [20].

General status. While treating diabetic foot, one should also

evaluate the general status of the patients as they may have ischemic heart disease, chronic kidney disease etc which are important in outcomes of the patients. In a recent study by Jain et al [21], it was seen that around 60% of diabetic foot patients had hypertension, 16.7% had ischemic heart disease and 13.3% had retinopathy and CKD each [21].

Offloading/Orthotics. Always offload the foot especially in non-healing plantar ulcers and Charcot foot. There are numerous offloading available and one can use the Amit Jain's triangle of offloading that provides guidance on available options for offloading ranging from simple offloading like felted foam to complicated offloading like total contact cast [15]. Many patients will also require orthotics and prosthetics and they should be referred at right time for their usage.

Never give up. Various wounds in diabetic foot are chronic and may require long time to heal. Always have patience towards such patients, passion while treating diabetic foot and perseverance to achieve success.

Conclusion

Teaching in diabetic foot can be fun filled if it is simple, easy to remember and serves its purpose. Amit Jain's diabetic foot 'Pentagon' is one such effective acronym that aids in understanding diabetic foot in extremely simplified method for health care professionals like nurses and general practitioners.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
The financial support no have.

References

1. Jain AKC, Gopal S. Comparing foot evaluation in hospitalized diabetic patients between Surgeons, Orthopedicians and Physicians through Amit Jain's triple assessment. East African Scholars J Med Sci. 2020;3:169-78.
2. Aalaa M, Malazy OT, Sanjari M et al. Nurses role in diabetic foot prevention and care; a review. J Diabetes Metab Disorder. 2012;11:24.
3. Jain AKC. Amit Jain's project for diabetic foot care- the largest independent diabetic foot project in India. Diab Foot J Middle East. 2017;3:71-5.
4. Jain AKC. Amit Jain's project for diabetic foot care – a national and international initiative to improve and standardize diabetic foot practice around the world. IJMSCI. 2016;3:2298-301.
5. Gopal S, Haridarshan SJ. Amit Jain's system of practice for diabetic foot: the modern diabetic foot surgery. Int J Res Orthop 2019;5:532-9.
6. Jain AKC, Kumar K, Kumar H, Kumar S. Amit Jain's triple assessment-a new screening method for the diabetic foot. Wounds Middle East. 2018;5:10-1.
7. Jain AKC. Amit Jain's diabetic foot pentagon. East African Scholars J Med Sci. 2020;3:154-6.
8. Jain AKC. Amit Jain's destructive/amputation ladder and its variants. Saudi J Med. 202;5:214-21.
9. Jain AKC. Amit Jain's diabetic foot wheel. EAS J Med Surg. 2020;2:111-112.
10. Pendsey SP. Understanding diabetic foot. Int J Diabetes Dev Ctries. 2010;30:75-9.
11. Thiruvoipati T, Kielhorn CE, Armstrong EJ. Peripheral artery disease in patients with diabetes: Epidemiology, mechanisms, and outcomes. World J Diabetes. 2015;6:961-9.
12. Ren M, Yang C, Lin DZ, et al. Effect of intensive nursing education on the prevention of diabetic foot ulceration among patients with high-risk diabetic foot: a follow-up analysis. Diabetes Technol Ther. 2014;16:576-81.
13. Yazdanpanah L, Nasiri M, Adarvishi S. Literature review on the management of diabetic foot ulcer. World J Diabetes. 2015;6:37-53.
14. Gianino E, Miller C, Gilmore J. Smart Wound Dressings for Diabetic Chronic Wounds. Bioengineering (Basel). 2018;5:51.
15. Jain AKC. Amit Jain's Destructive/ Amputation ladder and its variants. Saudi J Med. 202;5:214-21.
16. Jain AKC. Triangle of therapeutic footwear. SAR J Med 2020;1:31-3.
17. Nather A. Team approach for diabetic foot problems. Malaysian Orthopaedic. J 2007;1:3-6
18. Zakaria Z, Afifi M, Sharifudin MA. Clinical Factors affecting Minor Amputation in Diabetic Foot Disease at Tengku Ampuan Afzan Hospital, Kuantan. Malays J Med Sci. 2015;22:41-7.
19. Jain AKC, Viswanath S. Distribution and analysis of diabetic foot. OA Case Reports. 2013;2:117.
20. Everett E, Mathioudakis N. Update on management of diabetic foot ulcers. Ann N Y Acad Sci. 2018;1411:153-65.
21. Jain AKC, Viswanath S. A study of diabetic foot patients in a tertiary care premier teaching hospital. Int J Surg Sci. 2019;3:183-7.

Available online at www.medicinescience.org

REVIEW ARTICLE

Medicine Science International Medical Journal

Medicine Science 2021;10(1):241-5

Recent advances in treatment of cerebral ischemic stroke

Satish Rajkumar, Sathees B Chandra

Barry University, College of Nursing and Health Sciences, Biomedical Sciences Graduate Program, Hollywood, FL USA

Received 22 July 2020; Accepted 01 September 2020
Available online 20.12.2020 with doi: 10.5455/medscience.2020.07.144

Abstract

Ischemic stroke occurs when there is an obstruction or collapse of a blood vessel in the head or neck, which causes a lack of oxygen to the brain. Due to the lack of oxygen, detrimental motor and sensory deficits transpire in the areas of the brain that are affected. When an individual suffers an ischemic stroke, there is a specific time window and treatment regimen that is used to manage symptoms of a stroke. The principal concerns with stroke treatments are that don't fully recover motor and sensory function lost during a stroke occurrence. With the use of stem cells from several sources, they can be reprogrammed and transplanted into the brain to facilitate full recovery of motor and sensory function. The purpose of this review article is to investigate the precursors, diagnostic methods, treatment techniques and new stem cell treatment research associated with ischemic stroke in anticipation to cure cognitive, sensory and motor dysfunction.

Keywords: Ischemic stroke, treatment, stem cells, research, motor and sensory function

Introduction

Stroke is currently ranked fifth for global causes of death, dramatically dropping from third [1,2]. The term stroke is quite broad but it can be broken down into three different subtypes; one of which is ischemic stroke and will be the focus of this paper. The medical definition of an ischemic stroke is when a portion of the brain's blood flow is cut off by a blockage from an embolus. Ischemic stroke can be brought about by an unhealthy lifestyle, which can be worsened by excessive drinking, smoking and lack of cardiovascular activity [3,4]. Strokes can drastically change the lives of those who experience it by causing massive sensory, cognitive and motor dysfunction.

Though strokes are detrimental to those that are affected by it, current research is being conducted to prevent stroke occurrences, find the root of common ischemic stroke incidences and find a cure for ischemic stroke brain damage. Research facilitated in finding the primary causes of strokes such as an increase in age, hypertension, diabetes, diet, and smoking [2,4,5].

***Corresponding Author:** Sathees B Chandra, Barry University, College of Nursing and Health Sciences, Biomedical Sciences Graduate Program, Hollywood, FL USA. E-mail: schandra@barry.edu

Another finding was the use of specific medications such as Aspirin, Clopidogrel, and anticoagulants to help with stroke patients and for individuals who are at risk for ischemic stroke [6,7]. Through this, the window to administer treatment for ischemic stroke would decrease to three hours, instead of four. As well as treatment, confirming ischemic stroke with a CT scan was also a major breakthrough in research. It allowed researchers to see an association between secondary and initial stroke occurrences [8,9].

With today's technology and advancing research, ischemic stroke treatment and potential cures seem more like reality instead of a theory. Current treatment consists of medication to increase blood flow to prevent another clot from forming and physical therapy to help improve declining motor function. But with research that's being conducted at this moment, there is the possibility of regenerating cells that die during ischemic stroke which can bring back and improve sensory and motor function. This is possible through the use of stem cells that can be reprogrammed and transplanted into stroke patients. With the utilization of stem cells, the realm of stroke can altogether change. Instead of administering a treatment that is used to manage deficits received from ischemic strokes, stroke patients can perhaps regain the motor and sensory function they lost [10,11]. This can be done through the manipulation of stems to differentiate them into different

types of brain cells such as neurons to improve neuroplasticity and neuroprotection. The purpose of this paper is to investigate recent advancements in modern treatment regimens of stem cell implantation for cerebral ischemic strokes to aid in the recovery of sensory and motor dysfunction.

General History of Ischemic Stroke

Before the 21st century, a stroke would be described as a neurological shortage brought about by intense central damage of the focal sensory system [12]. This broad definition covers a widespread reason as to why an individual would have a stroke but would never pinpoint the exact cause. Nevertheless, it goes beyond the definition; although stroke was globally impactful, stroke wasn't classified correctly in clinical practice or in evaluations of the general wellbeing. This is important to note because ischemic strokes make up most of the strokes that occur (85%), are typically embolic and affect men more than women [8]. Clinical practices and research labs would drastically change when the definition of a stroke was accurately defined when a clot cuts off a segment of the brain's circulation. After the American Stroke Association created a proper meaning of stroke for the overall population, subtypes of strokes such as cerebral ischemic strokes were created [12,13]. With many subtypes that fall under the ischemic stroke, one integral notion to consider is the misconception between ischemic stroke and transient ischemic attack. These two conditions were confused from one another because a transient ischemic attack (TIA) is similar to stroke with the exception that neurological deficits that accompany TIA last less than 24 hours [14,15]. The probability of a stroke occurrence after a TIA increases dramatically. Another aspect of stroke that has been altered dramatically is stroke treatments. Early stroke treatments consisted of basilar thrombolysis via catheter, which showed brilliant results but these treatments used intravenous (IV) and not intra-arterial (IA) delivery. This would be a major breakthrough since most sites of stroke incidents would occur in the carotid artery [14,16]. Approval for the first official ischemic stroke treatment was in 1996 by the FDA with the formal name of intravenous tissue-type plasminogen activator (IV-tPA) [17]. Since the support of the primary stroke treatment, several improvements have been made such as decreasing the four-hour window for treatment. Consequently, it would also prolong the process of approving these improvements and left many patients untreated due to unknown causes of stroke.

Major Causes of Cerebral Ischemic Stroke

There are multiple reasons why an individual would suffer a stroke but the biggest reason can be attributed to their lifestyle. The daily activities, career field, exercise; genetics and diet that an individual has in their lives can greatly affect their risk for ischemic strokes [5]. Some general precursors of stroke consist of an increase in age, hypertension, diabetes, and smoking [2,4]. Although older age is a precursor for ischemic strokes, younger male individuals suffer from stroke and this can be attributed to numerous precursors corresponding to smoking, high blood pressure and systemic lupus [18]. While males are largely predisposed to having ischemic strokes compared to women, studies have shown that contraceptives, frequent migraines, and hormone replacement therapies are precursors to strokes in women [19]. Another noticeable precursor for stroke involves race and ethnicity with younger aged African Americans and Mexican Americans having a higher prevalence of stroke incidents [1]. Globally, the United States remains the country with the highest mortality rate and occurrences of stroke [4]. Studies have also shown that those living in poor socioeconomic conditions and lower levels of education have a higher risk of strokes [20].

Medically, there are several precursors to cerebral ischemic strokes that can expand the plausibility of a stroke yet transient ischemic attack (TIA) remains the number one precursor [14,15,18]. Typically, when an individual has a TIA, there is a recurrence of an attack or a stroke 90 days after the first occurrence. Early imaging can help notice precursors such as ischemic lesions in cortical white matter areas, which slowly accrue causing both motor and cognitive issues [21]. It is imperative to know the medical factors that play a role in a stroke, such as genetics. Individuals with single-gene disorders are more prone to having ischemic strokes [22]. Though these are the medical precursors, there are certain events that occur on the cellular level that can also cause a stroke.

Histological Changes of The Brain After an Ischemic Stroke

Reactive oxygen species are formed unnaturally in our bodies, and it consists of an unstable oxygen molecule that can react readily with other molecules in the cell. When there is an accumulation of ROS, it can cause catastrophic damage when it does react with these other molecules [23]. ROS has been linked to ischemic strokes and can cause further brain and tissue damage after stroke occurrences [24]. Currently, there is no definitive solution to prevent increased damage from ROS. ROS can be attributed to chemical destruction of brain tissue but there are other factors that can cause damage to the structure of the brain. Gray and white matter play a fundamental job in the functional and structural connectivity of the brain's network. When an individual experiences a stroke, they form focal brain lesions that affect the brain's functional connectivity associated with gray matter [25]. Though these lesions can cause damage to these cortical regions, the structural connectivity, which is directly correlated to the white matter of the brain, is disregarded. Damage to the structural connectivity of the brain is one of the major contributors to the dysfunction of the brain following a stroke. Regardless of chemical or structural injury, there are measures the body takes to prevent further brain damage. The human body has a set of immune responses when organs or tissues begin to fail. Following a cerebral ischemic stroke, the brain begins to swell up, reactive oxygen species begin to form and the blood-brain barrier is compromised [26]. While these cascade of events are occurring the brain activates microglia. Microglia are cells in the brain that are responsible for removing wastes and pathogens from the brain via phagocytosis. But recent studies have shown microglia play a larger role in attempting to protect the brain after a stroke. They eliminate the harmful cells that cause extensive damage, lessen neuroinflammation and serves as a "neuroprotector" [27].

Various Approaches for The Diagnosis of an Ischemic Stroke

OFAST is a mnemonic that is used to help diagnose and evaluate whether an individual is having a stroke. It means facial drooping, arm weakness, speech difficulties and time. It is imperative to note whether these indications point to a stroke because there are other

disorders that can imitate a stroke such as migraine headaches, seizures and hypoglycemia [28]. Another quick assessment to predict whether an individual is suffering a stroke is the ABCs; Airway, breathing, and circulation because some patients may lose consciousness during an occurrence. Though, the most important aspect of diagnosing is time, because as more time passes, more neurological damage can occur. These quick steps can help diagnose possible stroke occurrences and help save the lives of those affected by restoring blood circulation in the blocked area. Other than physiological disabilities an individual may display, there is another way of diagnosing strokes. By using a functional MRI, physicians can scan the brain to look for any deformities [29]. This can help evaluate whether it is an ischemic stroke, an intracerebral or subarachnoid hemorrhage [30]. The most widely recognized stroke that happens is ischemic strokes. They make up 85% of stroke cases and are termed supratentorial meaning that they are easily recognizable [2,4,5,8]. Ischemic strokes are usually a cause of a failing blood vessel, which creates a blockage in the arteries leading to the brain. Another important aspect of stroke occurrences is the confirmation of one. To help confirm the diagnoses of a stroke and its severity, doctors use CT scans mainly because of how fast and easily accessible it is [8,9]. These scans can aid in locating where the blockage occurred and allows for the assessment of treatment. Ideally, the patient should receive professional medical assistance within four and a half hours of the stroke incidence. Within these four and a half-hour window, treatment should also be administered to prevent massive brain damage.

Current treatment and risk management of ischemic stroke

Current studies have shown that there is no definitive cure for ischemic strokes but with recent developments, there are treatments to assist with recovery and prevention of recurrent strokes. As mentioned before, any type of treatment used for stroke patients must be administered within a four and a half-hour window to prevent further brain damage. Intravenous thrombolysis, one of the more common forms of treatments, is used to disintegrate the embolus that is causing the arterial obstruction, thus restoring blood flow [14,16,17]. Other forms of treatment are endovascular treatments such as recombinant tissue-type plasminogen activator and repetitive transcranial magnetic stimulation. These treatments are used to improve sensory and neurological function [31]. For every type of treatment used, it is imperative that imaging techniques such as CT scans or MRIs are used. These scans can help determine the course of treatment and locating the site of stroke [8,9]. The next step of action after medication and recuperation of sensory and neurological function would be to improve motor function. One current course of treatment available is transcranial direct current stimulation (tDCS), which sends impulses to reduce or destroy lesions that cause sensorimotor deficiencies [32]. Physical therapy is typically given those who need it to help improve motor function [31,33]. Exercise combined with physical therapy can help regain motor function, increase muscle tone that may have diminished, and prevent recurrences of stroke incidents [6,34]. Even though there are many current treatments to manage stroke, recent studies suggest that risk management is the best way to avoid stroke occurrences [1]. Risk management applies to those who have had initial stroke occurrences and for the individuals who are in danger for a stroke. Techniques to reduce and/or prevent stroke occurrences start with lifestyle, such as diet, exercise and avoiding substances that can increase the likelihood of a stroke. For exercise, there are multiple avenues to venture through such as weight lifting, cardio, and yoga. However, the most important rehabilitation technique for stroke patients is aerobics to heighten cardiovascular health [33]. As well as exercise, having a healthy diet, increased intake of fruits and vegetables, lessened use of tobacco, and a decrease in alcohol consumption can help avoid stroke [6,34].

Reoccurrence of ischemic stroke

Depending on the risk factors, there is a possibility of a reoccurrence of stroke. Recurrence of stroke is common, but it is difficult to pinpoint the reason for its occurrence because there are many factors that attribute to it. Research shows that there is a link between secondary strokes when the initial stroke was a cause of atherothrombotic or cardioembolic embolism [15]. Initial risk factors that contributed to the first stroke can be used to determine whether an individual will suffer more strokes in the future [34]. This is important to note during recovery and treatment. While there is no definitive way to determine whether an individual will have a recurrence of stroke, there are predictors and indicators that can help gauge the likelihood of another stroke. The majority of recurrences occur within a 90-day window of the initial stroke [35]. Major factors that can cause the recurrences of stroke are age, typically the age of 65, a continued state of hypertension and occurrences of transient ischemic attacks [36]. Another key aspect to take into consideration when evaluating and predicting recurrence is gender (females frequently have a recurrence of stroke), type of stroke that initially occurred, and location of stroke [37]. Imaging such as MRIs can help detect cortical lesions on the brain that can cause the recurrence of stroke. Unfortunately, CT scans and ultrasounds haven't proven to help predict strokes [8,9,38]. Although it is difficult to predict whether there will be a recurrence of a stroke, it is possible to avoid stroke occurrences with prevention and risk management. Risk management consists of correct dieting, exercise, reduced alcohol use and low tobacco use [5,6,34]. Managing the above will help stop initial stroke occurrences and will effectively help prevent strokes in younger adults. In recent studies, one major contributor to the prevention of secondary strokes is the medication, aspirin, which is a blood thinner that prevents blood from clotting up [39]. Anticoagulants and antiplatelets are also used as preventive medicine for secondary strokes and have been proven to be effective in reducing stroke recurrences [7]. However, the goal is to cure stroke disorders as a whole, which can be achieved with recent stem cell research.

Modern development of treatment regimens of cerebral ischemic stroke

Currently approved treatments that show significant results in patients that suffer an acute ischemic stroke are recombinant tissue plasminogen activator. The only problem that arises from this treatment is that it can only be used within a four and a half-hour window after the initial stroke occurrence. Consequently, this calls for a new type of treatment, the utilization of human dental pulp stem cells. Using these stem cells would be essential because they are easily obtainable from teeth that have been disposed of as medical waste and have higher proliferation in vitro

[40]. Human dental pulp stem cells have shown to be helpful for cerebral ischemia treatment and to improve neurological function and neuroplasticity. In another recent stem cell research, there are two sorts of stem cells that show advances in stroke patients with little to no complications. There are multiple sources to extract stem cells from but many of them pose problems to neurological recovery that cannot be overcome. By using a developed human neural stem cell line, these stem cells can differentiate into different types of cells such as neurons. These stem cells also show improvement in several stroke patients' neurological deficits. Bone marrow-derived stem cells also have the potential to help with the adverse effects of stroke because they have shown to have endogenous neurogenesis in damaged cells [10]. Even though there are many treatments to help aid patients moments after a severe ischemic stroke, there are currently no definitive cures. However, by using stem cells, there is the possibility of a cure even hours after a stroke incident. These stem cells can also assist in the improvement of motor and neurological disabilities. With the use of combining somatic cells and stem cells, they can be transplanted and reprogramed to become neurons. The healthy cells can then take the place of damaged cells in the brain, which are used for neuroprotection [10]. These stem cells show much promise and have shown improvements in animal models but their mechanisms are still unclear.

Concluding Remarks

Cerebral ischemic strokes are commonly arbitrary because they can be unpredictable even with healthy lifestyles. Many factors play a role in increasing the odds of having a stroke but risk management tactics can be used to lessen them. Although treating cerebral ischemic stroke within a specified time frame can prevent sensory and motor function to decline, this is not guaranteed. With sensory and motor dysfunction, patients have trouble regaining these abilities due to the death of neurons that play crucial roles in neuroplasticity and neuroprotection. With recent advancements in modern treatment regimens, full recovery of motor and sensory function can be a possibility with the use of stem cell implantation. Through implantation, neurons can regenerate, regain their function and should assist in the recovery of the patient.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
Barry University

Ethical approval
Consent of ethics was not received.

References

1. Guzik A, & Bushnell C. Stroke epidemiology and risk factor management. CONTINUUM: Lifelong Learn in Neuro. 2017;23:15–39.
2. Randolph S. A. Ischemic Stroke. Workplace Health & Safety. 2016;64, 444.
3. Allaoui A, Echchilali K, Moudatir M, et al. Etiologies des accidents vasculaires cérébraux ischémiques chez les jeunes: apport de l'interniste. Pan African Med J. 2018;30:114.
4. Howard G, Kleindorfer DO, Cushman M, et al. Contributors to the excess stroke mortality in rural areas in the united states. Stroke. 2017;48:1773–8.
5. Caldwell M, Martinez L, Foster J, et al. Prospects for the Primary Prevention of Myocardial Infarction and Stroke. J Cardio Phar Thera. 2019;24:207–14.
6. Rupal O, Kristen R, and Miriam G. Recurrent Ischemic Stroke: Strategies for Prevention. Am Fam Phys. 2017 Oct 1;96:436–40.
7. Faure M, Castilloux A, Lillo-Le-Louet A, et al. Secondary stroke prevention: a population-based cohort study on anticoagulation and antiplatelet treatments, and the risk of death or recurrence. Clinic Phar Thera. 2019; 107:443-51.
8. Musuka TD, Wilton SB, Traboulsi M, et al. Diagnosis and management of acute ischemic stroke: speed is critical. CMAJ: Canadian Medical Association journal. J de l'Association med canadienne. 2015;187:887–93.
9. Masdeu JC, and Ramón GG. Neuroimaging. Amsterdam: Elsevier. 2016.
10. Kokaia Z, Tornero D, and Lindvall O. Transplantation of reprogrammed neurons for improved recovery after stroke. Prog Brain Res. 2017;231:245-63.
11. Loubinoux I, Demain B, Davoust C, et al. Stem cells and motor recovery after stroke. Annals Phy Reh Med. 2014;57:499–508.
12. Sacco RL, Kasner SE, Broderick JP, et al. Council on Nutrition, Physical Activity and Metabolism. An updated definition of stroke for the 21st century: A statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2013;44:2064–89.
13. Adams HP, and Biller J. Classification of Subtypes of Ischemic Stroke: History of the Trial of Org 10 172 in Acute Stroke Treatment Classification. Stroke. 2015;46:114–7.
14. Béjot Y, Daubail B, and Giroud M. Epidemiology of stroke and transient ischemic attacks: Current knowledge and perspectives. Revue Neuro. 2016;172:59–68.
15. Toni D, Di Angelantonio E, Di Mascio MT, et al. Types of Stroke Recurrence in Patients with Ischemic Stroke: A Substudy from the PRoFESS Trial. Int J Stroke. 2013;9,873–8.
16. Mair G, and Wardlaw JM. Imaging of acute stroke prior to treatment: current practice and evolving techniques. The British J Radio. 2014;87:20140216.
17. Smith WS, and Furlan AJ. Brief History of Endovascular Acute Ischemic Stroke Treatment. Stroke. 2016;47.
18. Cruz-Flores S. Acute Stroke and Transient Ischemic Attack in the Outpatient Clinic. Medical Clinics of North America.2017;101:479–94.
19. MacGregor EA. Migraine and female hormones - what factors increase the risk of ischemic stroke? Vascular Med. 2000;5:113–33.
20. Errata: Vol. 66 No. 34. Morbidity and Mortality Weekly Report (MMWR). CDC. 2017;66:1030.
21. Baltan S. Stroke in CNS white matter: Models and mechanisms 2019. Neuroscience Letters. 2019;711:134411.
22. Della-Morte D, Guadagni F, Palmirotta R, et al. Genetics of ischemic stroke, stroke-related risk factors, stroke precursors and treatments. Pharmacogenomics. 2012;13:595–613.
23. Rodrigo R, Fernandez-Gajardo R, Gutiérrez R, et al. Oxidative Stress and Pathophysiology of Ischemic Stroke: Novel Therapeutic Opportunities. CNS & neurological disorders drug targets. 2013;12:698-714.
24. Griendling KK, Touyz RM, Zweier JL, et al. Measurement of Reactive Oxygen Species, Reactive Nitrogen Species, and Redox-Dependent Signaling in the Cardiovascular System: A Scientific Statement From the American Heart Association. Circulation research. 2016;119:39-75.
25. Griffis JC, Metcalf NV, Corbetta M, et al. Structural disconnections explain brain network dysfunction after stroke. Cell reports. 2019;28:2527–40.
26. Wang S, Zhang H, and Xu Y. Crosstalk between microglia and T cells contributes to brain damage and recovery after ischemic stroke. Neurological research. 2016;38:495-503.
27. Wolf SA, Boddeke HW, and Kettenmann H. Microglia in Physiology and Disease. Annual Rev Phy. 2017;79:619–43.
28. Erbguth F. Stroke Mimics und Stroke Chamäleons – Differenzialdiagnose des Schlaganfalls. Fortschritte Der Neurologie. Psychiatrie. 2017;85:747–64.
29. Savić T, Gambino G, Bokharaie VS, et al. Early detection and monitoring

of cerebral ischemia using calcium-responsive MRI probes. Proceedings of the National Academy of Sciences. 2019;116:20666-20671.

30. Yew KS, and Cheng E. Acute stroke diagnosis. American family physician. 2009;80:33–40.

31. Zong X, Dong Y, Li Y, et al. Beneficial effects of theta-burst transcranial magnetic stimulation on stroke injury via improving neuronal microenvironment and mitochondrial integrity. Trans Stroke Res. 2019;11:450–67.

32. Itoh H, and Saeki S. Transcranial direct current stimulation for improving upper limb function after stroke. Japanese Journal of Stroke. 2019;41:523-8.

33. MacKay-Lyons M, Billinger SA, Eng JJ, et al. Aerobic Exercise Recommendations to Optimize Best Practices in Care After Stroke: AEROBICS 2019 Update. Phy Thera. 2019;00:149–56.

34. Powers WJ, Derdeyn CP, Biller J, et al. 2015 American heart association/ american stroke association focused update of the 2013 guidelines for the early management of patients with acute ischemic stroke regarding endovascular treatment. Stroke. 2005;46:3020–35.

35. Arsava E. M, Kim GM, Oliveira-Filho J, et al. Prediction of Early Recurrence After Acute Ischemic Stroke. JAMA Neurology. 2016;73:396.

36. Kawada T. Factors of recurrence in patients with ischemic stroke or TIA. Acta Neuro Scandinavica. 2019;141:258.

37. Ay H, Gungor L, Arsava EM, et al. A score to predict early risk of recurrence after ischemic stroke. Neuro. 2009;74:128–35.

38. Kauw F, Takx R, de Jong H, et al. Clinical and Imaging Predictors of Recurrent Ischemic Stroke: A Systematic Review and Meta-Analysis. Cerebrovasc Dis. 2018;279-87.

39. Diener HC, Bernstein R, and Hart R. Secondary Stroke Prevention in Cryptogenic Stroke and Embolic Stroke of Undetermined Source (ESUS). Curr Neurol Neurosci Rep. 2017;17:64.

40. Nito C, Sowa K, Nakajima M, et al. Transplantation of human dental pulp stem cells ameliorates brain damage following acute cerebral ischemia. Biomedicine & Pharmacotherapy. 2018;108:1005–14.

Available online at www.medicinescience.org

INVITED REVIEW

Medicine Science International Medical Journal

Medicine Science 2021;10(1):246-54

Psychotraumatology and dissociation: A theoretical and clinical approach

Erdinc Ozturk[1], Barishan Erdogan[2], Gorkem Derin[1]

[1]*Istanbul University-Cerrahpaşa, Institute of Forensic Sciences and Legal Medicine, Department of Social Sciences, Istanbul, Turkey*
[2]*Istanbul Arel University, Faculty of Letters, Department of Psychology, Istanbul, Turkey*

Received 10 February 2021; Accepted 10 February 2021
Available online 22.12.2021 with doi: 10.5455/medscience.2021.02.041

Abstract

The term "psychotraumatology" can be considered as a fundamental term which consists of the whole of research and studies related to the post-traumatic stress disorder. This discipline, of which rise can be thought as simultaneous with the emergence of the increase in the number of studies on the post-traumatic stress disorder, can under no circumstances be examined and explained without referring to the dissociative disorders which refer to the whole of the short and long-term effects of early chronic childhood traumas by its very nature. The main goal of this study is, thus, to consider the relationship between the field of psychotraumatology which involves the factors causing psychological trauma, the traumatic process itself and the outcomes of it with the post-traumatic stress disorder and dissociation, both of which are trauma-based clinical phenomena, in a historical dimension and various perspectives. In accordance with this goal, academic approaches in the recent psychotraumatological literature will be discussed in the context of trauma and dissociation.

Keywords: Psychotraumatology, trauma, dissociation, dissociative disorders, post-traumatic stress disorder, psychotraumatologist academicians' movement

Introduction

Psychotraumatology is closely associated with clinical psychology, psychiatry and psychohistory. Recently, psychotraumatologically oriented studies with wide perspectives have been continuously conducted in these disciplines. Psychotraumatology is a base field of study that focuses on the reactions of people and societies to trauma-based situations or experiences as well as the psychotherapies and prevention policies of traumas. Psychotraumatology, defined as a scientific discipline that provides the treatment of trauma-related psychiatric disorders by evaluating the negative impacts of acute and chronical traumatic experiences on individuals and the transformation of those into possible life-long psychopathologies, as well as scrutinizing the traumatic stress and traumatic dissociation originating from natural disasters such as earthquakes, floods or fires and from human-made traumas such as physical, emotional and sexual abuse, forced migration, wars and terrorism, has been continuously collaborating in no small measure with the disciplines of clinical psychology, psychiatry and psychohistory [1-3].

***Corresponding Author:** Erdinc Ozturk, Department of Social Sciences, Institute of Forensic Sciences and Legal Medicine, Istanbul University-Cerrahpaşa, Istanbul, Turkey, E-mail: erdincerdinc@hotmail.com

It is unlikely to be able to conduct an effective psychotraumatological study without including early childhood traumas and dissociative disorders; as a matter of fact, some psychotraumatologists claim that post-traumatic stress disorder consists of a subset of psychiatric symptoms of dissociative disorders [2,4]. It is, thus, possible to refer dissociative disorders to be closely associated with chronic and early childhood traumas. Therefore, the prognosis of dissociative disorders needs to be taken into consideration with as equally great importance as that of post-traumatic stress disorder in trauma-related psychiatric disorders. Studies on dissociative disorders that peaked in early 1990's all over the globe has been contributing to the field of psychotraumatology on both theoretical and clinical grounds. It is also possible to claim that post-traumatic stress disorder and dissociative disorders are in no way mutually exclusive prognoses; on the contrary, they tend to promote each other by their very natures. Due to all these reasons, post-traumatic stress disorder and dissociative disorders have vastly significant and premissing contributions to the development of modalities and paradigms related to modern psychotraumatology [2,5,6].

Psychotraumatology by its widest definition, refers to the study of psychological trauma which might more specifically be regarded as involving with the treatment, prevention and research of experiences perceived as traumatic by individuals and their possible reactions to such conditions [7]. The introduction of the diagnosis of Post-Traumatic Stress Disorder in the 1980 edition of

the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders is one of the cornerstones of modern psychotraumatology. With this diagnosis, trauma, dissociation and crisis intervention have been among the main topics studied both clinically and academically. The term itself arose in the beginning of 1980s with the inclusion of post-traumatic stress disorder (PTSD) in the third edition of the American Psychiatric Association's Diagnostic and Statistical Manual [8]. The legitimization of PTSD as a separate psychological disorder has, thus, initiated the rise of psychotraumatology as a scientific field on its own. In this regard, it is highly possible to consider these two concepts as indivisible [9].

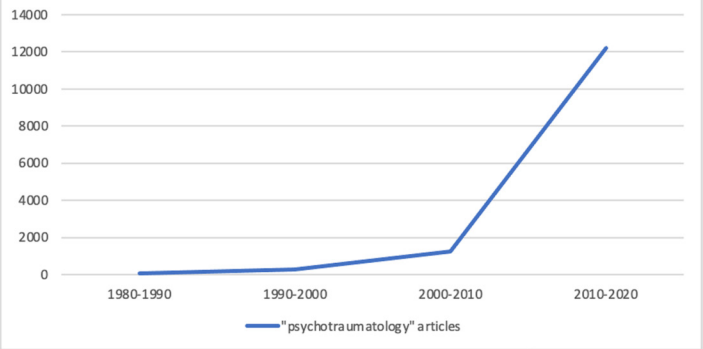


Table 1. Number of articles on Google Scholar that refer to "psychotraumatology" (as of September, 2020)

It was not until 1980's, i.e. the aftermath of the research on the effects of the Second World War that psychotraumatology was considered as a separate discipline within the then-mainstream psychology and psychiatry literatures; it is, however, possible to trace the commence of the emergence of psychotraumatology back into an earlier period, namely the work of Pierre Janet in the late 19th century. Janet commenced the studies on dissociative disorders from his observations on hysteric patients and made it possible with his discoveries and definitions to explain and comprehend the role of dissociation in the case formerly named as post-traumatic hysteria. Janet, in this context, happens to be the first scholar to systematically and clearly demonstrate that dissociation is a direct psychological defense against compelling traumatic experiences [10]. His work has shown that dissociative symptomatology plays a crucial role on the wide range of post-traumatic stress reactions which was -in accordance with the 19th century classification- treated under the diagnosis of hysteria.

More clearly, the discipline of psychotraumatology which is defined as the collective body of studies on trauma focuses precisely on individuals' reactions to traumatic situation and/or experiences, treatment of trauma and prevention techniques. It may be considered a discipline that centers upon traumatic stress and traumatic dissociation that occur as a consequence of not only natural, but also human-made disasters and traumas such as sexual, psychological and physical abuse, migration, asylum-seeking, wars and terrorism as well as providing their treatment by evaluating the process of transformation into psychopathology of acute and chronic traumas [1,2,11]. In this study the discipline of psychotraumatology will be dealt and explained within its historical development in terms of its relation with the concepts of trauma, post-traumatic stress disorder and dissociation, and together with its psychosocial dynamics.

Traumas, Traumatic Situations and Experiences

The term "trauma" which was used as an equivalent to physical wounds through centuries has then adopted a wider sense and definition to include all experiences that threaten or affect an individual's psychological and physical integrity. Trauma may, thus, be considered a fundamental term which refers to any damage in the bodily integrity and psyche of an individual which is difficult but inevitably required to be restored [12]. Although today it is possible to consider trauma as an inclusive term which refers not only physical but also psychological dynamics, this was not always the case as it is not until the late 19th century that psychological trauma was begun to be studied with a scientific approach. Not unlike Janet, Neurologist Jean-Martin Charcot was another doyen of the Pitié-Salpêtrière Hospital in Paris who pioneered the path that leads to an increase in the interest of neurology and later psychiatry in the concept of trauma by asserting that hysteria occurs as a result of trauma [13]. The assertion that hysterical symptoms are observed as a result of an individual's former experiences of destructive events, i. e. traumatic experiences and memories in the studies of Charcot, Janet and Breuer may be considered as the first significant explanation and initiating attempt at the field of psychotraumatology in terms of the results of trauma on one's psyche [14]. Even in the earliest years of childhood, it is possible to mention various stressors in every individual's life. When optimum conditions are provided, it is unlikely that these stressors would result in a trauma [12]. The imbalance between these objective stressors and the subjective coping skills of the individual leads to a traumatic situation [11].

Three major recent paradigms can be emphasized as dealing with traumatic processes: (a) the psychiatric paradigm that focuses on types of physical survival in dealing with traumatic stress [15], (b) the psychanalytic and developmental paradigm that underlines the early childhood loss and abandonment [16,17], and (c) the intergroup paradigm that refers to politically-generated aggressions to varying degrees such as discrimination, genocide and torture [18]. Kira et al. point out the cumulative nature of traumatic experiences by unifying these three valid paradigms under a development-based traumatology framework, giving crucial importance to past traumas without any possible neglect of ongoing ones [19]. In accordance with this, the first dimension of the developmentally based trauma framework covers mostly human-made traumas including attachment traumas (referring to parental abandonment, for example), personal identity traumas (associated with a violation of self-autonomy), collective identity traumas (with reference to major traumas such as discrimination) and self-actualization traumas (including significant failures in life). The second dimension of this bi-dimensional development-based traumatology framework, on the other hand, focuses on the objective properties of a traumatic experience including its severity and frequency; emerging into at least two sub-groups as single episode and complex traumas [19]. Cumulative trauma in this context refers to a wide conceptualization that includes not only previous traumatic experiences of any developmental stage of an individual's life, but also their ongoing traumas in various dimensions from personal identity crises to major social stresses such as targeted genocide or slavery.

Such a novel and multidimensional approach on traumas

and traumatic experiences plays a vital role in recognition of psychotraumatology studies as trauma happens to be a multi-component phenomenon which affects an individual's functionality in various fields, nourishes from various experiences and extends over a wide time interval and therefore requires to be scrutinized accordingly. Today it is a well-known fact that childhood traumas such as sexual abuse or physical violence are intense traumatic experiences that have long-lasting and destructive effects [20]. The emergence of a wider perspective and a more detailed definition of trauma with relatively less startling experiences such as verbal violence to much more extensive traumatic events such as genocides, as well as the ever-growing number of studies on preventing policies, theoretic explanations and new conceptualizations may be considered an achievement of the field of psychotraumatology and psychotraumatologists working in this field.

Trauma Self in Chronic and Complex Dissociative Disorders

The term "trauma self", which can be described as a self that gains independence from the original personality after the interruptions in consciousness caused by traumatic experiences, was first defined by Öztürk [21,22]. In 2009, it was defined in more detail as "traumatic self and its resistances" by Öztürk [23], and in 2016 it was updated with a new arrangement by Öztürk and Şar, still preserving the same basis as "trauma self and its resistances". The "trauma self", which Öztürk defines as the "preface" of chronic and complex dissociative disorders, can be included in all treatment models in the field of trauma and dissociation [21,23,24].

When an individual encounters traumatic experiences, their positive expectations about life are shaken and even these once positive expectations can turn into negative ones. In this respect, subclinical psychopathologies that develop in an individual after traumatic events are actually the process and effort of the individual to adapt to these traumatic events and to overcome them. When the individual is unable to process and cope with traumatic events or encounters new ones, the traumatized person, who is most probably in an effort to adapt to subclinical diagnoses, will most likely submit to a mental illness because the defense systems will begin to lose their functionality. At this stage, the individual begins to relate to their environment via their psychiatric symptoms, and the self happens to continue to function as a symptomatic (or "trauma") self [2,21].

"Trauma self" or this "symptomatic structure", finds its expression in being open to external influences and abuse in actual life, inability to develop protection against abuse, frequent complaints in life, self-pity, tantrums, being in an anxious state, loss of communication reciprocity, loss of control, distance problems (insecure attachment or attachment to the perpetrator) and adjustment problems such as emotional dysregulation, labile mood and mood transitions. This symptomatic structure is reflected as a resistance to both relationships and psychotherapy of the individual. Unless the "resistances of the trauma self" stated below are known, an effective approach cannot be provided in the psychotherapy of dissociative identity disorder [2,23].

The resistances of the trauma-self related to both psychotherapies and the actual life consist of three main groups: Depressive manifestations, traumatic obsessions, and loss of psychosocial mutuality. Detemporalization, treating oneself as an object, suicidality, obsessions of abnormality, rupturing the mutuality of the patient-therapist relationship, and dissociative somatic crises are among clues of these resistances. Approaching the patients' experiences from multiple dimensions, i.e. not only from the perspective of the therapist but also from the patient's distinct perspectives is crucial in working through the resistances of the trauma-self. The trauma self projects onto the individuals' relationships as well as their psychotherapeutic processes as a resistance. An effective approach towards trauma-relates disorders is therefore impossible without recognizing the resistances of the trauma self [2,23,24].

Trauma, Incomplete Response and Expectancy of Completion

Traumatic experiences, defined as incidents of vital incompatibility between threatening factors and individual coping capacities, has subjective and objective dimensions [25]. Every individual is faced with stressful events in their childhood and these experiences do not inevitably turn into a traumatic process as long as they can be neutralized under normal conditions. However, both the severity of the stressful events experienced and the incompatibility of the family and environmental conditions in which they occur may lead these experiences to turn into a traumatic process [1,2,26]. Traumatic experiences are inherently incompatible with a person's internal working patterns [27]. Traumatic experiences, characterized by the loss of control, make individuals' conceptualizations of the self and the world questionable [25,28].

Responses that can be possibly given to traumatic experiences are generally named as fight, flight, freeze and fawn [29]. Since freeze and fawn are responses of a completely dissociative nature, half of the reactions that individuals may manifest in case of traumatic experiences are dissociative defenses. However, there is actually no "best response" to be given to traumatic experiences. The impossibility of an appropriate response to this threat (i.e. trauma), despite its extent being existential, is called the "trauma paradox" [2,25]. As a consequence of the inability to process the trauma, individuals have to make more effort to process these negative life events. In this process, the memory of the individual deals with the traumas that occurred in the past as if they were being experienced in the present [27]. Repetitive reproduction of traumatic experiences in memory is inevitable, and each repetition creates a new version of the traumatic reality. Each new traumatic reality causes more cognitive distortions in individuals [4].

It is possible to mention three main clinical consequences of the traumas whose processings remain incomplete: loss of temporality, loss of sense of control, and increase or decrease in interpersonal distance. The traumatized individual loses the leading role in their life and becomes an object rather than a subject. One of the most important points during the processing of traumas is the prioritizing the effort and thoughts made to develop an adequate response rather than questioning the possibility of an adequate response to these negative life events. Individuals who devote all their energy and motivation to the processing these negative events maintain their expectations for "metabolizing the trauma". This comprehensive expectation of "metabolization" leads to the emergence of a resistance to the trauma that is processed in psychotherapies [28,30].

Traumatic Turning Point, Dualization of Time and Detemporalization

Traumatic experiences interfere with individuals' basic skills such as defense mechanisms, problem solving and coping strategies, thus interrupting their linear psychological development. These interruptions can cause inadequacies precisely in the emotional personalities and intellectual dimensions of traumatized people [26,28]. Unforeseen, unexpected and destructive experiences such as childhood traumas cause intense interruptions in psychological integration. Unprocessed traumas create two distinct life periods as the one before and the one after the specific traumatic event. This experience that divides an individual's life into two has been conceptualized by Öztürk as a "traumatic turning point" [22]. Although the traumatic turning point is expressed as the most distressing and stressful experience in childhood, it differs immensely from the first traumas that individuals remember and notice over time [22,28].

As previously stated, the "traumatic turning point", which can be expressed as a double-bind that interferes with the expectations of individuals' lives to be completed, divides life into two. The life expectancy of a person whose life is not divided by major traumas consists of mostly positive predictions. Individuals' positive thoughts about the future significantly help them to overcome their current frustrations. The increase in the severity of a psychopathology that occurs in an individual after a traumatic turning point causes the person, continuing to be exposed to acute or chronic traumas, to make an intense effort to regain their previous integrated and positive psychological characteristics [28]. Traumatic experiences that are most difficult to metabolize constitute traumatic turning points for individuals. When a traumatic experience is not metabolized, the individual's internal and external realities as well as the perception of time begin to change. Major traumatic events that are conceptualized as traumatic turning points divide both individuals' lives and their perceptions of time into two [21,28].

Time perception, which may also be described as the traumatic time perception, becomes dual after the traumatic experience. Individuals with interruptions and losses in the focus of control due to traumas may also become unable to control their perception of time. One of the reasons that interrupt the perception of time is maladaptive thoughts, feelings and behaviors that appear more severely as a result of the previous failure of coping strategies before the traumatic experience. The traumatic aspect of the self –namely the past time- falls behind the actual time, and the sense of the present, where traces of the past are seen, prevails in traumatized individuals. With the effect of traumatic experience, "time" is divided into two as time determined by traumas and determined by real time. In its most severe and extreme form, individuals who are victims of trauma have a distorted perception of time and cannot experience the past, present and future. The alienation of traumatized individuals against time is defined as detemporalization [31]. Traumatized individuals actually begin to alienate everything and the development of personalities that vary between dissociative subjects becomes easier [4].

The lives of trauma victims are divided into two parts as before and after the trauma. This psychopathological process may lead to attachment and identification with the abuser; the lives and time perceptions of traumatized individuals may be dualized on a dissociogenic ground and imprison them in multiple lives. Experiencing the present as interdependent with trauma detracts the person from real time and causes the feeling of time to disappear by mixing the past, present and future. Traumatic turning point, dualization of time and detemporalization constitute important research topics of psychotraumatology studied on a dissociative ground [2].

Unpredicted Possibility and Loss of Control

A traumatic event as an "unpredicted possibility" is closely related to the unpredicted and/or uncontrollable nature of stressors [32]. People try to control stressors by predicting them more accurately in order to maintain their existence in daily life [33,34]. Traumatic experiences, on the other hand, cause the emergence of a temporary loss of control by creating interruptions in individuals' reasoning skills. People exposed to traumatic experiences characterized by loss of control see themselves as an object of the unpredictable traumatic situation rather than being a "subject" [25,28]. The loss of control that occurs in traumatized individuals prevents the processing of these negative life events. Unprocessed traumatic experiences create behavioral consequences in individuals that are associated with irregular patterns ranging widely from unresponsiveness to overreaction. After major traumatic experiences, individuals become more fragile and feel more vulnerable against external factors [22,28].

Psychotraumatology and Post-Traumatic Stress Disorder

Post-traumatic stress disorder (PTSD) is a condition triggered by a life-threating event or a series of events. It may occur either by directly experiencing or witnessing the terrifying and traumatic event. Its diagnosis is characterized by three distinct clusters of symptoms: (i) re-experiencing the traumatic event through flashbacks, dreams, and/or intrusive, stressful thoughts; (ii) avoidance of reminders of the traumatic event and numbing of related emotions; and (iii) hyperarousal, characterized by irritability and hypervigilance [9]. Today, PTSD is a well-defined clinical picture whose manifestations and consequences have been studied and prevention policies have been developed [35].

A relatively novel concept is "complex post-traumatic stress disorder" (CPTSD) which was defined in light of developments and studies in the field of psychotraumatology. CPTSD was initially used to define a situation experienced by survivors of repetitive, prolonged traumas with a certain amount of affect dysregulation, alterations in consciousness, self-perception and relationships [36]. In addition to the requirements of PTSD, its diagnosis includes evidence of disturbances in self-organization, affect dysregulation, a negative self-concept and disturbed relationships [37].

The fact that PTSD literature is being enriched with such novel clinical presentations may well be seen as an indicator of an extension and deepening in the scope of psychotraumatology studies. Psychotraumatology enables the concept of trauma to be considered with all its dimensions before, during and after its experience as well as the opportunity to deeply scrutinize its effects and consequences on individuals' lives. It is stated that different sub-groups of patients have been detected in research on PTSD depending on which classification system was chosen

[38]. Contributions of psychotraumatologist scholars that study in the fields of trauma and dissociation in order to unify the existing theoretical information with clinical experience would play a vital role in the study, treatment and prevention of trauma-related clinical cases.

Research shows that a common feature of PTSD is dissociation [39]. Even a specific dissociative subtype of PTSD with separate neurobiological characteristics that distinguish it from its non-dissociative counterpart was introduced [40]. As dissociative symptoms almost exclusively emerge as the sequela of coercive and traumatic childhood experiences [41,42].

Modern Definitions of Dissociation

Öztürk, who defines dissociation with a modern and innovative approach on a psychotraumatological basis, is regarded as a respected scholar in both national and international scientific platforms with his work in the field of trauma and dissociation. According to Öztürk, dissociation is an extreme and intense effort of integration of a divided and multiple consciousness system. Dissociation as a process, on the other hand, is a strong desire or struggle for integration or unification rather than division. Dissociative disorders that occur as a result of dissociative reactions to minimal traumas in actual life, dissociative experiences that develop in the face of wrong child-rearing styles, and repetitive trauma that started at an early age, are quite ordinary life experiences that continue to manifest their adaptive as well as psychopathogenic psychological effects that have been parallel to each other in a wide spectrum throughout human history, in a complicated and chaotic process [2].

According to Öztürk, who developed a novel explanation in order to better perceive chronic complex dissociative disorders, that is dissociative identity disorder, the most clinically appropriate and comprehensive definition of dissociation is as follows:

"Dissociation, which functions as the ordinary life experience that keeps an individual away from the traumatic memories, is the experience of an individual's alienation to themself, to their environment and to the time by losing the feeling of belonging and possessing towards one's own identity before, during or after repetitive and distressing traumatic events; reconnecting with the individual's own and multiple realities as well as multiple selves by focusing on their trauma self without breaking their connection with the absolute reality [2]."

Öztürk, with a simple explanation of dissociation as "the body of experiences that an individual faces in the face of traumatic incidents and wrong child-rearing styles in which the singular consciousness, in an attempt to adapt by differentiating, transforms into a multi-conscious system with the pathological effects of encompassing defences and ordinary life experiences that keeps it away from the traumatic memories that were once witnessed" underlines Hilgard's statement that the uniqueness of consciousness is an illusion and that there is a dissociative spectrum for normal mental functions [43]. Dissociative identity disorder is an individual's effort to re-identify themself against chronic childhood traumas that begin at an early age. This undeliberate effort of identification actually begins as a defense system against traumas; and over time it transforms into a psychiatric disorder in a revision cycle in which the frequency, severity and duration of these chronic traumas increase [2].

Dissociative Disorders from a Psychotraumatological Perspective

Coercive and traumatic childhood experiences have been linked to various symptoms, including particularly dissociation [44]. According to the comprehensive definition of "mental health" introduced by Janet, "the existence of a high capacity of integration that unifies numerous psychological phenomena is the main condition of an individual to be considered healthy" [3]. This obvious attribution to the capacity of integration finds its meaning when it is taken into consideration that Janet asserted that dissociative symptoms can be attributed to the existence of disaggregated fractions within personality by taking psychopathological dynamics between traumatic experiences, dissociative reaction and identity into consideration within a psychotraumatology framework. Even though the initial definition of dissociation as a clinical picture dates back to more than a hundred years, this diagnostic group with all its criteria and prognosis being well-documented, still tends to be neglected by some therapists and scholars in contemporary psychiatry and clinical psychology disciplines [2].

Recent literature shows that half of the possible reactions to trauma, namely fight, flight, freeze and fawn, are in a dissociative nature. Beyond these, dissociative reactions to trauma, including dissociative disorders themselves, are found to be much more common than most mental health professionals are aware of [45]. It is, in this context, impossible to consider the phenomenon of trauma without referring to dissociation. Hence today the most comprehensive contribution in the field of psychotraumatology happens to be generated from scholars that focus on concepts of trauma and dissociation [2]. Dissociative disorders, characterized by multiple repetitious early childhood traumatic experiences as well as suicidality, constitute a diagnostic group that is impossible to be considered without a multidimensional approach within the disciplines of psychiatry and clinical psychology [26].

Studies in the fields of trauma, dissociation and the discipline of psychotraumatology itself develop with a great velocity in accordance with the Zeitgeist. It is possible to state that recent studies on novel conceptualizations such as cyber alters and cyber dissociation catch up with the necessities of the time when the fact that human life is to a large extent canalized to the cyberspace. Rapid changes in the contemporary paradigm direct psychotraumatologist scholars such as mental health experts like psychologists and psychiatrists and social scientists like sociologists to develop innovational ideas, conceptualizations, solutions and prevention strategies. The developments and deepening in the fields of trauma and dissociation has thus a direct nourishing and enriching effect on the discipline of psychotraumatology [46-48].

The treatment of severe and chronic dissociative disorders requires a trauma-based approach that typically involves long-term psychotherapy and pharmacotherapy [49]. It is by no means possible to consider the treatment of dissociative disorders in modern therapeutic interventions in clinical psychology and psychiatry separately from trauma [6,23]. The "traumatic self", described by Öztürk [21] constitutes one of the most significant

psychic components of the "Trauma Based Alliance Model Therapy" which is also first described by Öztürk and forms the short-term psychotherapy of dissociative identity disorder. With the completion of the treatment of dissociative identity disorder, the traumatic self reaches back to the harmony it once had with the natural self; the individual whose therapeutic process has been terminated, thus, may continue their life with an integrated self as well as a singular identity [4].

The Academic Mass Against Psychotraumatology Studies: The Backlash Movement

The academic movement against psychotraumatology studies has a history focused on denial of traumatic reality that exceeds a century. Traumatic experiences are the most powerful and brutal weapons used to control individuals and societies and they negatively affect the well-being of both individuals and societies. This outdated academic movement has been repulsed by clinical psychologists, psychiatrists, psychohistorians, lawyers and judges that follow ethical values. The increasing academic and clinical interest in psychotraumatology, more specifically in dissociative disorders, has been very influential in this repulsion process. Experts in psychotraumatology, who are able to detect the longitudinal negative effects of chronic childhood traumas that start at an early age on the mental health of an individual and report these effects with scientific methods, are of vital importance in the struggle against this anti-trauma mass. In other words, they tend to function as neutralizers of the effects of the backlash movement that is repugnant to psychological trauma studies. Psychotherapists, who undertake the treatment of the immediate and long-term negative effects of dissociative identity disorder cases both in Turkey and all over the world have gained proud and significant success in combating this aforementioned anti-trauma mass in recent years [2,3,50].

The term "Backlash Movement" is used to describe both former and present anti-trauma masses, colleagues, academicians and mental health professionals. Gedney used the Backlash Movement in sense of spreading silence against the reality of child sexual abuse [51]. The mass who denies traumatic experiences (in the past as well as present) that is repugnant to trauma and dissociation studies may be found all over the world in a quite significant extent. This primitive mass can seriously hinder the development of policies to prevent childhood traumas. "This academic mass" is positioned in the ranks of the abusers under the influence of their unscientific approaches, and they may misinterpret the "apparently contradictory" testimonies and "tendency to hide" that can be observed in trauma victims due to the very natures of their psychiatric disorders such as dissociative disorders, post-traumatic stress disorder and borderline personality disorder as a proof of the lack of trauma. These apparently contradictory testimonies and tendencies to hide, however, occur after traumatic experiences and it is due to these experiences that trauma victims are diagnosed with a mental disorder. Both this psychiatric diagnosis and apparently contradictory testimonies and hiding tendencies are the clearest and definitive proofs of the reality of traumatic experiences [2,30].

Psychotraumatologist Academicians' Movement

Janet, with his ideations that provided a basis for countless treatment approaches such as the "functional dissociation of the self" taken into consideration, may be defined as the founder of the modern discipline of psychotraumatology [2]. It is possible to state that trauma-based psychotherapy models towards the treatment of dissociative disorders base upon Janet's conceptualizations [52]. Today, psychotraumatology studies are likewise nourished by clinicians and researchers that continue their practice without neglecting dissociative situations and utilizing trauma as a base point. It may be asserted that a great majority of these research includes those in the fields of clinical psychology, psychohistory and psychiatry [2]. When contemporary psychotraumatology approaches are taken into consideration, this integrative, innovative and pioneering role may be told to be played by clinical psychologists and psychiatrists that adopt trauma-based techniques with traumatized individuals as well as psychohistorians that richen the discipline with their studies on child-rearing styles and the history of childhood that is fraught with traumas. In this context, psychotraumatology includes a scientific movement that encapsulates both academic and clinical practices within: "Psychotraumatologist Academicians' Movement" as described by Öztürk [2]. Outputs of scientific journals on psychotraumatology as well as the studies of academicians on individual and collective traumas from all over the globe greatly contribute not only to the wider dissemination of the aforementioned movement, but also to the increase in its academic and general awareness [53].

Even though trauma and trauma-based dissociative disorders happen to be issues on which there is an increasing number of pioneering studies by scholars connected with the Psychotraumatologist Academicians' Movement being published in prestigious scientific journals, it is unfortunately likely to state that there is also a mass that neglects, even ignores these concepts. Referring to the general population as well as some mental health specialist, this "anti-trauma mass" [2] that particularly denies childhood abuse cases or widely avoids confronting such experiences is included in a backlash movement as defined by Gedney [51]. This indifference, insensitivity, apathy and even resistance [30] towards trauma and especially childhood traumatic experiences in mainstream psychology and psychiatry literatures are still present as an issue that needs to be considered in a collective scope in relation to its psychosocial dynamics by mental health specialists. Due to the fact that this issue may manifest itself either as negligence of traumas in clinical settings during therapeutic processes or misinterpretation of some phenomena in forensic proceedings, such as (apparently) contradictory statements and/or tendency for hiding that are inherent to trauma [54], it requires an extensive scrutiny.

Natural and Guiding Parenting Style: A Childhood Trauma Prevention Strategy

Today, the supportive parenting style that prioritizes growth, development and individualization has been considerably increasing in significance [50,55]. Especially among parents with a high socioeconomic level and education background, this style may be observed to be abused more. The most pathological form of supportive parenting is practiced today as the "friendly parenting style". In this parenting style, although parents desire to have children, they do not want to fulfill the responsibilities of being a parent in a semi-conscious or subconscious manner. In the friendly parenting style, parents in the family are in a constant competition with their children. Such parents are willing to look

young as their children do, and live their unoptimal childhood over. Parents who “apparently” fill their children’s schedules with private lessons, artistic, sports or cultural activities for them to be excluded from their parents, try to make the intolerance of spending one-on-one time with them and the rejection of parenthood more reasonable with this regressive strategy. What children need is the sincere interest and care of a parent who is capable of devoting the necessary time and providing a real, “natural and guiding” style to them. Öztürk recommends the "Natural and Guiding Parenting Style" that can be preferably applied by parents, who have an important share in the process of preventing childhood traumas [2,3,11].

The ability of both parents and children to use their instincts, intuition and predictions is the key element to prevent traumas, and instincts and intuitions prevail the natural parenting style. In child-rearing styles, it is essential that intuitions can be used as well as instincts. Especially in children, it is very important to use natural parenting styles until the abstract thinking stage. The notion of intuition refers to comprehend, feel, observe, immediately grasp, catch in a moment, sense and discover [56]. Intuition is also described as the ability to directly comprehend the truth without resorting to experimenting or reasoning, to sense events in advance without the help of any source, and to predict the truth without clear evidence. In terms of parenting, "intuition" should be an aspect of the correct parenting style. The most common feature that parents with the right parenting styles can use in their children's development is their intuition skills. There is a possibility of predicting and recognizing situations that may turn out to be traumatic. Since negative and stressful situations are often not intuited, they turn into traumatic experiences and cause dissociative reactions [2,11].

In this parenting style, methods that are generally transmitted from previous generations and whose accuracy has been proven in the intergenerational process may also be included. The guiding parenting style can be described as the mature form of the natural parenting style. In this respect, it includes the intuitive, empathic and emotional reciprocity of the natural parenting style. The usage of the guiding parenting style is especially when children develop abstract thinking. The basis of this parenting style is the trust-based, natural, empathic and emotional reciprocity established between children and parents, as well as the fact that parents are the most effective and functional guides with their exemplary behaviors to children in the formation of their characters and value judgments, career choices and future plans [2,3,11,26]. In the natural and guiding parenting style, parents may adapt to the lifestyles of their developing child on an empathic emotional basis with both a directive and an active orientation. In this parenting style, parents also have to protect their children from the negative life events of that accurate period. According to Öztürk, static parenting styles or parents who seek professional help only when a crisis occurs are constantly decreasing in number. Parents are required to informedly and correctly apply the primary intervention techniques to crises that do not require expertise regarding the negative experiences that the child will most likely to experience in each developmental period [2,3].

Results

The increase in the numbers of academic research in the fields of trauma and dissociation is accompanied by progress in the discipline of psychotraumatology and developments in clinical settings. Comprehension, explanation and prevention of these trauma-based clinical pictures have a major importance for all professionals and social scientists in the field of mental health, notably clinical psychologists and psychiatrists. Not unlike the very concept of “therapeutic alliance” that refers to the harmony and collaboration of an individual and their therapist and is seen as a basic component of a successful therapeutic process which also has a great importance according to the psychotraumatological approach, there is also a significant need of an “academic alliance” in the psychotraumatology axis which gives all specialists in social sciences as well as mental health professionals the opportunity to produce effective solutions to recent issues by following the most recent paradigm.

In his “Trauma Based Alliance Model Therapy” (TBAMT), Öztürk prefers the term “therapeutic reciprocity” over “therapeutic alliance” due to the fact that the former is more comprehensive as well as considering this reciprocity to be the most fundamental cornerstone of the procedure of treatment in all trauma-related psychiatric diagnostic groups. According to Öztürk, the therapeutic reciprocity, which possesses both stable and dynamic characteristics, is a treatment reconciliation in parallel to an experience of establishing an intellectual and affective bond that occurs within the frames of ethical limitations between the psychotherapist and the patient. In the cases of dissociative identity disorder, according to the method of Trauma Based Alliance Model Therapy, the therapeutic collaboration (alliance) between the host personality and the psychotherapist is not sufficient. This alliance or reciprocity requires to be constructed on a multitude of fundamental axes. A trilateral and tridirectional therapeutic alliance/concord/reciprocity between the psychotherapist, the host and alter personalities is especially prerequisite in the guidance of the psychotherapist. This prior condition constitutes the first and most basic axis of the treatment [30].

As a result, as it was emphasized before, it is unlikely to be able to conduct an effective psychotraumatological study without including early childhood traumas and dissociative disorders; as a matter of fact, some psychotraumatologists claim that post-traumatic stress disorder consists of a subset of psychiatric symptoms of dissociative disorders [2,4]. It is, thus, possible to refer dissociative disorders to be closely associated with chronic and early childhood traumas. Therefore, the prognosis of dissociative disorders needs to be taken into consideration with as equally great importance as that of post-traumatic stress disorder in trauma-related psychiatric disorders. Studies on dissociative disorders that peaked in early 1990’s all over the globe has been contributing to the field of psychotraumatology on both theoretical and clinical grounds. It is also possible to claim that post-traumatic stress disorder and dissociative disorders are in no way mutually exclusive prognoses; on the contrary, they tend to promote each other by their very natures. Due to all these reasons, post-traumatic stress disorder and dissociative disorders have vastly significant and premissing contributions to the development of modalities and paradigms related to modern psychotraumatology [2,5,6].

Conflict of interests

The authors declare that they have no competing interests.

References

1. Everly GS. Psychotraumatology: a two-factor formulation of posttraumatic stress. integrative physiological and behavioral science: Pavlovian Society. 1993;28:270-78.
2. Öztürk E. Travma ve dissosiyasyon: psikotravmatoloji temel kitabı. 2nd Edition. Nobel Tıp Kitabevi, İstanbul, 2020.
3. Öztürk E. Psikotarih, travma ve dissosiyasyon: çocukluk çağı travmaları, savaşlar ve dissosiyasyonun anamnezi. In: Öztürk E, ed, Psikotarih. Ankara: Türkiye Klinikleri. 2020;1-21.
4. Şar V, Öztürk E. Functional dissociation of the self: a socio-cognitive approach to trauma and dissociation. J Trauma Dissociation. 2007;8:69-89.
5. Derin G, Öztürk E. Savaş ve terörizm: psikotravmatolojik temelli teorik bir yaklaşım. Aydın İnsan ve Toplum Dergisi. 2020;6:11-36.
6. Ross CA, Halpern N. Trauma model therapy: a treatment approach for trauma dissociation and complex comorbidity. Greenleaf Book Group, Texas, USA. 2009.
7. Lating JM. Psychotraumatology: key papers and core concepts in post-traumatic stress. Plenum, 1995.
8. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (revised 3rd edition). Washington, DC, USA. 1987.
9. Maercker A, Augsburger M. Developments in psychotraumatology: a conceptual, biological, and cultural update. Clin Psy in Europe. 2019;1:1-18.
10. van der Haart O, Horst R. The dissociation theory of pierre janet. J Traumatic Stress. 1989;2:397-412.
11. Öztürk E. Psikotarih, ruhsal travma ve dissosiyasyon. In: Celbiş, O, ed, Turaz Akademi 2018. Ankara: Akademisyen Kitabevi. 2018;92-106.
12. Erdoğan B, Öztürk E. Ruhsal travmanın aktarımında narsisizm. Bartın Üni Edebiyat Fakültesi Dergisi. 2018;3:11-20.
13. Goetz CG. Charcot, the clinician: the tuesday lessons. excerpts from nine case presentations on general neurology delivered at the salpetriere hospital in 1887-88 by jean-martin charcot (translator). New York: Raven Press, 1987;1-6.
14. Ellenberger HF. The discovery of the unconscious: the history and evolution of dynamic psychiatry. New York: Basic Books. 1970;1:280-81.
15. van der Kolk BA, Weisaeth L, van der Hart O. History of trauma in psychiatry. In BA van der Kolk, AC McFarlane, L Weisaeth, eds, Traumatic stress. The effects of overwhelming experience on mind, body, and society. New York: Guilford Press, 1996;47-74.
16. Bowlby J. A secure base: parent child attachment and healthy human development. New York: Basic Books, 1988.
17. Freyd JJ, DePrince AP, Gleaves D. The state of betrayal trauma theory: reply to mcnally (2007)-conceptual issues and future directions. Memory. 2007;15:295-311.
18. Helms JE, Nicolas G, Green CE. Racism and ethnoviolence as trauma: enhancing professional training. Traumatology. 2010;16:53-62.
19. Kira IA, Templin T, Lewandowski L, et al. Cumulative trauma disorder scale (ctd): two studies. Psychology. 2012;3:643.
20. Teicher MH, Samson JA, Polcari A, et al. Sticks, stones, and hurtful words: relative effects of various forms of childhood maltreatment. American J Psychiatry. 2006;163:993-1000.
21. Öztürk E. Psikoterapide travmatik kendilik ve kendileşme. VIII. Bahar Sempozyumu, 14-18 April 2004. Antalya, Turkey, 55-7.
22. Öztürk E. Ruhsal bölünme: dissosiyasyon ve dissosiyatif bozukluklar, (psychological dividedness: dissociation and dissociative disorders). XIII. Annual Conference of the Turkish Psychological Association, 2004. Istanbul, Turkey.
23. Öztürk E. Dissosiyatif kimlik bozukluğunun psikoterapisi. PsikeDergi. 2009;2:39-49.
24. Öztürk E, Şar V. The trauma-self and its resistances in psychotherapy. J Psychol Clin Psychiatry. 2016;6:7-
25. Fischer G, Riedesser P. Lehrbuch der psychotraumatologie. München: Ernst Reinhardt Verlag, 1999.
26. Öztürk E. Travma kökenli dissosiyatif bozukluk vakalarının ailelerinde çocukluk çağı travmalarının sıklığı. Ph.D. Thesis, Istanbul University, Istanbul, 2003.
27. Horowitz MJ. Stress response syndromes (2nd ed.). Northwale NJ: Jason Aronson Inc. 1986.
28. Şar V, Öztürk E. What is trauma and dissociation?. J Trauma Practice. 2005;4(1-2):7-20.
29. Price J. Explaining human conflict: human needs theory and the insight approach. In Avruch K, Mitchell C, eds, Conflict resolution and human needs. New York, NY, USA: Routledge, 2013;108-23.
30. Öztürk E. Travma merkezli alyans model terapi: dissosiyatif kimlik bozukluğunun psikoterapisi. In Öztürk E, ed, Ruhsal Travma & Dissosiyasyon. Ankara: Türkiye Klinikleri, 2018;31-8.
31. Beere D. Loss of 'background': a perceptual theory of dissociation. Dissociation. 1995;8:165-74.
32. Basoglu M, Mineka S. The role of uncontrollable and unpredictable stress in post-traumatic stress responses in torture survivors. In M Basoglu, Ed, Torture and its consequences: current treatment approaches. Cambridge: Cambridge University Press, 1992.
33. Harvey JH, Weary G. Attribution: basic issues and application. Orlando: Academic Press, 1985.
34. Weiner B. An attributional theory of motivation and emotion. New York: Springer Verlag, 1986.
35. Galea S, Basham K, Culpepper L, et al. Treatment for posttraumatic stress disorder in military and veteran populations: initial assessment. Washington, DC: The National Academies, 2012.
36. Herman JL. Complex ptsd: a syndrome in survivors of prolonged and repeated trauma. J Traumatic Stress. 1992;5:377-91.
37. Brewin CR. Complex post-traumatic stress disorder: a new diagnosis in ICD-11. BJPsych Advances. 2020;26:145-52.
38. Barbano AC, van der Mei WF, Bryant RA, et al. Clinical implications of the proposed ICD-11 PTSD diagnostic criteria. Psy Med. 2019;49:483-90.
39. Stovall-McClough KC, Cloitre M. Unresolved attachment, ptsd, and dissociation in women with childhood abuse histories. J Cons Clin Psy. 2006;74:219.
40. Lanius RA, Vermetten E, Loewenstein RJ, et al. Emotion modulation in ptsd: clinical and neurobiological evidence for a dissociative subtype. American J Psychiatry. 2010;167:640-47.
41. Putnam FW, Guroff JJ, Silberman EK, et al. The clinical phenomenology of multiple personality disorder: review of 100 recent cases. J Clin Psychiatry. 1986;47:285-93.
42. Kluft RP. Dissociative identity disorder. In Handbook of dissociation. Springer, Boston, MA, USA. 1996;337-66.
43. Hilgard ER. Divided consciousness: multiple controls in human thought and action. John Wiley & Sons Inc, New York, USA. 1977.
44. Bailey TD, Brand BL. Traumatic dissociation: theory, research, and treatment. Clin Psy: Science and Practice. 2017;24:170-85.
45. Brand BL, Schielke HJ, Brams JS, et al. Assessing trauma-related dissociation in forensic contexts: addressing trauma-related dissociation as a forensic psychologist, part II. Psy Injury and Law. 2017;10:298-312.
46. Derin G, Öztürk E. Klinik siber psikolojiden adli siber psikolojiye: siber travma ve siber reviktimizasyon. In: Öztürk E, ed, Siber psikoloji. Ankara: Türkiye Klinikleri. 2020;14-24.
47. Erdoğan B, Öztürk E. Siber psikopatolojiler. In: Öztürk E, ed, Siber psikoloji. Ankara: Türkiye Klinikleri. 2020;25-32.
48. Öztürk E. Siber toplumlar ve siber hayatlar: dissosiyojen bir ajan olarak dijital iletişim ağları. In: Öztürk E, ed, Siber psikoloji. Ankara: Türkiye Klinikleri. 2020;1-13.
49. Brand BL. The necessity of clinical training in trauma and dissociation. J Depression and Anxiety. 2016;5:2167-1044.
50. Öztürk E. Psikotarih açısından çocuk yetiştirme tarzları ve çocuk istismarı. In: F Aşıcıoğlu, N Ziyalar, eds, Adli davranış bilimleri. Ankara: Türkiye Klinikleri. 2016;24-34.

51. Gedney N. A european response to the backlash movement. J Psychohistory. 1995;22:265.

52. van der Hart O, Nijenhuis ER, Steele K. The haunted self: structural dissociation and the treatment of chronic traumatization. WW Norton & Company, 2006.

53. Olff M. Psychotraumatology on the move. European J Psychotraumatology. 2018;9:1-7.

54. Öztürk E. Travma vakalarının klinik ve adli görüşmelerdeki görünürde çelişkili bilgi ve gizleme eğilimi açısından değerlendirilmesi. 1. Türk Adli Bilimler Kongresi, 20-30 April-1 May 2018. Amasya, Turkey, 55-7.

55. DeMause L. Foundations of psychohistory. London: Creative Roots Pub, 1982.

56. Özdemir O. Psikiyatride tanıya yardımcı bir araç: sezgi. Düşünen Adam. 2012;25:283.

Available online at www.medicinescience.org

MINI REVIEW

Medicine Science International Medical Journal

Medicine Science 2021;10(10):255-61

What are the best methods of airway management in COVID-19 patients?

Adel Hamed Elbaih[1,2], Moaaz Khaled Mohammed[2]

[1]Suez Canal University, Faculty of Medicine, Department of Emergency Medicine, Ismailia, Egypt
[2]Emergency Medicine, Sulaiman Al-Rajhi University, Clinical Medical Science, College of medicine, Saudi Arabia.

Received 05 October 2020; Accepted 02 November 2020
Available online 05.01.2020 with doi: 10.5455/medscience.2020.06.122

Abstract

COVID-19 (Corona Virus Disease-2019) is a viral contagious disease that spread through droplets and direct contact. although medical staff are equipped with personal protection gear but still there are increasing incidence of covid-19 among health care providers and airway management specialists in order to reduce this incidence it is Important to follow a special criterion when managing airway with covid-19 patients including staff distribution, equipment's preparing and intubation techniques Targeted Population: Adult patients COVID-19 who are in need endotracheal intubation to manage the airway at Emergency Department (ED), the hospital wards, or in the Intensive Care Units (ICU). Targeted End User: ER, ICU Physicians and all paramedics deals with COVID-19. this review article aims to provide the Doctors that are dealing with confirmed or suspected cases of COVID-19 with needed to maintain the airway with an organized method to manage the airway of those patients in the ED, isolation rooms in the wards or even in ICU, to secure the health of those physicians, optimize their efficiency, and increase the odds of achieving a successful airway maintenance from the first time. Collection of all possible available data about COVID-19 airway management in ED. By many research questions to achieve these aims so a midline literature search was performed with the keywords "critical care", "emergency medicine", "principals of COVID-19 airway management ", "COVID-19 and infections". All studies introduced that the initial airway management is a serious condition that face patients of the emergency and critical care departments. Literature search included an overview of recent definition, causes and recent therapeutic strategies. All studies introduced that initial airway management of COVID-19 in ER and ICU is a serious condition that face patients and physicians which may lead to death in both. Airway management in COVID-19 patients requires specific measurements to assure safety of the medical staff. Accuracy is crucial, and the physician must avoid ineffective techniques through the procedure of airway management, which will enable it to be safe, accurate and timely controlled.
.

Keywords: Airway management, COVID-19, physicians

Introduction

Since the appearance of the novel corona virus (2019-CoV) in Wuhan city, in China, it has been spreading in an accelerating pattern all over China and the whole world.

The Clinical data collection has been showing that. The incubation period is known to be from one day up to fourteen days, The World Health Organization (WHO) called this virus the new coronavirus 2019 (2019 – nCoV). On January 30, 2020, the WHO declared the 2019-nCoV as an epidemic, On February 11, 2020, the WHO announced a new name for the 2019-nCoV epidemic disease: coronavirus disease (COVID-19) [1].

On March 11 the WHO declared COVID-19 as pandemic. The numbers of people infected with this disease has reached 10,835,257 people around the world with 519,601 deaths and 6,054,119 recovered cases around the world the most infected countries are USA, Brazil, Russia and Spain which express that this pandemic disease has been [2].

All over the world and hitting all countries despite the wealth of the country or the level of the health care system More than half of the Emergency Department (ED) visits are non-urgent and do not require emergency care. [1] The increasing numbers of patients visiting the ED lead to crowdedness, long waiting time and a negative impact on patients' satisfaction. [2] Yet, more importantly, it results in unnecessary costs and wastes the resources of the institution and the time of physicians that would be otherwise directed to more serious cases. [3] Thus, Emergency Physicians (EP) need to follow a systematic approach in order to prioritize the care of patients based on their clinical urgency and highly infectious to hospital community.

***Corresponding Author:** Adel Hamed Elbaih, Suez Canal University, Faculty of Medicine, Department of Emergency Medicine, Ismailia, Egypt.
E-mail: elbaihzico@yahoo.com

Triage is defined as the process of sorting patients based on the acuity of their condition. When patients are sorted according to their immediate presentation this ensures that severely ill or highly infectious patients rapidly isolated before their condition gets worse or spreading to all. [4, 5]

Coronaviruses are a large family of viruses, which may cause illness in animals or humans. In humans, several coronaviruses are known to cause respiratory infections ranging from the common cold to more severe diseases such as Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS). The most recently discovered coronavirus causes coronavirus disease COVID-19 [7].

The most common symptoms of COVID-19 are fever, tiredness, and dry cough. Some patients may have aches and pains, nasal congestion, runny nose, sore throat or diarrhea. These symptoms are usually mild and begin gradually. Some people become infected but do not develop any symptoms and do not feel well. Most people (about 80%) recover from the disease without needing special treatment. Around 1 out of every 6 people who gets COVID-19 becomes seriously ill and develops difficulty breathing. Older people, and those with underlying medical problems like high blood pressure, heart problems or diabetes, are more likely to develop serious illness. People with fever, cough and difficulty breathing should seek medical attention [8].

People can catch COVID-19 from others who have the virus. The disease can spread from person to person through small droplets from the nose or mouth which are spread when a person with COVID-19 coughs or exhales. These droplets land on objects and surfaces around the person. Other people then catch COVID-19 by touching these objects or surfaces, then touching their eyes, nose or mouth. People can also catch COVID-19 if they breathe in droplets from a person with COVID-19 who coughs out or exhales droplets. This is why it is important to stay more than 1 meter away from a person who is sick [9].

While we are still learning about how COVID-2019 affects people, older persons and persons with pre-existing medical conditions (such as high blood pressure, heart disease, lung disease, cancer or diabetes) appear to develop serious illness more often than others do. The mortality of critically ill patients with SARS-CoV-2 pneumonia is considerable. The survival time of the non-survivors is likely to be within 1–2 weeks after ICU admission. Older patients (>65 years) with comorbidities and ARDS are at increased risk of death. The severity of SARS-CoV-2 pneumonia poses great strain on critical care resources in hospitals, especially if they are not adequately staffed or resourced [8].

While some western, traditional or home remedies may provide comfort and alleviate symptoms of COVID-19, there is no evidence that current medicine can prevent or cure the disease. WHO does not recommend self-medication with any medicines, including antibiotics, as a prevention or cure for COVID-19. However, several ongoing clinical trials include both western and traditional medicines. WHO will continue to provide updated information as soon as clinical findings are available. Not yet. To date, there is no vaccine and no specific antiviral medicine to prevent or treat COVID-2019. However, those affected should receive care to relieve symptoms. People with serious illness should be hospitalized. Most patients recover thanks to supportive care [7].

The most effective ways to protect yourself and others against COVID-19 are too frequently clean your hands, cover your cough with the bend of elbow or tissue, and maintain a distance of at least 1 meter from people who are coughing or sneezing.

Call your doctor: If you think, you have been exposed to COVID-19 and develop a fever and symptoms, such as cough or difficulty breathing, call your healthcare provider for medical advice these symptoms may appear 2-14 days after exposure [9].

If you develop emergency warning signs for COVID-19 get medical attention immediately. Emergency warning signs include*:

- Difficulty breathing or shortness of breath
- Persistent pain or pressure in the chest
- New confusion or inability to arouse
- Bluish lips or face

Early information out of China, where COVID-19 first started, shows that some people are at higher risk of getting very sick from this illness. This includes:

- Older adults
- People who have serious chronic medical conditions like:

Heart disease

Diabetes

Lung disease

If you are sick with COVID-19 or suspect you are infected with the virus that causes COVID-19, you should take steps to help prevent the disease from spreading to people in your home and community [7].

The ED is one of the busiest departments at these hospitals, providing care for all kind of cases, including road traffic accidents (RTA) and patients with medical, surgical, obstetrics or pediatrics emergencies. Therefore, it is usually crowded with patients and their families these increase incidence of infections. The increasing number of patients presenting to ED necessitates applying an efficient triage system in order to stop wasting our resources and provide the best care for patients in need within the ideal time without harmful infectious hazards. Furthermore, it helps to attain patients trust and boosts patients' satisfaction.

Therefore, out of the above-mentioned reasons, this study provides the Doctors that are dealing with confirmed or suspected cases of COVID-19 with needed to maintain the airway with an organized method to manage the airway of those patients in the ED, isolation rooms in the wards or even in ICU, to secure the health of those physicians, optimize their efficiency, and increase the odds of achieving a successful airway maintenance from the first time.

Definition of the pathogen and identifying the problem

Severe acute respiratory syndrome-corona virus-2 (SARS-CoV-2), which causes

COVID-19 is a single-stranded ribonucleic acid -encapsulated

corona virus and is highly contagious.

The virus is primarily spread between people during close contact most often via small droplets produced by coughing sneezing, and talking. The droplets usually fall to the ground or onto surfaces rather than travelling through air over long distances However, research as of June 2020 has shown that speech-generated droplets may remain airborne for tens of minutes Less commonly, people may become infected by touching a contaminated surface and then touching their face. It is most contagious during the first three days after the onset of symptoms, although spread is possible before symptoms appear, and from people who do not show symptoms, common symptoms include fever, cough, fatigue, shortness of breath, and loss of sense of smell [8].

Complications may include pneumonia and acute respiratory distress syndrome which require urgent medical intervention and quick airway management or introducing endotracheal tube

Although the virus spread through droplets but aerosol producing measures that stimulate coughing and promote the generation of aerosols can convert the method from droplet spread into air borne which increase the risk for health care providers who are dealing with airway management procedures, in the following are ranked airway procedures in descending order of risk as:

1. Endotracheal intubation approach.
2. Cricothyroidotomy approach.
3. Tracheotomy approach.
4. Bi-level positive airway pressure.
5. High Flow Nasal Oxygen therapy
6. Bag valve mask.

Incidences of covid-19 in health care providers in some countries

Increased numbers of sick people specially those who went into hospitals cause the illness to spread faster during the hospital staff and environment. doctors then have a higher chance of exposure and acquiring the infection. For example In China, there was more than 3,300 physicians got the disease (4% of the 81,285 reported infections). On the side of the world Spain reported, nearly 6,500 health care provider got infected and (13.6%) of the country's 47,600 total cases – 1% of the health system's workforce [9].

Indication of intubation which exacerbate the problem

despite that most of patients are going to have mild symptoms and will not come to the hospital, the prognosis of the disease for those who may develop severe symptoms and end up with severe respiratory distress are relatively slow (9-10 days). Those patient may have severe symptoms throughout the isolation that end up requiring emergency intubation. such as the following:

- Elevated breathing effort
- Patient developed acute hypoxia indicating respiratory failure that is not responding to high flow nasal oxygen therapy or bi-level positive airway pressure for two hours.
- Patient with hypoxia and losing consciousness or control of his/her airway.
- Hypoxic patient with huge amount of secretions that block the airway.
- Patient with hypercapnia respiratory failure which is not responding to high flow nasal oxygen therapy or the bi-level positive airway pressure therapy.
- Patient with Hemodynamic instability.
- Patient on high flow nasal oxygen therapy or bi-level positive airway pressure therapy that needs transferring by ambulance [10].

Contraindications

Any patient that does not have any of the indication is considered as contraindicated for intubation due to the lack of benefit and increase of harm.

Rationale and description of the problem

Covid-19 is a highly contagious respiratory infection that spread throughout droplets and direct contact.

It is found that the highest viral load of the Severe Acute Respiratory Syndrome of Coronavirus 2 (covid-19) present in the patient sputum and saliva. Then why the general infectious measurements and precautions is not sufficient to protect the Health Care Workers Specially Airway management specialists? Because endotracheal intubation is a risky way of managing the airway due to high percentage of exposure to viral load. And also it is believed that intubation and ventilation can change the mode of transmission from droplets into air-borne and for this matter, health care workers whom provide airway management must take special measurements and precautions that is made for this specific disease and not the general precautions for other infectious diseases. And here comes the importance of this article explaining not only the method of securing the airway, providing the appropriate way of controlling the environment to reduce risk of contamination and also to demonstrate the proper way of wearing and disposing the personal protective equipment [11].

The study question

What is the best guideline to prevent the increased incidence of Covid-19 in Airway? Management specialists and healthcare providers, despite the use of personal

Protective equipment?

Why this study is necessary?

During covid-19 epidemic, health care system is already overwhelmed due to the rapid transmission of the disease an increase of the infection among health care providers will increase the problem and will exacerbate and speed up the failure of the health care systems and this why we need to protect the doctors by equipment and guidelines.

Methods

This paper was done by reviewing over 20 research papers,

excluding the un-matched Papers and summarizing the included studies

Inclusion criteria

1-researches discussing the airway management in covid-19 patients

2-papers must be in English

3-Papers must be recent (last 4 months)

Collection of all possible available data about COVID-19 airway management in ED. By many research questions to achieve these aims so a midline literature search was performed with the keywords “critical care”, “emergency medicine”, “principals of COVID-19 airway management ", "COVID-19 and infections”. All Literature search included an overview of recent definition, causes and recent therapeutic strategies.

Discussion of the research question

In order to reduce the incidence a complete set of actions must be done and specific guidelines must be followed along the process of approaching the patient, approaching the intubation and during the process of before and after care process [12-14] (Figure1,2,3).

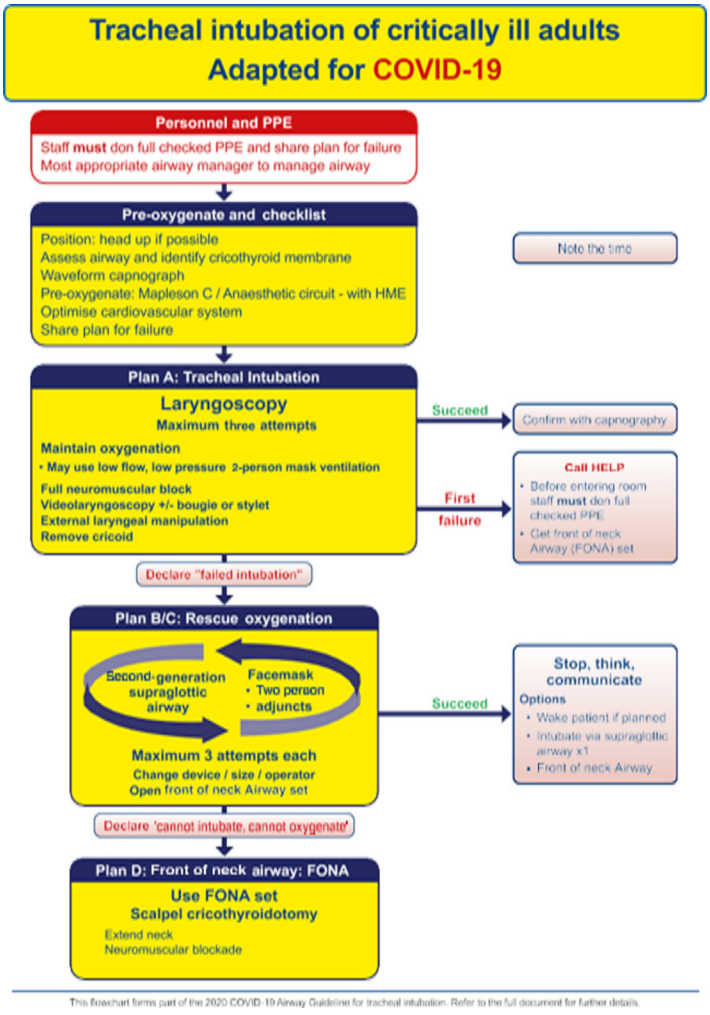


Figure 1. Approach to Covid-19 patient

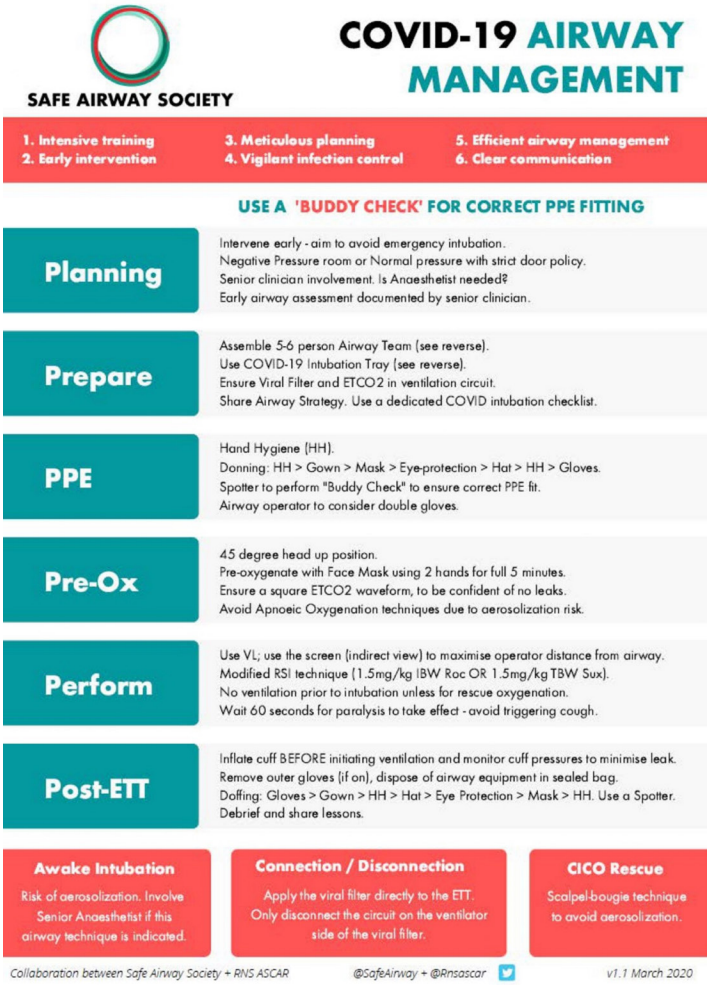


Figure 2. Criteria of intubation in Covid-19 patient

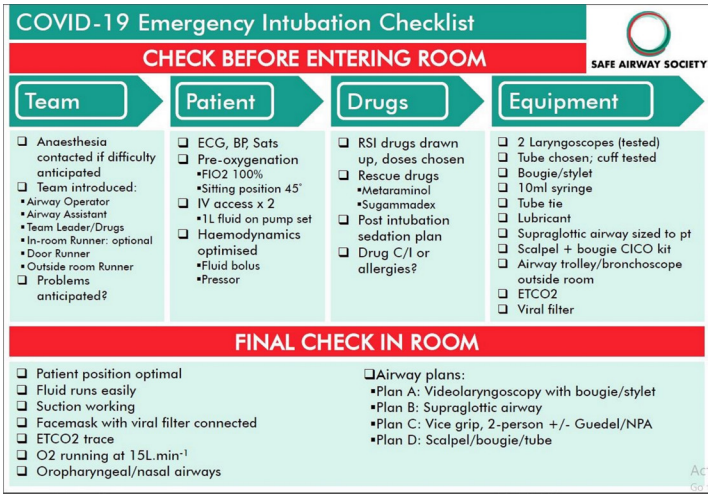


Figure 3. Check list for covid-19 intubation

If the intubation failed

1. Secure the airway by applying an oral airway,
2. Apply oxygen via your Bag Valve Mask using both hands
3. Ask for co-worker help if available with full personal protective equipment
4. The risk of controlled ventilation (6-10 breaths over 1 minute)

must be balanced against worsening hypoxemia that results in cardiac arrest.

5. If you are able to maintain saturations than you have to consider whether a second attempt
6. try to use bi-level positive airway pressure ventilation
7. If you cannot keep level of oxygenation by the previous methods perform an emergency cricothyrotomy [15].

The best method to prevent or reduce the environmental contamination

- Always prepare your equipment and the use the appropriate ones [16] (Figure 4).

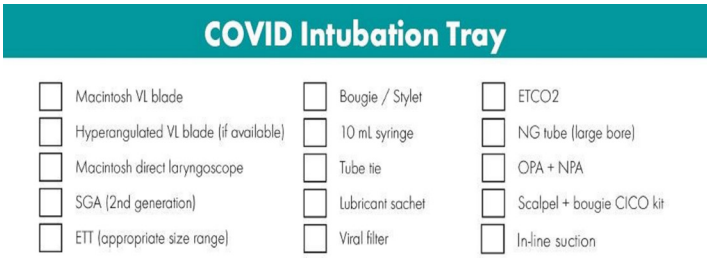


Figure 4. COVID intubation tray

- Reduce the contamination by distributing the staff in an appropriate way (Figure 5).

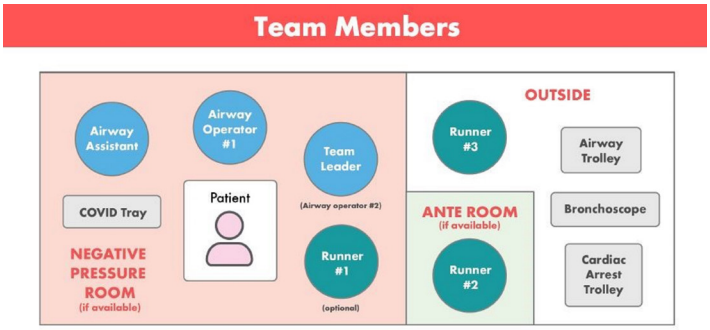


Figure 5. Team members

- Reduce the contamination by controlling the equipment involved [17] (Figure 6).

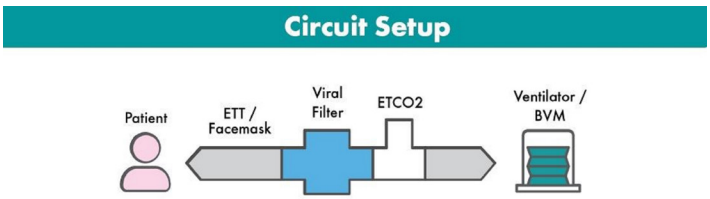


Figure 6. The Controlling Circuit setup

Drugs needed during intubation (Table 1,2).

Table 1. Sedative drug to help introduce endotracheal tube

Name	Dose (IV)	Advantages	Disadvantages
Etomidate	0.3mg/kg	Rapid onset, ultrashort duration, reduced ICP, no effect on hemodynamics	nausea and vomiting, adrenal insufficiency (rare)
Propofol	1- 1.5mg/kg	Rapid onset, short duration, reduced ICP, anti-nausea, anti- seizure	Lower BP, pain at site of administration (use large bore cannula in large peripheral veins), allergy (very rare and in people with anaphylaxis secondary to Eggs)
Ketamine	1- .5mg/kg	Rapid onset, duration 10-15 min, analgesic effect, bronchodilators, no effect on hemodynamics, improved CPP	Masseter muscle spasm, urgence hallucination
Midazolam	0.05- 0.1mg/kg	Rapid onset, short duration, antiseizure	Negative inotropic effect, variable effect
Fentanyl	1-2mcg/kg	Analgesic, fast onset, duration 30- 60 min, decrease sympathetic stimulation	Negative inotropic effect, acute chest rigidity syndrome

Table 2. Paralytic Agent for Intubation

Name	Dose (IV)	Advantages	Disadvantages	Antidote
Etomidate	0.6-1mg/kg	No side effects	Longer action (30-60 sec). Duration (30-60 min).	Sugammadex (16mg/kg IV)
Propofol	1-1.5mg/kg	Rapid Onset (10-15 sec) Short duration (6-10 min)	Hyperkalemia. Malignant hyperthermia. Cardiac dysrhythmias	Not found

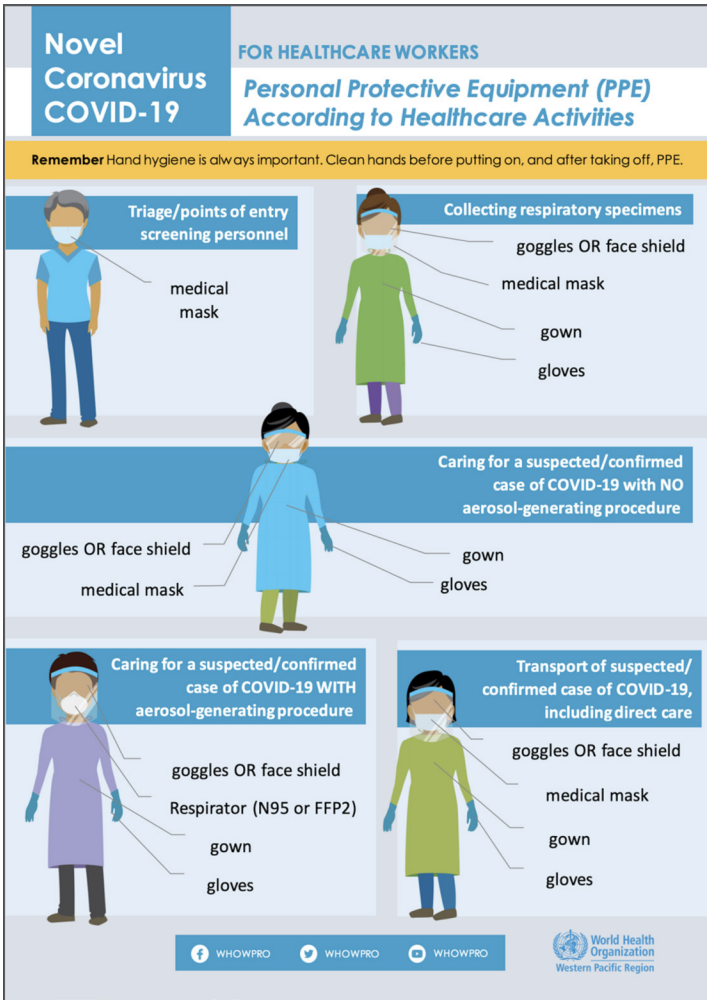


Figure 7. Personal protective equipments needed for contact with Covid-19 patients

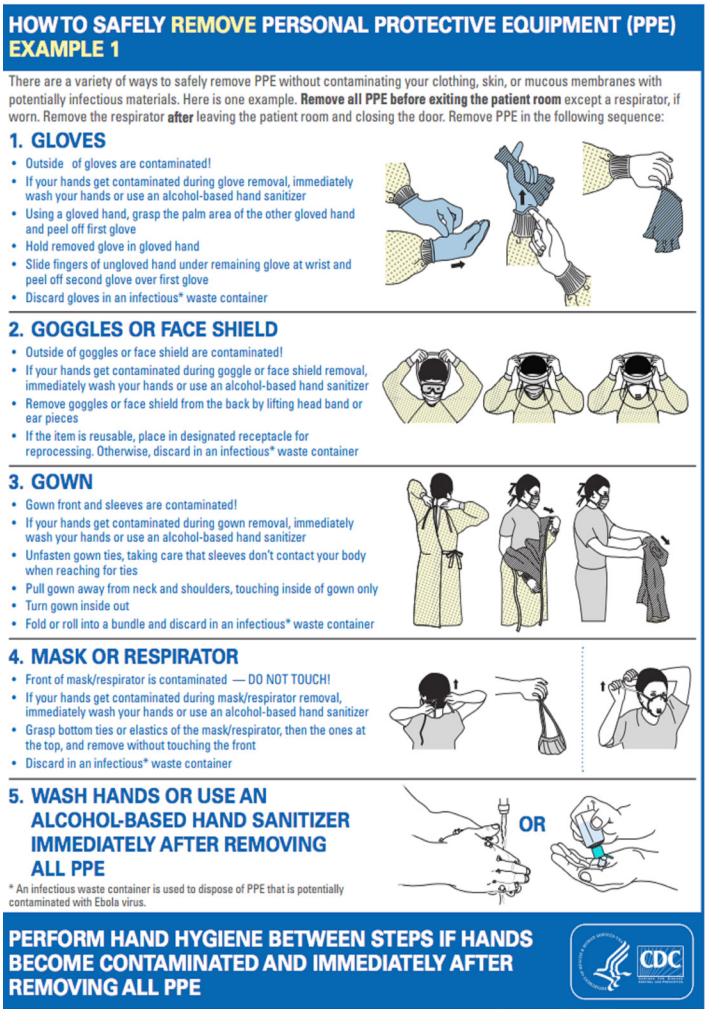


Figure 8. Personal protective equipments needed for contact with Covid-19 patients

Recommendations

Because of the new structure and clinical features of novel corona virus (covid-19), there are very few amount of information about the disease, and no available vaccines or specific medications yet. So at the moment the guidelines are mainly concentrated and concerned on stopping the spread of the disease (primary prevention). The Health care providers whom are responsible of airway management in infected patients should be aware of the following recommendations to reduce the risk of getting the infection.

- Always Follow the 6Ps rules
- Always Use the criteria that is found for covid-19 not general infectious diseases
- Practice on wearing the personal protective equipment in the best way
- Practice on performing efficient airway management while wearing the personal protective equipment
- Although there is lack of evidence it is better for doctors with chronic diseases such as hypertension, diabetes, or above 60 years old to avoid airway management areas

Conclusion

Airway management in COVID-19 patients requires specific measurements to assure safety of the medical staff. Accuracy is crucial, and the physician must avoid ineffective techniques through the procedure of airway management, which will enable it to be safe, accurate and timely controlled. We have highlighted principles that may achieve these goals such as the 6Ps, the distribution of the medical team and the appropriate equipment and depending on only one aspect will not be enough rather it is essential to follow and obey to all these measures, all details of these methods may change as new information may appear to the surface.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
All authors declare no financial support.

References

1. Tsai JC, Liang Y, Pearson WS. Utilization of emergency department in patients with non-urgent medical problems : patient preference and. J Formosan Medl Association. 2010;109:533-42.
2. Yang KK, Shao S, Lam W. Managing emergency department crowding through improved triaging and resource allocation. Operations Res Healt Care. 2016;10:13–22.

3. Elbaih, AH. Different Types of Triage. Arşiv Kaynak Tarama Dergisi . Arch Med Rev J. 2017;26:441–67.

4. Rominski S, Bell SA, Oduro G, et al. The implementation of the South African Triage Score (SATS) in an urban teaching hospital, Ghana Sarah. African J Emerg Med. 2014;4:71-5.

5. Twomey M, Wallis LA, Myers JE. Limitations in validating emergency department triage scales. Emerg Med J EMJ. 2007;24:477–9.

6. Farrohknia N, Castrén M, Ehrenberg A, et al. Emergency Department Triage Scales and Their Components : A Systematic Review of the Scientific Evidence. Scand J Trauma Resusc Emerg Med. 2011;19:42.

7. Elbaih1AH, Alnasser SR. Teaching approach for START triage in disaster management. Med Science 2020;9(4):1109-12.

8. Olmedo LLF, Ruiz DSC, Rivera AP, et al. Airway Management Recommendations in Coronavirus Disease 2019 (Covid-19) Patients. Anaesth & Surg Open Access J. 2020;1:1-3.

9. Consensus guidelines for managing the airway in patients with COVID-19: guidelines from the difficult airway society, the association of anaesthetists the intensive care society, the faculty of intensive care medicine and the royal college of anaesthetists. Anaesthesia. 2020;75:785-99.

10. Airway Management in COVID 19 Patients Guidelines. Ministry of Health. Published Online: May 13, 2020.

11. Elbaih AH, Basyouni FH. Teaching Approach of Primary Survey in Trauma Patients. Sun Text Rev Surg. 2020;1:1:7.

12. Kovacs G, Sowers N, Campbell S. Just the Facts: Airway management during the coronavirus disease 2019 (COVID-19) pandemic. CJEM. 2020;22:440-4.

13. Wang W, Xu Y, Gao R, et al. Detection of SARS-CoV-2 in different types of clinical specimens. JAMA. 2020;323:1843-4.

14. Elbaih AH, Elsayed Z, Ahmed RM, et al., Sepsis patient evaluation emergency department (SPEED) score & mortality in emergency department sepsis (MEDS) score in predicting 28-day mortality of emergency sepsis patients, Chin J Traumatol. 2019;22:316-22.

15. Wu Z, McGoogan JM. Characteristics of and important lessons from the Coronavirus disease 2019 (COVID-19) outbreak in china. Summary of a report of 72,314 cases from the chinese center for disease control and prevention. JAMA. 2020;323:1239-42.

16. Cheung JCH, Ho LT, Cheng JV, et al. Staff safety during emergency airway management for COVID-19 in Hong Kong. Lancet Respir Med. 2020;8:e19.

17. Elbaih AH, Ahmed MY, Nemr NA, et al. Validity of systemic inflammatory response syndrome (sirs) criteria, interleukin-6 and (meld) score as prognostic tools in cirrhotic patients with acute renal failure admitted to emergency department in suez canal university hospital, Egypt. Med Sci. 2017;6:319e327.

18. Public Health England. COVID-19: infection prevention and control guidance. 2020. https://www.gov.uk/government/ .

Available online at www.medicinescience.org

MINI REVIEW

Medicine Science International Medical Journal

Medicine Science 2021;10(1):268-70

Bee…. my honey, you are now my first love" – A whimsical review

Amit Kumar C Jain

Amit Jain's Diabetic Foot and Wound Research Unit, Amit Jain's Institute of Diabetic Foot and Wound Care, Brindhavvan Areion Hospital, Bengaluru, India
Department of Surgery, Raja Rajeswari Medical college, Bengaluru, India

Received 12 September 2020; Accepted 01 November 2020
Available online 17.01.2021 with doi: 10.5455/medscience.2020.09.185

Abstract

Honey is a natural therapeutic agent with many health-related benefits. Used in ancient era, it has found its place in modern wound care in view of its antimicrobial properties. Effective for different types of wounds, medical grade honey places an essential role in biofilms management and in cases of multidrug resistant bacterial infection. After knowing its properties, this agent is increasingly being used in different parts of the world by wound care experts to promote wound healing and sterilize the wound. This article aims to describe honey in a whimsical manner highlighting its properties.

Keywords: Diabetic foot, honey, wounds

Introduction

Honey, which is considered to be the nectar of the gods, is a wonder of nature [1, 2]. The nutritional and health benefit of it has been described since ages [3]. This sweet, flavorful nectar is gathered by bees from plants and is stored in the honey combs' [2, 4, 5]. The nectar is converted to honey by bees through process of regurgitation and evaporation and this is stored in bee hive [6]. Using honey and other bee products is known as Apitherapy [5].

History

Use of honey has been long in human history [7]. The humans started hunting honey around 8000 years ago [8]. The honey was first mentioned in wounds in ancient Egypt between 2600-2200 BC [9]. The healing properties of this golden yellow liquid have been found in Bible, Vedas, Quran and the Torah [6, 10]. The ancient Egyptians, Greeks and Romans employed honey for wounds and intestine problems [11]. Honey was used for embalming the dead in ancient Egypt [11]. In ancient India, the Vedic civilization also acknowledged honey to be a beneficial gift of nature [11]. In Ayurvedic scriptures, honey was called Madhu [6]. The honey was classified into 2 types namely, Navina Madhu, which is the fresh honey and the Purana Madhu, which is the old honey [6]. Hippocrates also observed that honey could clean sores and ulcers of lips [12]. Babylonians used honey for eye and ear infections whereas Greeks used honey to treat fatigue [12].

Honey Composition

Honey is made up of sugars, water and contains various proteins and vitamins like B complexes and vitamin C along with minerals like Zinc, Calcium, etc [13]. Natural honey is believed to have more than 300 constituents [4].

The sugar content in honey could be as high as 80-90% with fructose and glucose being the main sugars [5, 12]. The water content in honey is less than 20% [14]. The PH of honey is between 3.4 - 6.1 and there are about 30 organic acids in honey with gluconic acid being most common and it ranges from 0.23-0.98% [12, 14]. Honey has around 18 amino acids and more than 600 volatile organic compounds like ketones, aldehydes, etc [12].

Types of Honey and Honey Bees

There are different types of bees like honey bee, stingless bee, nectarina wasps, etc [12]. In South Asia and countries like India, honey is obtained from Apis species [11, 15]. In India, more than 90% of honey is believed to be from Apis dorsata [16].

Based on the source of nectar, honey could be floral and non-floral honeys. Honey can also be unifloral or multifloral depending

***Corresponding Author:** Amit Kumar C Jain, Amit Jains Institute of Diabetic foot and Wound Care Brindhavvan Areion Hospital, Bengaluru, India
E-mail: dramitkumarcj@yahoo.in

whether it is collected from same flower or different type of flower [5]. Non-floral honeys are obtained from fruits, tissues of plants or from excretions of insects (Aphids) [5]. The honey obtained from plant sucking Insects (Aphids) is called Forest honey/honey dew [4, 12].

The floral honey or blossom honey is obtained from nectars and are also called nectar honeys [4]. A bee hive has 3 honeybee caste namely the Queen (Alpha), the Worker (Beta) and drone (Gamma). The worker bees travel up to 9km to obtain this nectar [12].

HONEY IN WOUNDS

As one of the experts in diabetic foot and wound care, we often use medical grade honey in wounds. Medical grade honeys are those which are gamma irradiated [17]. Gamma irradiation sterilizes the honey effectively and does not alter its physico-chemical properties [18].

Different honeys are used with success in different parts of the world and they include manuka, gelan, tulang honey, etc [19]. There are different studies from different countries like Egypt, India, Nigeria, Saudi Arabia, etc that have shown the effectiveness of those honey [20]. We use medical grade Indian honey obtained from giant Coombs of Apis dorsata [21] at our Institute (Figure 1).

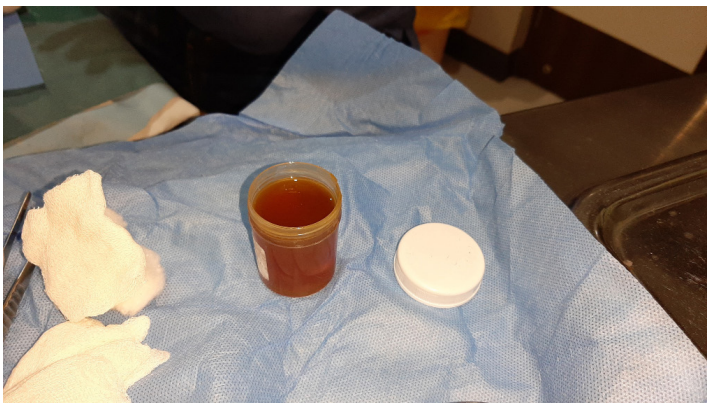


Figure 1. Gamma irradiated Indian honey from Apis species used at our institute. It is applied on sterile gauge which is then placed on the wounds

The antimicrobial activity of honey in modern medicine was first recognized by Van Ketel in 1892 [11]. Honey has both bacteriostatic and bactericidal activity and its antibacterial activity can be up to hundred folds [20, 21].

Honey inhibits around 60 species of bacteria including resistant strains apart from being fungicidal [11, 17]. The organism's sensitive to honey include staphylococcus pseudomonas, streptococcus, salmonella, klebsiella, etc [9, 11, 17].

The antimicrobial properties of honey are due to its hygroscopic effect from its high sugar, due to its low PH as acidity inhibits growth of most organism, hydrogen peroxide and several phytochemical factors [9, 11]. It is known that apart from hydrogen peroxide, the flavonoids like Pinocembrin, Pinobanksin and Chrysin along with phenolic acids are also antimicrobial/Inhibines in nature [8]. Hydrogen peroxide (concentration low) being a main antimicrobial, is known to cause oxidative damage that leads to bacterial growth inhibition and DNA degradation [12].

It is known that wound treated with honey are rendered sterile in 7-10 days of starting the treatment and it promotes healthy granulation tissue [22]. However, when one uses medical grade honey topically, it is better to be applied on the gauze first which is then placed on the wound and then pads are placed over it [21]. One should not apply honey directly on exudating wounds as it can be washed away by exudate [23].

Honey has been used in various different acute and chronic wounds and has found to be very effective. These wounds include diabetic foot ulcers, venous ulcers and pressure ulcers that are often seen in extremities [9]. Studies have shown that when honey is used in venous leg ulcers, it reduced pain and wound size [20]. A study by Othman et al showed that honey leads to wound healing and decrease amputations in diabetic foot ulcers [24]. Other sites where honey is also used is sacral wounds and in head and neck wounds [9, 19]. Honey was found protective in radiation induced mucositis in head and neck cancers [9]. Honey is also used in burns [14, 19]. Honey is also used in malodorous malignant wounds [23]. Some studies also found honey to be effective in mouth ulcers [23].

Studies have been done comparing honey with different antimicrobial agents like nitrofurazone and povidone iodine wherein honey was found to be better or as effective as these agents [20]. A study from north India showed honey to be better than povidone dressings in terms of healing, allergy, reduction in amputation and hospital stay [25].

At our institute, we have used honey commonly for extremity wounds especially in diabetic wounds, frequently in situation where there are persistent biofilms that were not controlled with other antimicrobial agents. After seeing its good results, it has now become our first preference that led us to open a new eponymous wing in the year 2020 within our Institute, that is known as "Amit Jain's Centre for Apitherapy" wherein we started using gamma irradiated honey on most wounds where biofilms are not irradicated easily and also in non-healing wounds. This unique Centre on apitherapy will treat wounds with honey and it also aims in teaching, propagating benefits of honey on wounds and publishing research work on honey. In one of our recent publication [21], we showed honey to be effective in moisture associated skin damage especially when there is high exudate as honey has good anti-inflammatory properties [9].

The side effects and resistance to honey is rare though it can cause stinging sensation [13]. We too noticed in a few patients, especially those who don't have neuropathy, to complaint of stinging sensation in first one or 2 sittings of honey after which they don't complaint. Another important issue we noticed is the presence of red ants in one of our case This can happen where the padding is inadequate or the external surface of the dressing is touched by gloves or instrument having honey remnants. We started using lot of pads and also, we change our gloves and segregate the honey laden instrument after applying honey from the sterile pads which are applied only after changing the gloves. Even the person handling the honey is strictly advised not touch any surface on dressing trolley till gloves are disposed to avoid red ants. We store our honey in double containers too.

A caution has been often advised when using unsterile honey as it can contain yeast and bacteria in it. Even spores of bacteria are found in it [22]. It is better to sterilize it with gamma irradiation before considering it to be used on wounds. We sterilized our honey with 15 kGy gamma irradiation (cobalt 60) and post sterilization, the honey was re-cultured and it found to have no growth after which we use the honey on wounds [21].

Honey is also used along with alginates and hydro fiber dressings [23].

Conclusion

Honey is a natural therapeutic agent with many health benefits. Its role in wound care is well established and is used frequently in different parts of the world. With broad spectrum antimicrobial activity along with anti-inflammatory action, it sterilizes wound and promotes wound healing. With many benefits of this god's nectar, there is no doubt that honey is now my first love in wound care with other wound care products being second choice, especially when there is multi-resistant bacterial infection and in biofilms.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
The financial support no have.

References

1. White E. Honey: Antimicrobial and antibacterial nectar of the gods. Wounds UK 2019;15:70.
2. Kumar KPS, Bhowmic D, Chiranjib, et al. Medicinal uses and health benefits of honey: An overview. J Chem Pharm Res. 2010;2:385-95.
3. Samarghandian S, Farkhondeh T, Samini F. Honey and health: A review of recent clinical research. Pharmocognosy Res. 2017;9:121-7.
4. Ajibola A. Novel insights into the health importance of natural honey. Malays J Med Sci. 2015;22:7-22.
5. Manu-Loh CE, Clarke AM, Ndip RN. An overview of honey: Therapeutic properties and contribution in nutrition and human health. Afr J Microbiol Res. 2011;5:844-52.
6. Arawwawala LDAM, Hewageegana HGSP. Health benefits and traditional uses of honey: A review. J Apither. 2017;2:9-14.
7. Meo SA, Al –Asiri SA, Mahesar AL. Role of honey in modern medicine. Saudi J Bio Sci. 2017;24:975-8.
8. Xaidi MZ, Sharma J. Honey and its beneficial therapeutic effects: A review. J Pharmo Phytochem. 2019;8:1056-61.
9. Song JJ, Salcido R. Use of honey in wound care: An update. Adv Skin Wound Care. 2011;24-40-4.
10. Bangaroo AK, Khatri R, Chauhan S. Honey dressing in Pediatric burns. J Indian Assoc Pediatr Surg. 2005;10:172-5.
11. Eteraf-Oskouei T, Najafi M. Traditional and modern uses of natural honey in human diseases: A review. Iran J Basic Med Sci. 2013;16:731-42.
12. Saranraj P, Sivasakthi S. Comprehensive review on honey: biochemical and Medicinal properties. JAIR. 2018;69:165-81.
13. Nanda MS, Mittal SP, Gupta V. Role of honey as adjuvant therapy in patients with sore throat. Natl J Physiol Pharm Pharmacol. 2017;7:412-5.
14. Cooper R. Honey as an effective antimicrobial treatment for chronic wounds: Is there a place for it in modern medicine. Chronic Wound Care Management Res. 2014;1:15-22.
15. Nagir MT, Atmowidi T, Kohono S. The distribution and nest site preference of Apis dorsata bingheimi at Maros forest, South Sulawesi, Indonesia. J Insect Biodiversity. 2016;4:1-14.
16. Basavarajappa S, Raghunandan KS, Hegde SN. Physico-biochemical analysis of multifloral honey of Apis Dorsata Fab. (Hymenoptera:Apidae) in southern Karnataka, India. Current Biotica. 2011 5:144-56.
17. Cooper R. The use of honey in diabetic foot ulcers. Diabetic Foot J. 2017;20:154-9.
18. Bera A, Almeida-muradian LB, Sabato SF. Effect of gamma radiation of honey quality control. Radiation Physicis Chemistry. 2009;78:583-4.
19. Yaghoobi R, Kazerouni A, Kazerouni O. Evidence for clinical use of honey in wound healing as an antibacterial, anti-inflammatory, antioxidant and antiviral agent: A review. Jundishapur J Natural Pharmaceutical Products. 2013;8:100-4.
20. Alam F, Islam MA, Gan SH, et al. Honey: A potential therapeutic agent for managing diabetic wounds. Evidence Based Complementary and Alternative Medicine. 2014;169130.
21. Jain AKC, Apoorva HC. Medical grade Indian honey is an effective agent in moisture associated skin damage. SAR J Med Case Rep. 2020; 1:21-5.
22. Singh MP, Chourasia HR, Agrawal M et al. Honey as complementary medicine- a review. Int J Pharma Bio Sci. 2012;3:12-31.
23. Simon A, Traynor K, Santos K et al. Medical honey for wound care- still the "Latest Resort". Evid Based Complement Alternat Med. 2009;6:165-73.
24. Othman AA, Balila RMH, Mahdi SI, et al. Healing potential of propolis and bee's honey on diabetic foot ulcers in Jabir Abu Eliz Diabetic Centre-Khartoum. Sudan Med J. 2016;52:81-4.
25. Yadav AK, Dwivedi S, Desai S. A comparative study in between tropical honey and povidone dressing in diabetic wounds in a medical college of Northern India. Int Surg J. 2018;5:3391-3.

Available online at www.medicinescience.org

Medicine Science
International
Medical Journal

Correction

Medicine Science 2021;10(1):271

Correction of ethics committee approval

The ethics committee approval number of the study named "Evaluation of the effects of occupational arsenic exposure on human reproductive hormones" (2019; 8 (2): 306-110, DOI: 10.5455 / medscience.2018.07.8957) is incorrect.

We want to inform you, correct ethics committee approval number is "Ankara Keçiören Training and Research Hospital Research Ethics Committee" (Decision No: B.10.4.ISM.4.06.68.49).