AZJCVS
AZerbaijan Journal of CardioVascular Surgery

AZJCVS 2022;3(2):36-42
DOI: 10.5455/azjcvs.2022.08.013

Original Article

Is there a relationship between thyroid hormone change and postoperative arrhythmia in patients undergoing coronary bypass surgery? A prospective randomized controlled trial

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Received: 3 Auguost, 2022
Accepted: 22 Auguost, 2022
Published: 25 Auguost, 2022

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CITATION
Donmez K, Akca B, Erdil N. Is there a relationship between thyroid hormone change and postoperative arrhythmia in patients undergoing coronary bypass surgery? A prospective randomized controlled trial. AZJCVS. 2022;3(2):36-42 DOI: 10.5455/azjcvs.2022.08.013

Abstract

Aim: Several factors are known to be associated with arrhythmias after cardiac surgery. This paper examines the changes in thyroid hormones after cardiac surgery and the relationship with arrhythmias.

Material and Methods: A random sample of euthyroid patients scheduled for isolated coronary artery bypass surgery were recruited for a randomized prospective study. Patients were divided into two groups based on developing a new-onset arrhythmia (NOA) or atrial fibrillation (NOAF) after surgery (Group 2, n=18), and patients without NOA or NOAF after surgery were included in Group 1 (n=66). Blood samples for free triiodothyronine (fT3) and free thyroxin (fT4) levels were collected preoperatively and at the time of arrival to intensive care unit (D0), 24th hour (D1), 48th hour (D2), 72nd hour (D3) and 96th hour (D4).

Results: Arrhythmia was detected in 21.43% of patients. Twelve patients had NOAF and six patients had ventricular NOA. The postoperative second day was the most common day for arrhythmia. fT3 values were lower than preoperative values in both groups. When intra-group decreases were compared, the fT3 value decrease was more prominent in the arrhythmia group and fT3 regression at the D2 term (p=0.036) was especially significant. Postoperative fT4 values were higher than preoperative values in both groups. When intra-group raises were compared, fT4 values increased in both groups. This raising was more significant in the arrhythmia group and the fT4 rise at D1 term (p=0.022) was especially important.

Conclusion: The decrease of fT3 values in the arrhythmia group (Group 2) was greater. This is more prominent on the postoperative second day, which is the most common day for arrhythmia after cardiac surgery. There is a rise in fT4 values and this is higher in the arrhythmia group. These relatively high values may be mimicking hyperthyroidism and may be considered a predisposition for arrhythmia and atrial fibrillation.

Keywords: Coronary artery disease, Cardiopulmonary bypass, Thyroid hormones, Euthyroid sick syndrome

INTRODUCTION

Arrhythmia and atrial fibrillation (AF) are fundamental problems of cardiac surgery. In the normal population, AF prevalence is about 3% and after cardiac surgery, it may be as high as 15-45% (1). Evidence suggests that electrolyte imbalance, reperfusion injury, mechanical ventilation, valvular disease, and increased age are among the most important factors for arrhythmia and atrial fibrillation after cardiac surgery (2-4). These complications have contributed to the increase in the incidence of stroke, duration of hospital stay, hospital costs, and early and late mortality rates (1,5).

The euthyroid sick syndrome is a response of the body to control the catabolic period in cachexia, prolonged intensive care requirement, or serious surgical operations (4). It is associated with decreased total triiodothyronine and/or fT3 levels and usually normal or slightly changed thyroid-stimulating hormone

(TSH) and thyroxin (T4) levels.

Coronary artery disease, valvular heart disease, and heart failure are associated with high inflammatory load and possess high atrial fibrillation risk. After surgery, the systemic inflammatory response is induced, resulting in higher atrial fibrillation risk, especially on the second and third days (6).

Understanding the changes in thyroid functions after surgery and its relationship with arrhythmia and atrial fibrillation may help to prevent postoperative devastating complications and increase cost-effectiveness.

The purpose of this prospective, randomized investigation is to explore the relationship between postoperative changes in thyroid hormones and arrhythmia and atrial fibrillation in patients with normal preoperative thyroid functions.

MATERIAL AND METHODS

A random sample of euthyroid patients with isolated coronary artery disease was recruited from our clinic. 84 adult euthyroid patients who had been admitted to our clinic for elective on-pump coronary artery bypass grafting surgery were prospectively enrolled in the study between August 2012- January 2013.

Before commencing the study, ethical clearance was sought from the Ethics Committee of the Medical Faculty of Inonu University (116/2011). Written informed consent was obtained from each individual. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Preoperative TSH, fT3, and fT4 were measured to decide on euthyroid patients. After cardiac surgery, blood samples were collected for fT3 and fT4 levels at the time of arrival to the intensive care unit (D0), 24th hour (D1), 48th hour (D2), 72nd hour (D3), and 96th hour (D4). If the patient required antiarrhythmic therapy due to NOAF or arrhythmia last blood sample was achieved before initiating therapy and taking blood samples was terminated. Patients were divided into two groups based on developing NOA or NOAF in the first 96 hours period after surgery. Patients without NOA or NOAF after surgery were included in Group 1 (n=66) and patients with NOA or NOAF after surgery were included in Group 2 (n=18). Each sample was centrifuged at 4500 rates per minute for ten minutes at self-cooling devices. Plasma samples were stored at 86 °C deep freezers. All samples were defrosted and studied on the same day and calibration. Free T3 and free T4 levels were obtained (Immulite 2000, Siemens AG Healthcare Sector, Erlangen, Germany). Results were compared between pre and postoperative values of fT3 and fT4 among the groups.

Exclusion criteria were emergency operations, patients with renal or hepatic dysfunctions, low ejection fraction (<30%), known thyroid disease or operation, additional cardiac or aortic surgery, infection, malignancy, cachexia, patients who received amiodarone or stayed in an intensive care unit other than coronary causes in last six months.

All patients were continuously monitored with electrocardiogram and blood pressure measurements. Data was collected at the time of hospitalization, during the first postoperative day, and at the time of discharge. The primary endpoint of the study was NOA or NOAF in the first 96 hours. Atrial fibrillation was diagnosed in case 12-lead ECG showed rapid oscillations or fibrillatory P waves that varied in size, shape, and timing, and were associated with irregular QRS complexes. For this study, postoperative AF was defined as AF of any duration in the postoperative period, with AF diagnosis being based on physician assessments and 12-lead ECG findings. Patients who developed AF were treated with a standard protocol of anticoagulation and amiodarone. None of the patients who developed AF required electrical cardioversion. All of these individuals were discharged home after conversion to sinus rhythm.

Surgical Technique: Patients were placed under general anesthesia and a conventional median sternotomy was performed. Each patient underwent on-pump coronary artery bypass grafting surgery, and cardiopulmonary bypass was established by cannulating the ascending aorta and right atrium. Heparin (3 mg/kg) was administered for anticoagulation. Activated clotting time was maintained longer than 450 seconds, and a roller pump and non-pulsatile flow (2.4 L/m2/min) were used. The body was cooled to a core temperature of 32°C to 34°C when performing distal anastomosis, and the body was rewarmed to 36°C before weaning from cardiopulmonary bypass. The choice of graft material was left to the surgeon, but certain protocols were followed. The left internal thoracic artery was used routinely as a graft for the left anterior descending artery; radial artery and saphenous vein graft conduits were used mainly to bypass vessels other than the left anterior descending artery. The surgical technique is similar as described in our recently published article (7).

Outcome parameters: The specific preoperative and intraoperative data obtained for each patient are shown in Table 1 and Table 2. The collected postoperative data are shown in Table 3. Hospital mortality is defined as death in the first 30 days after coronary artery bypass grafting surgery.

Data management and analysis were performed using Statistical Package for Social Sciences 16.0 (SPSS 16.0) for Windows (SPSS Inc., Chicago, IL). Data for patient characteristics and outcomes were expressed either as a percentage of total or as mean ±SD. Kolmogorov-Smirnov and Shapiro-Wilk tests were used for normally distributed continuous variables (expressed as mean ±SD). One-way student T-test and one-way ANOVA (variance analysis) were used to compare normally distributed groups. Mann-Whitney U and Wilcoxon tests were preferred for abnormally distributed parameters. The chi-square and Fisher's exact tests were used for categorical variables, as appropriate. The results were assessed within 95% confidence and at a level of $p<0.05$ significance.

RESULTS

Eighty-Four adult euthyroid patients with coronary artery disease were included in this prospective study. The mean age

was 60.83±9.61 years in Group 1 and 66.61±6.63 years in Group 2. There were no significant differences between the groups with respect to gender distribution, the prevalence of chronic obstructive pulmonary disease, the prevalence of hypertension, obesity (body mass index, ≥30 kg/m²), hyperlipidemia, smoking, diabetes mellitus, unstable angina, left ventricular ejection fraction and the proportions of patients with previous MI.

More distal anastomosis were performed in Group 1 than Group 2 (2.79±0.69; 2.28±0.96; p=0.013, respectively). When other intraoperative data were compared, there were not any significant differences between both groups (Table 2).

No significant differences were identified between these two groups except for mechanical ventilation time (7.89±2.99; 6.71±1.98; p=0.05, respectively) (Table 3).

fT3 values and fT4 values are presented in Table 4. What stands out in Table 5 is the intensity of arrhythmia or atrial fibrillation occurring on the postoperative second day.

There was not any considerable difference between both groups for preoperative fT3 (p=0.404) and fT4 (p=0.448) values.

Regression of the fT3 hormone was expected. Especially on the postoperative second day, this regression became dramatic and significant (p=0.003). p values seemed to be significant in postoperative 3rd and 4th days, but these data must be interpreted with caution because collected samples gradually decreased.

The fT4 hormone rises in both groups until the postoperative 1st day. A slow normalization period is observed afterward but it is not significant at all. Similar to fT3 levels, p values seemed to be significant in postoperative 3rd and 4th days but collected samples gradually decreased and these results, therefore, need to be interpreted with caution.

Relative change of daily fT3 levels to preoperative fT3 levels are marked as F0T3, F1T3, F2T3, F3T3, and F4T3 (representing the day of sample achievement). Relative changes in daily fT4 levels to preoperative fT4 levels are marked similarly (F0T4, F1T4, F2T4, F3T4, and F4T4) (Table 6).

The relative changes of postoperative fT3 levels to preoperative fT3 are especially significant for the F2-PreopT3 value (p=0.036). The general changes of F3-Preop T3 and F4-Preop T3 qualities ought not to be viewed as critical (Figure 1).

The relative changes of postoperative fT4 levels to preoperative fT4 is particularly significant for the F1-PreopT4 value (p=0.022). The relative changes of F3-Preop T4 and F4-Preop T4 values should not be considered significant as it is in the previous figure (Figure 2).

Table 1. Demographic characteristics of groups

Patient Data	Without new-onset arrhythmia Group (Group 1)	New-onset arrhythmia Group (Group 2)	p
N	66	18	
Age	60.83±9.61	66.61±6.63	0.019 *
Female	16 (24.2%)	6(33.3%)	0.437
BSA	1.85 ± 0.09	1.86 ± 0.12	0.860
BMI	27.39±2.02	29.063± 2.84	0.265
EF	52.85±8.47	50.28±9.31	0.267
EF (<40%)	9 (13.6%)	5 (27.8%)	0.154
Current smoker	27 (40.9%)	9 (50%)	0.490
USAP	8 (12.1%)	1 (5.6%)	0.425
Diabetes Mellitus	18 (27.3%)	3 (16.7%)	0.357
Hypertension	25 (37.9%)	6 (33.3%)	0.723
Obesity	11 (16.7%)	4 (22.2%)	0.585
COPD	5 (7.6%)	2 (11.1%)	0.630
Preop MI	19 (28.8%)	6 (33.3%)	0.708
Hyperlipidemia	31 (47%)	6 (33.3%)	0.302

BSA:Body Surface Area, BMI: Body Mass Index, EF: Ejection Fraction, USAP: UnstableAngina Pectoris, COPD: Chronic Obstructive Pulmonary Disease, MI: Myocardial infarction

Table 2. Intraoperative characteristics of groups

	Without new-onset arrhythmia Group (Group 1)	Nnew-onset arrhythmia Group (Group 2)	p
LIMA use	66 (%100)	17 (%94.4)	0.054
Cross-clamp time(minute)	79.36 ±22.78	75.06 ±20.77	0.471
Bypass time(minute)	91.35±26.01	86.56 ±22.14	0.478
Mean distal anastomosis (n)	2.79 ± 0.69	2.28 ± 0.96	0.013 *

LIMA:Left internal mamarian artery

DOI: 10.5455/azjcvs.2022.08.013

Table 3. Postoperative characteristics of groups

	Without new-onset arrhythmia Group (Group 1)	New-onset arrhythmia Group (Group 2)	p
Length of stay in ICU (day)	2.21±0.73	2.61±1.04	0.66
Mechanical ventilation length (hour)	6.71±1.98	7.89±2.99	0.05 *
Length of stay in hospital (day)	6.89±0.86	6.83±0.51	0.691
Inotrop Use in ICU	5 (%7.6)	2 (%11.1)	0.630
Revision surgery for bleeding	**0 (%0)**	**1 (%5.6)**	**0.214**

ICU: Intensive care unit

Table 4. Alterations of free T3 (fT3) and free T4 (fT4) levels in postoperative days

	Preop fT3	D0 fT3	D1 fT3	D2 fT3	D3 fT3	D4 fT3	Preop fT4	D0 fT4	D1 fT4	D2 fT4	D3 fT4	D4 fT4
Group 1	3.17±0.74	2.06±0.85	1.61±0.60	1.73±0.71	1.81±0.69	2.06±0.87	1.14±0.19	1.24±0.23	1.41±0.38	1.27±0.25	1.17±0.21	1.16±0.23
Group 1	3.07±0.65	1.81±0.87	1.44±0.69	1.04±0.87	0.25±0.52	0.08±0.24	1.09±0.16	1.26±0.22	1.56±0.34	1.00±0.62	0.49±1.37	0.13±0.38
P value	0.404	0.517	0.287	0.003	0.0001	0.0001	0.448	0.273	0.75	0.329	0.0001	0.0001

(*: p value is the difference between two groups)

Table 5. Distribution of patients due to onset days of arrhythmia or atrial fibrillation

	D0	D1	D2	D3	D4
n	**0**	**3**	**9**	**3**	**3**

Table 6. Alterations of free T3 (fT3) and free T4 (fT4) levels in postoperative days

	Compared to Preop fT3					Compared to Preop fT4				
	D0 (F0T3)	D1 (F1T3)	D2 (F2T3)	D3 (F3T3)	D4 (F4T3)	D0 (F0T4)	D1 (F1T4)	D2 (F2T4)	D3 (F3T4)	D4 (F4T4)
Group 1 (p)	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.072	0.538
Group 2 (p)	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.913	0.005	0.0001

(Relative change of postoperative hormone levels to preoperative level)

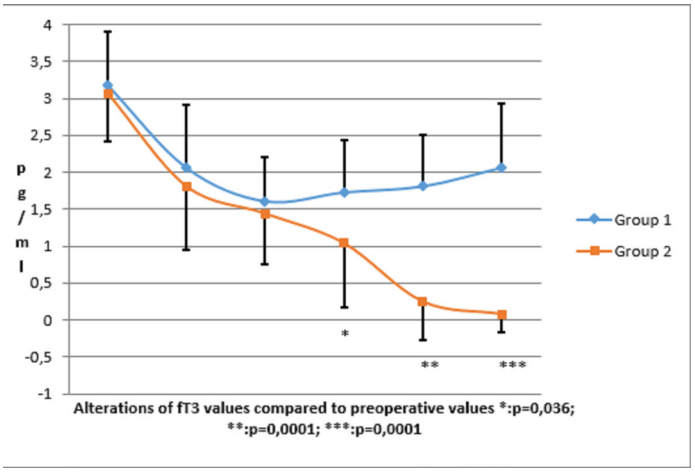

Figure 1. Comparison of fT3 alterations between groups

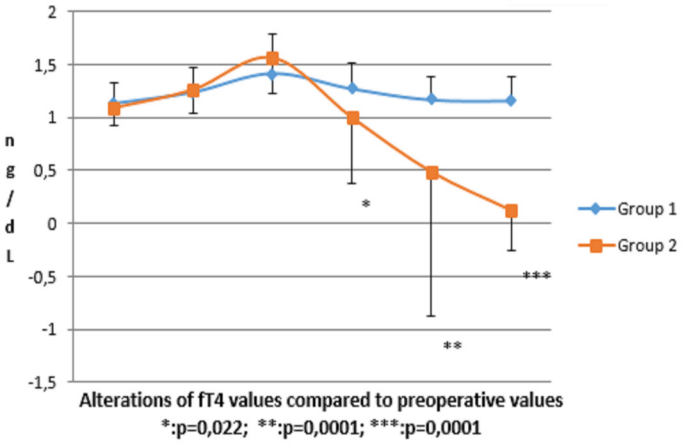

Figure 2. Comparison of fT4 alterations between groups

DISCUSSION

Postoperative atrial fibrillation is the most common type of arrhythmia after coronary artery bypass surgery. Its incidence changes between 15 and 45% (1). Cardiac rhythm problems generally occur between postoperative 2nd and 4th days, peaking on the postoperative 2nd day (8).

The euthyroid sick syndrome is described as alterations of TSH, serum, and tissue thyroid hormone levels due to non-thyroidal causes resulting in the deterioration of transformation of fT4 to fT3 in peripheral tissues or starvation (9). Catabolic processes like surgery, prolonged stay in the intensive care unit, or cachexia may result in this syndrome. The hormonal axis is intact. While fT3 levels significantly decrease, fT4 levels may lower, stay stable, or may rise. This system is a protective measure of the body but it may become catastrophic if the causing pathologic period increases.

When we compare demographic data of this study; patients in group 2 were significantly older than Group 1 (66.61±6.63, 60.83±9.61, and p=0.019; respectively). Currently, the most robust risk factor for postoperative AF is advanced age. Atrial fibrosis, dilatation, and comorbidities significantly increase with age (2,10,11).

A significantly higher distal anastomosis was performed on patients in Group 1 than on patients in group 2 (2.79 ± 0.69; 2.28± 0.96; p=0.013, respectively). Despite higher distal anastomosis numbers, cross-clamp and bypass lengths were similar in both groups.

Ventilation time was significantly longer in patients at Group 2 (Group 2: 7.89±2.99 h; Group 1: 6.71±1.98 h; p=0.05). The correlation between prolonged ventilation time and atrial fibrillation is well-known. Prolonged ventilation increases the right atrium pressure which predisposes to atrial fibrillation (12).

fT3 levels were reduced in all of our patients and this was consistent with the euthyroid sick syndrome. Alteration of fT4 levels was consistent with the transient increase due to impaired peripheral conversion. fT4 levels gradually normalized in the following days. An increase in fT4 levels was inversely correlated with fT3 levels. This situation is also consistent with the euthyroid sick syndrome.

A comparison of preoperative values and postoperative values revealed that the fT3 decline of group 2 on the postoperative 2nd day was greatest and this decline was significant. This data is consistent with the canon of knowledge, which makes us think that greater regression of fT3 in this period predisposes to atrial fibrillation. The same approach does not apply to fT4. The rise of fT4 levels is a reflection of impairment in the peripheral conversion of fT4 to fT3. Possibly fT4 will remain in its interval or slightly fall. This is related to the intensity of the catabolic process.

Frey et al investigated 758 patients with a left ventricular ejection fraction lower than 40% and commented that euthyroid sick syndrome is an important indicator of negative prognosis (13). This study does not include the catabolic process caused by surgery. Patients enter to catabolic process due to serious underlying pathology.

A study conducted by Pantos et al revealed that low thyroid hormone levels increase the stamina of the heart to ischemia and reperfusion (14). This situation was related to lower oxygen consumption by the mechanical effort of the heart.

Controversy on if the euthyroid sick syndrome is a physiological and protective system or it is a pathological system that requires treatment is still going on. This situation may be explained with the term “allostasis”. Threshold levels of systemic response mechanisms of the body are pulled back to protective values under temporary circumstances and usually just for days. This is called “allostatic response”. The body fights with the pathologic process by using its own resources (like amino acids from muscles and calcium from bones) but this system is designed to work for short periods. When the pathologic process prolongs, the allostatic response alters from protective to an ameliorating mechanism (15). Understanding this mechanism is very important for understanding euthyroid sick syndrome. Surgical stress is usually well-controlled and this protective mechanism ends before it becomes pathologic.

In our study, fT3 fall was less in Group 1. After a trough in postoperative 1st day, it raised gradually. In Group 2, the fall of fT3 was deeper and it was most significant on the postoperative 2nd day. We believe that a deeper fall of fT3 is an arrhythmogenic change.

fT4 rise at postoperative 1st day is important. fT4 serum concentration is relatively rising due to reduced peripheral conversion to fT3. This rise, which can mimic hyperthyroidism clinic, is higher in the arrhythmia group. Sinus tachycardia may occur in about 40% of hyperthyroidism patients. This situation may be the cause of tachycardia observed in the early period after surgery. Their response to beta-blocker drugs may be a sign of this situation. Alteration in the hormone levels of euthyroid patients may cause a more prominent response. Atrial fibrillation is the second most common arrhythmia in hyperthyroidism. It can be observed in about 10-15% of the patients and its prevalence increases with age (16). Besides, patients with subclinical hyperthyroidism may develop atrial fibrillation with a higher incidence (17,18).

Cerillo (5) and Velissaris (19) compared off-pump and on-pump surgery. Both have concluded that euthyroid sick syndrome may develop independently from cardiopulmonary bypass.

Another study by Cerillo et al demonstrated that patients with low preoperative fT3 levels are more prone to develop atrial fibrillation (20). We believe that fall of fT3, especially on the

postoperative second day, is a more valuable determinant.

Kokkonen et al performed a study on an elderly patient group. They concluded that fT3 falls in the postoperative period are related to atrial fibrillation (21). Elder age causes a predisposition to atrial fibrillation. In a study previously performed in our clinic, we demonstrated the relationship between elder age and atrial fibrillation (2). fT3 alterations in our study are concordant with the results of Kokkonen et al.

Interestingly, some studies reported that low total triiodothyronine levels in euthyroid patients who underwent coronary bypass surgery were significantly associated with increased risks of all-cause mortality, cardiovascular mortality, and MACE, but those associations were not observed in heart valve surgery patients (22).

A study performed by Caluk et al (23), demonstrated that fT3 and TSH levels were significantly lower 12 hours after surgery. fT4 levels rose during the same period. All values were returning to their initial values after the third evaluation. Off-pump and on-pump surgery did not differ in non-thyroidal illness syndrome. Their study is concordant with our results.

Recently, Lin et al (24) reported a nationwide, population-based study that aims to investigate the prognosis of hypothyroidism patients at the age under 65-year-old after coronary artery bypass grafting surgery. They concluded that hypothyroidism had no effect on post-operative atrial fibrillation.

Limitations

All patients were checked for arrhythmia with ECG before surgery. Patients with a history of any kind of arrhythmia were not included in the study. However, patients who have paroxysmal atrial arrhythmia without complaint and revealed sinus rhythm on preoperative ECG may be missed. Besides, we do not address episodes of AF occurring after discharge. Investigation of the relationship between thyroid functions and arrhythmia in patients who underwent off-pump coronary bypass surgery may reveal more data. Due to the relatively small group of patients, no risk analysis was performed to determine whether thyroid hormone changes are a risk factor for AF and arrhythmia. Further data collection is required to determine exactly how euthyroid sick syndrome affects the prognosis and development of new-onset arrhythmia after cardiac surgery.

CONCLUSION

Arrhythmias after coronary artery bypass surgery, increase mortality and morbidity and causes important economic losses. Prolonged or recurrent hospitalization and additional treatment costs are other aspects of the arrhythmia problem. Testing of thyroid hormone levels on the preoperative and postoperative second day may help to predict arrhythmias and initiation of protective medication. A serious decrease of fT3 levels and increase of fT4 levels on the postoperative 2nd day may be a warning sign of incoming arrhythmia.

We choose an isolated euthyroid patient group without comorbidities. Hormonal alterations after surgical interventions may increase morbidity and mortality of patients with known or subclinical thyroid disease. Changes in thyroid hormone levels should be investigated in patients with multiple pathologies. Although it is still controversial, alternative approaches and treatment options should be investigated and applied.

In conclusion; well-planned prospective, randomized, controlled trials in larger series are essential for investigating alterations of hormone levels for patients undergoing coronary bypass surgery.

Patient informed consent: Written informed consent of patients was taken preoperatively for each one.

Conflict of Interests: The author declares that there are no conflict of interests.

Financial Disclosure: There are no financial supports.

Ethics committee approval: Before commencing the study, ethical clearance was sought from the Ethics Committee of the Medical Faculty of Inonu University (116/2011).

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