RESEARCH

ASSOCIATION OF DUAL ANTIPLATELET THERAPY WITH ADVERSE OUTCOMES IN OCTOGENARIAN PATIENTS WITHOUT ATRIAL FIBRILLATION WHO UNDERWENT PERCUTANEOUS CORONARY INTERVENTION

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Abstract

Introduction: Dual antiplatelet therapy is routinely recommended to prevent stent restenosis and reduce ischemic complications after percutaneous coronary intervention. Octogenarians have a higher ischemic burden than younger patients on moreover they have a higher risk of bleeding. Therefore, we intended to analyze and compare the efficacy and safety of clopidogrel and the potent P2Y12 inhibitor ticagrelor in octogenarians undergoing percutaneous coronary intervention without atrial fibrillation.

Materials and Methods: This retrospective cohort study analyzed records from three local research hospitals. In our study, 226 patients aged 80 years or older undergoing had coronary intervention for both acute coronary syndrome and stable coronary artery disease were included after the exclusion criteria had been applied between January 2019 and April 2021.

Results: The median dual antiplatelet therapy duration was similar between two groups. 84.3% of patients in the clopidogrel group and 56.7% of patients in the ticagrelor group had no bleeding at one year follow-up, which was statistically significant ($p<0.001$). The minor bleeding rate was significantly higher among patients receiving ticagrelor (21.7%) compared to those receiving clopidogrel (7.2%; $p=0.02$). Also, the rate of major bleeding was significantly higher in patients receiving ticagrelor (20.0%) than in patients receiving clopidogrel (7.8%; $p<0.010$). Rates of all-cause death and ischemic endpoints were similar in both treatment groups at one year follow-up.

Conclusions: Clopidogrel and ticagrelor were similar in terms of all-cause mortality and ischemic events with increased rates of all types of bleeding in patients treated with ticagrelor.

Keywords: Octogenarians; Ticagrelor; Clopidogrel; Hemorrhage; Dual Anti-Platelet Therapy; Aged.

INTRODUCTION

Coronary artery disease (CAD) is the most common manifestation of atherosclerotic vascular disease. Despite pharmacological and interventional advances, CAD remains the primary cause of death worldwide (1). As the incidence of CAD increases with age and longevity continues to improve, we see more elderly people in cardiology clinical practice. The incidence of elderly patients with CAD is increasing as the prevalence of CAD increases with age, and longevity continues to increase (2). Percutaneous coronary intervention (PCI) relieves symptoms in patients with CAD and is a life-saving intervention for ACS, and is being performed extensively all over the world. Advanced age is an exclusion criteria in most of the clinical trials (3,4). Octogenarians have higher ischemic burden, more ischemic risk factors and increased risk of bleeding, than their younger counterparts (5). This increase in risk is also due to the increasing burden of comorbidities such as hypertension, chronic kidney disease, diabetes mellitus, which increases with age. Since atherosclerosis is a progressive disease by its nature, an increase in thrombotic events is observed with the increase of atherosclerotic plaques in elderly patients. Also, coagulation disorders and susceptibility to bleeding increase in elderly patients and care should be taken in the use of antithrombotic drugs in these patients.

Dual antiplatelet therapy (DAPT), which is acetylsalicylic acid in combination with a P2Y12 inhibitor, should be used to prevent stent restenosis, reoccurring ischemic events and stent thrombosis in patients after PCI. Guidelines recommend using potent P2Y12 inhibitors in CAD patients with acute coronary syndrome (ACS) and clopidogrel in stable coronary artery disease (SCAD) (3). Of the P2Y12 inhibitors, ticagrelor and clopidogrel can be used in patients over 75 years of age. Challenges remain in determining the best DAPT and duration due to drug compliance problems with increasing age, high ischemic burden, and increased risk of bleeding. Also new stent technologies allow us to use shorter-duration DAPT so we should also consider the type of stent before deciding the duration of DAPT. In this study, we compared the safety and efficacy of clopidogrel and the more potent P2Y12 inhibitor ticagrelor in patients 80 years and older, undergoing PCI.

MATERIALS AND METHODS

This study is a retrospective cohort study that analyzed the records of three local research hospitals. A total of 620 octogenarian patients who underwent PCI between January 2019 and April 2021 were screened, and 226 patients aged ≥ 80 years were recruited to the study after the exclusion criteria had been applied. The follow-up period was one year. The study was performed in accordance with the principles of the Declaration of Helsinki and approved by the Hospital Research Ethics Committee.

Patients aged 80 years and older who applied to the hospital with ACS or SCAD and underwent coronary stenting were included in the study. Patients with atrial fibrillation (AF) and those who started AF in their 1-year follow-up were excluded from the study; furthermore, patients with other indications that require anticoagulant therapy were not included. Intercalarily, in this study, exclusion criteria included patients having a history of severe intolerance or allergy to one of the study drugs (acetylsalicylic acid, clopidogrel, or ticagrelor), known intracranial aneurysm, cerebral arteriovenous malformation or intracranial mass, active bleeding at treatment initiation, thrombolytic therapy, an initial platelet count < 100,000 per microliter of blood, an Hb level < 10 g/dl, receiving oral anticoagulation, severe kidney failure requiring dialysis, severe liver dysfunction, mechanical complications due to ACS, and use of the following drugs in combination: antifungal agents, antiepileptic agents and specific antivirals.

The comorbidity status of the patients was calculated using the Charlson comorbidity index (6). The primary endpoint of our study was bleeding, as defined by the Bleeding Academic Research Consortium (BARC) (7). Secondary endpoints included minor and major bleeding, target vessel revascularization (TVR), non-fatal stroke, and all-cause mortality within 1 year of follow-up. Minor bleedings include ecchymosis of the skin, bleeding gums, and nosebleeds. Major bleeding is defined as life-threatening severe bleeding and this includes intracranial and gastrointestinal bleeding, hemoglobin decrease > 3 g/dL, significant bleeding requiring blood transfusion, and fatal bleeding (7). Trauma-related hemorrhages were excluded from the analysis.

All the statistical analyses in this study were conducted using STATA software (version 17.0; Stata Corp., College Station, TX). Continuous data are presented as mean ± standard deviation, and quantitative variables are presented as numbers and percentages. Student's t-test if continuous variables are parametric, Mann-Whitney test was used to detect statistical differences. In addition, chi-square test and Fisher's exact test were used to compare categorical data. All tests were two-sided, and p-values <0.05 were considered statistically significant. Predictors of major bleeding were determined using univariate and multivariate regression analyses. Variables that are significant in the literature and clinically were selected and analyzed.

RESULTS

Our study included a total of 226 patients, of which 166 patients were in the clopidogrel group and 60 patients were in the ticagrelor group. The mean patient age was 84.6 ± 3.4 and 54.4% of the patients were male. Diabetes mellitus, hypertension, stroke, heart failure rates and Charlson comorbidity index were similar between the two groups. Significantly there were more active smokers in the ticagrelor group than the clopidogrel group ($p < 0.001$). Approximately half of the patients in the clopidogrel and ticagrelor groups had non-ST-elevation myocardial infarctions (59.6% and 53.2%), respectively.

The median DAPT duration was 276 days in the clopidogrel group and 271 days in the ticagrelor group and was similar. The blood parameters of the two groups were similar. Table 1 shows the basic demographic and clinical characteristics of the patients.

No bleeding (BARC 0) was seen significantly more often in the clopidogrel (85.5%) group compared with the ticagrelor group (56.7%; $p<0.001$). Bleeding that did not require medical intervention (BARC 1) was observed in 4.8% of patients using clopidogrel and in 21.7% of those using ticagrelor. Bleeding that required medical intervention (BARC 2) was observed in 3.6% of patients using clopidogrel and in 8.3% of those using ticagrelor. Overt bleeding with hemoglobin drops of 3–5 g/dL and bleeding requiring transfusion (BARC 3a) were observed in 5.4% of patients receiving clopidogrel and 11.7% of those receiving ticagrelor. A drop in hemoglobin < 5 g/dL and overt bleeding requiring surgical intervention for control (BARC 3b) was observed in one patient in the clopidogrel group, and intracranial hemorrhage (BARC 3c) was observed in one patient in the clopidogrel group. Fatal bleeding (BARC 5a) was seen in only one patient in the ticagrelor group. Minor bleeding was significantly more prevalent in the ticagrelor group (25%) than in the clopidogrel group (7.2%; $p=0.01$). Major bleeding was also significantly more prevalent in the ticagrelor group (18.3%) than in the clopidogrel group (7.2%; $p=0.017$). The rates of stroke, TVR, and all-cause death during the 1-year follow-up period were similar between the treatment groups. All crude outcomes, including BARC bleeding, minor and major bleeding, stroke, TVR, and all-cause mortality, are shown in Table 2.

Table 1. Baseline Demographic and Clinical Characteristics of Patients

	All (n=226)	**Clopidogrel Group (n=166)**	**Ticagrelor Group (n=60)**	**p value**
Age, mean (SD)	84.6 (3.4)	84.9 (3.7)	83.7 (2.4)	0.012
Sex, n (%)				
Male	123 (54.4)	83 (50.0)	40 (66.7)	0.026
Female	103 (45.6)	83 (50.0)	20 (33.3)	
Diabetes Mellitus, n (%)	76 (33.6)	52 (31.3)	24 (40.0)	0.22
Hypertension, n (%)	183 (81.0)	131 (78.9)	52 (86.7)	0.19
Current smoker, n (%)	42 (18.6)	22 (13.3)	20 (33.3)	**<0.001**
Heart Failure, n (%)	9 (4.0)	6 (3.6%)	3 (5.0)	0.64
Left Ventricular Ejection Fraction, n (%)	51.5 (9.5)	51.2 (9.4)	52.2 (9.7)	0.51
Stroke, n (%)	33 (14.6)	27 (16.3)	6 (10.0)	0.24
Previous PCI, n (%)	41 (18.1)	37 (22.3)	4 (6.7)	**0.007**
Previous CABG, n (%)	20 (8.8)	18 (10.8)	2 (3.3)	0.079
Presentation Type, n (%)				
STEMI	84 (37.2)	58 (34.9)	26 (43.3)	0.46
Non-STEMI	131 (58.0)	99 (59.6)	32 (53.3)	
Stabile Angina	11 (4.9)	9 (5.4)	2 (3.3)	
Access Side, n (%)				
Femoral	214 (94.7)	156 (94.0)	58 (96.7)	0.43
Radial	12 (5.3)	10 (6.0)	2 (3.3)	
PRECISE DAPT Score, mean (SD)	29.8 (8.8)	30.3 (9.0)	28.5 (8.2)	0.19
DAPT duration (Days), mean (SD)	275.2 (124.4)	276.6 (123.6)	271.4 (127.8)	0.78
Charlson Comorbidity Index, mean (SD)	7.5 (1.8)	7.6 (1.8)	7.3 (1.8)	0.19
DAPT switch (%), n (%)	**30 (13.3)**	**1 (0.6)**	**29 (48.3)**	**<0.001**
DAPT Dyspnea, n (%)	8 (3.5)	1 (0.6)	7 (11.7)	**<0.001**
Systolic Blood Pressure, mean (SD)	125.8 (21.6)	124.2 (20.7)	130.4 (23.5)	0.055
White Blood Cell Count, mean (SD)	9.7 (3.6)	9.8 (3.8)	9.4 (2.9)	0.48
Hemoglobin, mean (SD)	12.7 (1.6)	12.6 (1.5)	12.8 (1.8)	0.32
Platelet Count, mean (SD)	230.9 (68.0)	231.8 (66.9)	228.6 (71.5)	0.75
Creatinine, mean (SD)	1.07 (0.3)	1.05 (0.3)	1.1 (0.2)	0.31
Total Cholesterol, mean (SD)	172.8 (43.8)	174.5 (46.1)	167.9 (36.5)	0.34
LDL Cholesterol, mean (SD)	108.1 (39.9)	110.1 (41.6)	102.3 (34.4)	0.21

CABG: coronary artery bypass graft, DAPT: dual antiplatelet therapy, LDL: low-density lipoprotein, PCI: Percutaneous coronary intervention

Table 2. Crude Outcomes of the Study Population

	All (n=226)	Clopidogrel Group (n=166)	Ticagrelor Group (n=60)	p value
BARC, n(%)				
0	176 (77.9)	142 (85.5)	34 (56.7)	
1	21 (9.3)	8 (4.8)	13 (21.7)	
2	11 (4.9)	6 (3.6)	5 (8.3)	
3a	16 (7.1)	9 (5.4)	7 (11.7)	**<0.001**
3b	1 (0.4)	1 (0.6)	0 (0.0)	
3c	1 (0.4)	1 (0.6)	0 (0.0)	
5a	1 (0.4)	0 (0.0)	1 (1.7)	
Minor Bleeding, n (%)	27 (11.9)	12 (7.2)	15 (25.0)	**0.001**
Major Bleeding, n (%)	23 (10.2)	12 (7.2)	11 (18.3)	**0.017**
Stroke, n (%)	21 (9.3)	17 (10.2)	4 (6.7)	0.41
Target Vessel Revascularization, n (%)	12 (5.2)	9 (5.3)	3 (5)	0.61
All-cause Mortality, n (%)	31 (13.7)	23 (13.9)	8 (13.3)	0.92

Table 3. Results of Multivariate logistic regression analyses of major bleeding

	Odds Ratio	[95% Conf. Interval]		p value
		Lower	Upper	
Age	1.114	0.968	1.282	0.132
Ticagrelor	6.257	2.225	17.592	**0.001**
Stroke	2.576	0.783	8.477	0.119
Systolic Blood Pressure	0.977	0.954	1.000	0.046
Heart rate	1.007	0.971	1.044	0.705
Left Ventricular Ejection Fraction	1.012	0.957	1.071	0.670
White Blood Cell	1.000	1.000	1.000	0.905
Hemoglobin	0.681	0.509	0.911	**0.010**
Platelet	1.000	0.993	1.007	0.995
Creatinine	0.901	0.263	3.082	0.868

In the multivariate analysis, independent predictors of major bleeding included ticagrelor use (OR = 6.2; 95% CI: 2.2–17.5), systolic blood pressure (OR = 0.9; 95% CI: 0.9–1.0), and hemoglobin (OR = 0.7; 95% CI: 0.5–0.9). Age, stroke history, heart rate, left ventricular ejection fraction, white blood cell count, platelet count, and creatinine were not associated with major bleeding (Table 3). The results of the univariate and multivariate logistic regression analyses of major bleeding are shown in Figure 1.

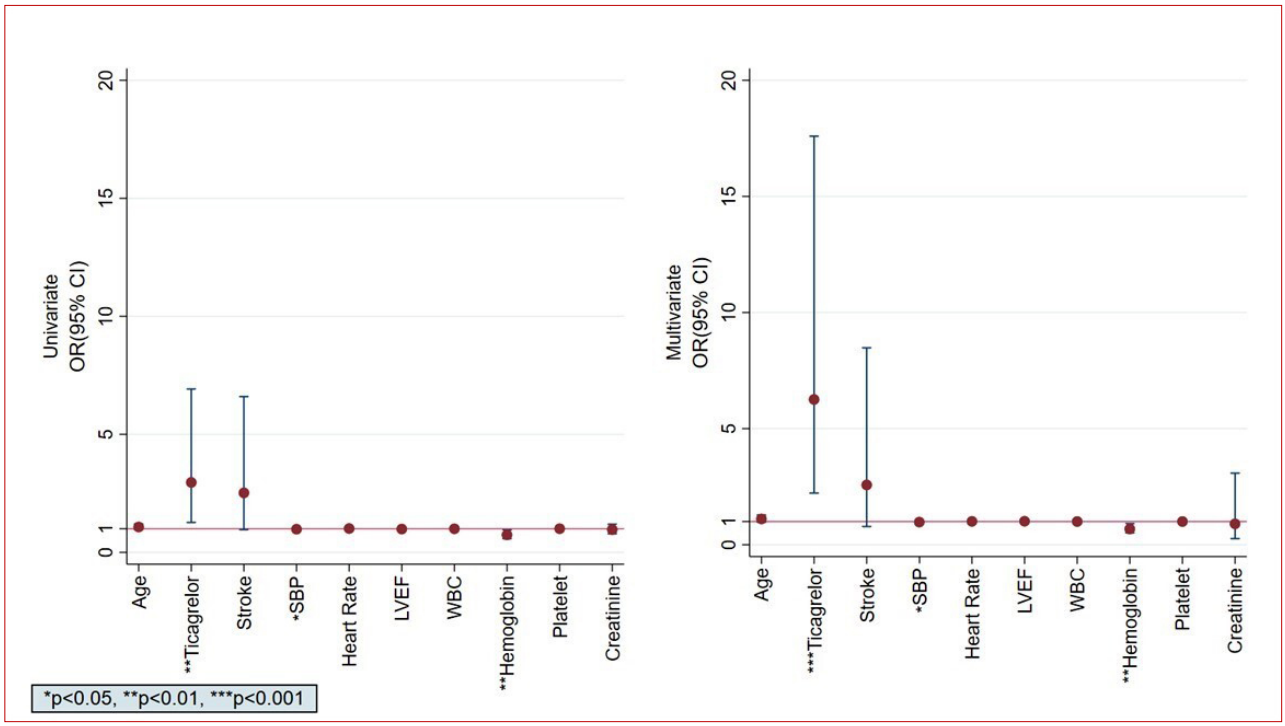

Figure 1. Univariate and Multivariate Logistic regression results for major bleeding.
SBP: Systolic blood pressure; LVEF: Left ventricular ejection fraction; WBC: White blood cell

DISCUSSION

Octogenarians are a fragile group and are often omitted from clinical trials. In this study, we intended to find out the effect of DAPT in octogenarians. We enrolled patients aged 80 years or older and were given DAPT following PCI and divided them into two groups according to their use of clopidogrel and ticagrelor. The most important exclusion criteria in this study were patients with AF and those requiring additional anticoagulant therapy. We did not find any significant difference between the clopidogrel and ticagrelor groups in terms of all-cause death, stroke, and TVR rates in our study. However, the ticagrelor group had higher minor and major bleeding rates. In this study, ticagrelor use was the most significant independent risk factor for major bleeding in octogenarians. In addition, patients in the ticagrelor group developed a higher rate of dyspnea rate than the patients in clopidogrel group which was the main reason for switching from ticagrelor to clopidogrel. The switching rate was 48,3% in ticagrelor group. Nuisance and minor bleeding were also more prevalent in the ticagrelor group.

Octogenarians have both tendency to thrombosis and bleeding at the same time. Vascular wall flexibility, coagulation, hemostatic system, and endothelial functions deteriorate with age. In addition, changes in endothelial functions, changes in metabolism and increase of the atherosclerotic burden also pose a risk in the elderly. For this reason, in elderly patients, medical treatments should be arranged with a profit-loss logic, considering the balance between bleeding and thrombosis. This can be explained with a yin-yang philosophy; if the potency of the antiplatelet drug increases, the risk of thrombosis decreases while the risk of bleeding increases, on the other hand

if the potency of the antiplatelet drug decreases, the risk of thrombosis increases while the risk of bleeding decreases. Increasing PCI rates in elderly patients have increased the need for DAPT, which has put clinicians in a difficult choice process. While considering the DAPT choice in elderly patients, the safety rather than the potency of the drug can be used as a criterion.

Previous studies have shown that clopidogrel and aspirin reduce the risk of myocardial infarction (MI), stroke, and death (8). Therefore, DAPT including clopidogrel is widely used to reduce cardiovascular events. The efficacy of aspirin and clopidogrel in patients with ischemic events has been proven and its safety has been demonstrated in this study. It is expected that the efficiency will increase and the reliability will decrease when the two are used together. Newer P2Y12 inhibitors, including ticagrelor and prasugrel, have stronger antiplatelet inhibitory effects than clopidogrel, which may increase bleeding while reducing thrombotic events (8-10). However, in elderly patients (>75 years old) prasugrel has not shown any net clinical benefit and is not recommended; only clopidogrel and ticagrelor should be used in this group (11). Since our study included patients aged 80 and over, clopidogrel or ticagrelor added to aspirin constituted the DAPT regimen.

A study of 18,624 patients with a median age of 62 found that ticagrelor was more effective than clopidogrel in reducing the rates of vascular death, stroke, and MI in patients with ACS (9). Similarly, in another study that included patients with a median age of 65 and previously implanted coronary stent, ticagrelor reduced vascular events compared to clopidogrel but increased the risk of major bleeding (12). Data on DAPT with ticagrelor for octogenarians remain insufficient, as this population is not included in randomized clinical trials, as mentioned above.

A prospective randomized study (POPular AGE trial) which included elderly patients (aged > 70 years), compared the efficacy and safety of clopidogrel versus ticagrelor or prasugrel in patients with non-ST-elevation ACS (13). 95% of patients in ticagrelor or prasugrel group received ticagrelor as a treatment so this study was more like a clopidogrel versus ticagrelor study. There was no difference between clopidogrel and ticagrelor in terms of mortality, stroke, or MI risk in elderly patients. Major bleeding and fatal bleeding were significantly less prevalent in the clopidogrel group than in the ticagrelor group. The median patient age in that study was 77 years, and only 36% were octogenarians. Our study is consistent with the POPular AGE trial as there was no difference between clopidogrel and ticagrelor group in terms of mortality, stroke, and TVR rates; however, major and minor bleeding were significantly less prevalent in the clopidogrel group than in the ticagrelor group. In the POPular AGE trial, only 53% of patients completed ticagrelor treatment (13). Due to significant bleeding and dyspnea, ticagrelor treatment compliance was low, especially in elderly patients. In our study, the rate of switching from ticagrelor to clopidogrel was high among octogenarians (48.3%), similar to the POPular AGE trial.

In a recently randomized trial; SCAD patients who underwent PCI, ticagrelor and clopidogrel had similar efficacy. Considering the 30-day bleeding rates, ticagrelor significantly increased minor bleeding but there was no significant effect on major bleeding (14). Patients with SCAD correspond to nearly 5%, therefore, subgroup analysis of patients with SCAD could not be performed in our study. However, since it was evaluated for all patient groups, ticagrelor increased minor bleeding as well as major bleeding in our study.

In contrast to trials mentioned above, a multinational registry study comparing ticagrelor and clopidogrel in 1,717 patients aged > 80 years found that bleeding risk was not a contraindication for choosing a more potent antiplatelet after ACS. According to this registry, ticagrelor reduced

the incidence of all-cause death compared to clopidogrel, without a statistically significant increase in major bleeding (15). Ticagrelor's hazard ratio for bleeding was 1.49, although this was not statistically significant due to the low number of events.

There are several scoring systems to predict the bleeding risk of patients on dual antiplatelet and/or anticoagulant therapy. Current guidelines recommend using the PRECISE-DAPT score to estimate bleeding risk and duration of DAPT, which is a composite of patients' age, creatinine clearance, hemoglobin level, white blood cell count and previous spontaneous bleeding. A score of ≥ 25 is accepted as a high risk for bleeding events and in this case, it is recommended to shorten the duration of DAPT. (16). In our study the mean PRECISE-DAPT score was 29.8; and was similar in both the clopidogrel and ticagrelor groups (30.3 vs 28.5; p=0,43). As can be seen, although the PRECISE-DAPT score was lower, there was more major bleeding in the ticagrelor group. We can interpret that scoring systems which are widely used are not sufficient to evaluate bleeding risk in elderly population. Since age is a variable for almost all of them, advanced age directly increases the score. In the future a subgroup scoring system could be developed for this population for a more accurate risk prediction.

The strength of this study lies in the fact that it was conducted on a frail group of patients, who are typically excluded from medical research, thus making a valuable contribution to our understanding of the healthcare needs of this vulnerable population. This study has several limitations, mainly its retrospective and has a non-randomized design. Since the study was retrospective, DAPT treatment duration was not standardized, but rather left to the attending physician's choice. Moreover, this study was based on hospital registries, so there is a chance patients may not have reported all of their minor bleedings. Due to the limited patient population, patients with SCAD unresponsive to medical treatment were also included in this study in addition to patients admitted with ACS. However, current guidelines only recommend ticagrelor over clopidogrel as part of DAPT in ACS. In addition, the frailty and cognitive status of the patients were not compared in our study. Frailty and cognitive status are an important parameter that will affect the outcomes.

CONCLUSIONS

In octogenarians, clopidogrel and ticagrelor have similar all-cause death, stroke, and TVR rates. However, major, and minor bleeding were significantly higher in the ticagrelor group than the clopidogrel group. Furthermore, due to the side effects, such as bleeding and dyspnea, many patients receiving ticagrelor switched to clopidogrel. According to our study DAPT is safer with clopidogrel than with ticagrelor in octogenarians. However larger, randomized trials are needed to evaluate the efficacy and safety of ticagrelor and clopidogrel in octogenarians.

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Conflict of Interest

The authors have no conflicts of interest to declare.

Ethical approval

This study was conducted following the Declaration of Helsinki and was approved by the Second Ethical Committee of the Ankara City Hospital with number E2-21-929.

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