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Research Article

Edoxaban therapy in non-valvular atrial fibrillation patients: Paradoxical effect on mean platelet volüme

Non-valvüler atriyal fibrilasyon hastalarında edoksaban tedavisi: Ortalama trombosit hacmi üzerinde paradoksal etki

Ilke Erbay*[1], Mert Aker[1], A. Furkan Suner[2], Yesim Akin[1], Orhan Onalan[1]

[1]Department of Cardiology, Karabük University Faculty of Medicine, Karabük, Turkey
[2]Department of Public Health, 9 Eylül University Faculty of Medicine, İzmir, Turkey

ABSTRACT

Aim: New generation oral anticoagulants (NOACs), which selectively and reversibly block the activity of clotting factor Xa, are now preferred as first-line therapy for preventing ischemic stroke in the treatment of atrial fibrillation (AF). Edoxaban, one of these NOACs, has been shown to be as effective as warfarin in preventing stroke or systemic embolism, while carrying a lower risk of bleeding and cardiovascular death. Mean platelet volume (MPV), as an indicator of platelet activity, is associated with an increased risk of ischemic stroke in patients with AF. Therefore, medical therapies that reduce MPV may play an important role in preventing unwanted ischemic events. The aim of this study is to determine whether edoxaban has an effect on platelet volume and other platelet indices, in addition to its protective anticoagulant effect against ischemic stroke.

Materials and Methods: The study was designed as a retrospective cross-sectional study. Two hundred non-valvular AF patients without a history of oral anticoagulant use were included in the study. Complete blood count (CBC) and basic biochemical parameters (urea, creatinine, electrolytes, etc.) were recorded from the hospital registration system before edoxaban treatment was started, along with basic demographic data. The CBCs of the patients were reevaluated an average of 6 months (184 ± 9 days) after edoxaban treatment initiation, and platelet indices after edoxaban treatment were compared. Results were presented as mean ± standard deviation and percentage. Data were compared using Student's t-test and Wilcoxon test, and $p<0.05$ was considered statistically significant.

Results: The mean age of the patients was 74±9 years. The majority of the patients in the study were female (52.5%). A significant increase in MPV value was observed after treatment [10.0 fL (6.0-13.8) vs. 10.2 fL (7.1-14.9), p=0.023], considering the change in MPV values of the patients. This increase in MPV was not observed in the group using 30mg/day edoxaban (p=0.333), while a significant increase was observed in the group using 60mg/day (p=0.041). In addition, no gender-related change was observed in MPV. No significant changes were observed in platelet count (PLT) (p=0.863), platelet distribution width (PDW) (p=0.085), or plateletcrit (PCT) (p=0.127) values during the six-month period of edoxaban use.

Conclusion: In oral anticoagulant naïve AF patients, edoxaban treatment led to an elevation in MPV levels after 6 months, without causing significant alterations in other platelet indices. These findings highlight the need for further research to explore the clinical implications and potential unknown pleiotropic effects of elevated MPV levels in patients receiving edoxaban therapy.

Keywords: Edoxaban, mean platelet volume (MPV), atrial fibrillation, NOAC

Corresponding Author*: İlke Erbay, Assist. Prof., Karabük University Faculty of Medicine, Department of Cardiology, Karabük, Turkey.
E-mail: ilkeerbay@karabuk.edu.tr
Orcid: 0000-0002-6817-4686
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ÖZ

Amaç: Atriyal fibrilasyon (AF) tedavisinde iskemik inmenin önlenmesi için artık yeni nesil oral antikoagülanlar (NOAK'lar) birinci basamak tedavi olarak tercih edilmektedir. Seçici ve geri dönüşümlü olarak pıhtılaşma faktörü Xa'nın aktivitesini bloke eden yeni nesil oral antikoagülanlardan biri olan edoxabanın, felç veya sistemik embolizmi önlemede varfarin kadar etkili olduğu, kanama ve kardiyovasküler nedenlerden ölüm oranları açısından daha düşük risk taşıdığı gösterilmiştir. Ortalama trombosit hacmi (OTH), trombosit aktivitesinin bir göstergesi olarak, AF'li hastalarda artmış iskemik inme riski ile ilişkilidir. Bu nedenle OTH'yi düşüren medikal tedaviler, iskemik istenmeyen olayları önlemede önemli bir rol oynuyor olabilir. Bu çalışmanın amacı, edoksabanın iskemik inmeye karşı koruyucu antikoagülan etkisinin yanı sıra trombosit hacmi ve diğer platelet indeksleri üzerine etkisinin olup olmadığını belirlemektir.

Gereç ve Yöntemler: Çalışma retrospektif kesitsel çalışma olarak tasarlandı. Çalışmaya daha önce oral antikoagülan ilaç kullanım öyküsü olmayan 200 non-valvüler AF hastası dahil edildi. Hastane kayıt sisteminden edoksaban tedavisi başlanmadan önce çalışılan tam kan sayımı (TKS) ve temel biyokimya parametreleri (üre, kreatinin, kan elektrolitleri vb.) ile temel demografik veriler kayıt altına alındı. Hastaların ortalama 6 ay (184 ± 9 gün) sonra tekrarlanan TKS'leri incelenerek edoksaban tedavisi ve sonrası platelet indeksleri karşılaştırıldı. Bulgular ortalama ± standart sapma ve % oranıyla gösterildi. Veriler Student's t testi ve Wilcoxon testleri kullanılarak karşılaştırıldı. $p<0.05$ istatistiksel olarak anlamlı kabul edildi.

Bulgular: Hastaların ortalama yaşı 74±9 yıldı. Çalışmaya katılan hastalarımızın çoğunluğu kadınlardan oluşmaktaydı (%52,5). Hastaların OTH değerlerindeki değişimi göz önünde bulundurarak, tedavi sonrası OTH değerinde anlamlı artış gözlendi [10,0 fL (6,0-13,8) vs. 10,2 fL (7,1-14,9), p=0,023]. OTH'de görülen bu artış 30mg/gün edoksaban kullanan grupta görülmezken (p=0,333), 60mg/gün kullanan grupta anlamlı artış izlendi (p=0,041). Ek olarak, OTH'de cinsiyetle ilgili bir değişiklik gözlenmedi. Edoxaban kullanımının altı aylık sürecinde kan trombosit sayısı (PLT) (p=0,863), trombosit dağılım genişliği (PDW) (p=0,085) veya trombokrit (PCT) (p=0,127) değerlerinde anlamlı değişiklikler gözlenmedi.

Sonuç: Edoksaban tedavisi, oral antikoagülan kullanım öyküsü olmayan AF hastalarında, 6. Ayın sonunda OTH düzeylerinde artışa neden olurken diğer trombosit indekslerinde anlamlı bir değişiklik yaratmadı. Bu bulgular, edoksaban tedavisi alan hastalarda yükselmiş MPV düzeylerinin klinik sonuçları ve potansiyel bilinmeyen pleiotropik etkileri için daha fazla araştırmanın gerekliliğini vurgulamaktadır.

Anahtar Kelimeler: Edoksaban, ortalama trombosit hacmi (OTH), atriyal fibrilasyon, NOAK

Introduction

Atrial fibrillation (AF) is characterized by the most common continuous cardiac arrhythmia in the elderly (1). While the prevalence of AF is 2-4% in the adult population, it increases with a sharp slope after the age of 65 and emerges as one of the most important causes of cerebrovascular mortality and morbidity (2). Furthermore, the increase in the prevalence of comorbidities such as coronary artery disease, heart failure, diabetes and hypertension with aging leads to AF, the most common cause of cardioembolic stroke (3-5).

Anticoagulation is the most effective treatment for stroke prevention in patients with AF. Indeed, cardioembolic stroke studies have demonstrated the superiority of anti-coagulation therapy in stroke prevention in the absence of any contraindications (1). In such cases, warfarin, an anticoagulant with a long clinical history appears to be effective in the prevention of thromboembolic events in patients with non-valvular AF (6). On the other hand, the heterogeneity in the pharmacologic response of different age groups to warfarin or its interaction with some common drugs pose limitations to its clinical use.

In clinical practice, new oral anticoagulants (NOACs) are used as an alternative therapy in patients with nonvalvular AF. This group of anticoagulants is known to prevent stroke in ischemic events in a manner non-inferior or superior to warfarin, resulting in lower intracranial bleeding complications (1-4). A retrospective study of 61678 patients with non-valvular AF who had not previously used oral anticoagulants and had no previous indications for valvular atrial fibrillation showed that NOACs are as effective and safe as warfarin (7).

Platelet volume is a marker of platelet activation that is easily measured as mean platelet volume (MPV) when a complete blood count (CBC) is performed and is positively correlated

with platelet activity. Larger platelets are hemostatically more active than normal-sized platelets and increase the tendency for thrombosis (8-10). It is known that the tendency of platelets to increase in size during ischemic events causes them to be more active and produce more thromboxane A2 (11). There are studies showing that MPV is an independent risk factor in the development of ischemic stroke due to its high granule concentration and secondarily increased thrombopoietic activity (11, 12). Considering that MPV may be an important parameter in predicting the development of ischemic stroke in AF patients (11, 13), it is highly important to prevent acute thrombotic events with the use of agents that reduce platelet volume and activation. Edoxaban, an anticoagulant that work by selectively and reversibly blocking the activity of clotting factor Xa, has been shown to be as effective as warfarin in preventing stroke or systemic embolism and is associated with significantly lower rates of bleeding and death from cardiovascular causes (14, 15). All these findings suggest that the effect of edoxaban on MPV, an important parameter in predicting stroke development in patients with AF, could be clinically important. Therefore, the aim of this study was to determine whether edoxaban has an effect on platelet volume and activation in addition to its protective anticoagulant effect against ischemic stroke.

Materal and Methods

Study population

A cross-sectional study was conducted at the Cardiology Outpatient Clinic of Karabuk University Faculty of Medicine from January 2020 to October 2022. The study involved 200 patients with paroxysmal and permanent non-valvular AF who had not previously received oral anticoagulant (OAC) treatment (16). Comprehensive clinical information was collected from the electronic medical records, including demographic data such as age and sex, medication history, smoking status, and co-existing medical conditions. The diagnosis of AF was confirmed in all patients through a 12-lead surface electrocardiogram at the time of initial presentation. Patients with moderate to severe mitral stenosis, autoimmune diseases, chronic kidney disease, thyroid disorders, acute infections, malignancies, AF related to acute coronary syndrome, and a history of hemorrhagic stroke were excluded from the study. Additionally, patients who required a medication change during the follow-up period, for any reason, were also excluded. Echocardiograms were performed on all patients, and CHA2DS2-VASc scores were calculated. Patients were assigned one point for congestive heart failure (signs/symptoms of heart failure and ejection fraction <40%), hypertension (taking antihypertensive medicine or systolic and diastolic blood pressure ≥140/90 mmHg), diabetes mellitus (defined as a fasting blood glucose level ≥126 mg/dl or blood glucose level ≥200 mg/dl or using anti-diabetic drugs), history of vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque), age 65–74 years, female gender, and two points for age 75 years or older and previous stroke or transient ischemic attack (16). Complete blood count, basic biochemistry parameters (urea, creatinine, blood electrolytes, etc.), and International Normalized Ratio (INR) were obtained before initiating edoxaban treatment. Repeated CBC and INR were obtained during routine follow-up visits after a mean period of 6 months (184±9 days). Changes in platelet indices were analyzed separately in patients using 30 mg and 60 mg daily doses of edoxaban. The study was designed in accordance with the 1964 Declaration of Helsinki, the principles of Good Clinical Practice and not contradicting the ethical rules of the subject research. The study was approved by the Bioethics Committee of Karabuk University (No. 2022/1151).

Laboratory analysis

The blood samples were collected from all patients using anticoagulated tubes containing tripotassium EDTA and citrate for CBC and INR measurements, respectively. To prevent platelet swelling, CBC measurements were performed within one hour using the automatic hematology analyzer SYMEX XE-2100 (Kobe, Japan) which utilizes both optical and impedance methods. INR values were measured with the Sysmex CA500 (Sysmex Corporation, Kobe, Japan) auto analyzer. Biochemical parameters were analyzed using the ROCHE COBAS 8000 molecular analyzer (Roche Diagnostics, Mannheim, Germany).

Statistical analysis

The statistical analysis was conducted using the SPSS for Windows 25.0 package program (SPSS Inc., Chicago, IL), while categorical variables were presented as numbers and percentages, and continuous variables were reported as mean ± SD or median, minimum, and maximum. The normality of the data was evaluated using the Kolmogorov-Smirnov test. For normally distributed continuous data, Student's t-test was

used for comparison, while the Wilcoxon test was utilized for non-normally distributed continuous data. A p-value less than 0.05 was considered statistically significant.

Results

The baseline clinical data of the patients are presented in Table 1. The study population had a mean age of 74±9 years, with a predominance of females (52.5%). The findings of this investigation indicate a high prevalence of chronic medical conditions among the participants, notably diabetes mellitus (49.5%) and hypertension (88.5%). Nearly half of the patients presented with dyslipidemia (49.0%), while 48.0% had a history of smoking. Moreover, the prevalence of deep vein thrombosis or pulmonary embolism was 4.0%, and approximately 46.0% of the patients exhibited coronary artery disease (CAD). Additionally, around one-quarter of the participants (23.5%) experienced cerebrovascular events (CVEs). The mean CHA2DS2VASc score was 4.3±1.2.

Table 1. Demographic, clinical and echocardiographic characteristics of the study population.

Parameters (n=200)	Value
Age in years (mean ± SD)	74 ± 9
Gender, male; n (%)	95 (47.5)
Diabetes mellitus, n (%)	99 (49.5)
Hypertension, n (%)	177 (88.5)
Dyslipidaemia, n (%)	98 (49.0)
Smoking (>20 cigarettes/d for more than 5 years) n (%)	96 (48.0)
DVT or PE, n (%)	8 (4.0)
CAD, n (%)	92 (46.0)
CVEs, n (%)	47 (23.5)
HF, n (%)	78 (39.0)
CHA2DS2-VASc score (mean ± SD)	4.3 ± 1.2
LVEF (mean ± SD) (%)	54.3 ± 10.0
LA diameter (mean ± SD) (mm)	43.3 ± 4.1
Drug use, n (%)	
Statin	88 (44.0)
Beta blocker	158 (79.0)
CCB	97 (48.5)
ACEi or ARB	156 (78.0)
Digoxin	50 (25.0)
Furosemide and/or thiazide	117 (58.5)

Abbreviations: SD: Standard deviation, ACEi: Angiotensin-converting-enzyme inhibitors, ARB: Angiotensin Receptor Blocker, CAD: Coronary artery disease, CCB: calcium channel blocker, CHA2DS2-VASc score: risk of stroke (for non-rheumatic atrial fibrillation), CVEs: Cerebrovascular events, DVT: Deep vein thrombosis, HF: Heart failure, LA: Left Atrium, LVEF: Left ventricular ejection fraction, PE: Pulmonary embolism

An increase in MPV values was observed after the treatment with edoxaban [10.0 fL (6.0-13.8) vs. 10.2 fL (7.1-14.9), p=0.023], as shown in Table 2. No significant gender-related changes were observed in MPV values. Additionally, there were no significant changes in blood platelet count (PLT) (p=0.863), platelet distribution width (PDW) (p=0.085), or plateletcrit (PCT) (p=0.127) values during the six-month period of edoxaban use, as illustrated in Figure 1.

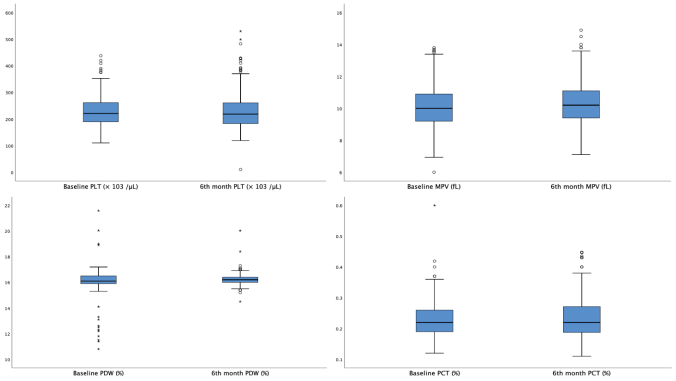

Figure 1. Platelet count (PLT), mean platelet volume (MPV), platelet distribution width (PDW) and plateletcrit (PCT) values before and after treatment with edoxaban.

The study findings demonstrated a significant increase in MPV values in patients, regardless of their comorbid conditions, (p<0.05, for all) (Table 3). Additionally, there was no significant change in MPV values among patients who were administered a daily dose of 30 mg edoxaban [10.4fL (± 1.4) vs. 10.6fL (± 1.5), p=0.333]. However, among those who received a daily dose of 60 mg, a significant increase in MPV was observed [10.0fL (± 1.2) vs. 10.2fL (± 1.2), p=0.041], (Table 4).

Table 2. Platelet count (PLT), mean platelet volume (MPV), platelet distribution width (PDW) and plateletcrit (PCT) values before and after treatment with edoxaban

Variables	Baseline Median (min-max)	6th month Median (min-max)	P
PLT (× 103 /µL)	221.0 (110.0-438.0)	218.3 (10.4-530.0)	0.863
PDW (%)	16.1 (10.9-21.5)	16.2 (14.5-20.0)	0.085
PCT (%)	0.2 (0.1-0.6)	0.2 (0.1-0.4)	0.127
MPV (fL)	10.0 (6.0-13.8)	10.2 (7.1-14.9)	0.023
INR	1.0 (0.8-1.8)	1.1 (0.8-1.9)	0.018

Abbreviations: INR: International Normalized Ratio, MPV: Mean Platelet Volume, PCT: Plateletcrit, PDW: Platelet Distribution Width, PLT: platelet count

Table 3. Comparison of MPV values at baseline and 6 months of edoxaban use in terms of comorbidities

Variable	Categories	Baseline value	6th month value	p
		Median (min-max)	**Median (min-max)**	
DM	(+)	10.1 (6.9-13.8)	10.4 (7.7-14.5)	**0.030**
	(-)	10.0 (6.0-13.6)	10.0 (7.1-14.9)	**0.049**
HT	(+)	10.4 (9.5-13.6)	10.9 (9.2-12.6)	**0.015**
	(-)	10.0 (6.0-13.8)	10.1 (7.1-14.9)	**0.020**
Dyslipidemia	(+)	10.1 (6.0-13.8)	10.3 (7.1-13.8)	**0.030**
	(-)	10.0 (7.4-13.5)	10.0 (7.4-13.5)	**0.049**
PE / DVT	(+)	10.0 (6.0-13.8)	10.2 (7.1-14.9)	**0.003**
	(-)	9.7 (8.8-11.3)	10.6 (8.6-12.2)	**0.025**
CAD	(+)	10.0 (6.0-13.7)	10.2 (7.1-14.9)	**0.001**
	(-)	10.0 (6.9-13.8)	10.1 (7.8-13.8)	**0.037**
CVEs	(+)	10.0 (6.0-13.8)	10.1 (7.7-13.8)	**0.015**
		10.0 (6.9-13.6)	10.3 (7.1-14.9)	**0.014**

Abbreviations: CAD: Coronary artery disease, CVEs: Cerebrovascular events, DM: Diabetes mellitus, DVT: Deep vein thrombosis, HT: Hypertension, PE: Pulmonary embolism

Table 4. Comparison of baseline and 6th month MPV according to daily edoxaban dose

Edoxaban Dosage (mg)	Baseline MPV(fL)	6th month MPV(fL)	p
30 mg	10.4 ± 1.4	10.6 ± 1.5	0.330
60mg	10.0 ± 1.2	10.2 ± 1.2	0.041

Abbreviations: MPV; Mean Platelet Volume

Discussion

To the best of our knowledge, our study is the first to investigate the effects of edoxaban on platelet indices. We found a significant increase in MPV at 6 months compared to baseline in OAC-naïve patients with AF. The results showed that there was no significant change in MPV values among patients who were administered a daily dose of 30 mg edoxaban. However, a significant increase in MPV was observed only among those who received a daily dose of 60 mg. This suggests that edoxaban may affect MPV values in a dose-dependent manner.

Platelets in circulation exhibit variability in size and hemostatic potential. The size of platelets, as MPV, is often considered a reflection of platelet activity (17). However, emerging research suggests that platelet size and density are determined during thrombopoiesis, where megakaryocyte ploidy influences platelet volüme (18). This suggests the existence of a complex megakaryocyte-platelet hemostatic axis that may be disrupted in the presence of certain comorbidities, such as hypertension, hyperlipidemia, and diabetes mellitus (19). While some drugs, such as antihypertensives, antidiabetics, and lipid-lowering agents, may impact MPV, no clear correlation has been established between antiplatelet agents and MPV (20). Indeed, these conditions have been known to alter the regulation of this axis. However, thrombopoiesis and megakaryopoiesis may be regulated by different humoral factors. Thus, a decrease in platelet volume may not occur in situations where active megakaryocyte ploidy induces megakaryopoiesis (19). Higher MPV values have been reported in patients with HT, DM, dyslipidemia, and CAD (18-20). In our study, most of the patients had comorbid conditions, but we observed a significant increase in MPV values following edoxaban use regardless of the presence of comorbidities. In addition, the dose-dependent effect of edoxaban on MPV values suggests that the drug has a pleiotropic effect.

Our study, in line with previous research, has revealed an intriguing phenomenon where certain medications, expected to reduce MPV, can actually lead to an increase in MPV. De Luca et al. observed a paradoxical rise in MPV during the initial five days of dual antiplatelet therapy in patients with acute coronary syndrome (20). Similarly, nicotinic acid, known for its lipid-modifying activity and additional effects in ischemic heart disease, was found to increase MPV while simultaneously decreasing platelet count (21). Another study conducted by Duzen et al. examined the effect of NOACs such as apixaban, rivaroxaban, and dabigatran on MPV in non-valvular AF patients. Remarkably, they did not find a significant decrease in MPV following the use of these medications [(9.36 ± 1.70) vs. (9.63 ± 1.68), p=0.072] (22).

There may be several contributing factors that explain the lack of any functional effect of increased platelet size. The increase in MPV could be a process driven by the increased production of larger reticulated platelets in the bone marrow (23). In fact, it has been shown that MPV correlates with both megakaryocyte ploidy and the percentage of reticulated platelets in circulation. Therefore, larger MPV may not necessarily indicate higher platelet reactivity, but rather larger platelets may be indicative of immature platelets, which may be associated with further decreased aggregation (24). Our hypothesis is that the rise in MPV levels detected after edoxaban treatment could be linked to the pleiotropic effects of the drug on bone marrow, which may have been amplified by the relatively higher dose of 60mg/day.

Platelet Distribution Width is a laboratory test parameter that serves as an indicator of platelet activation. Previous studies

have consistently shown higher levels of both MPV and PDW in diabetic patients compared to healthy individuals, with PDW being particularly elevated in those with microvascular complications (25, 26). Furthermore, elevated PDW has been identified as a significant risk factor for stroke in patients with AF (27). In our study, despite observing an increase in MPV values, we did not find a significant impact of edoxaban on PDW. This suggests that while edoxaban treatment may affect platelet volume, it does not exert a substantial influence on platelet activation as measured by PDW.

Study limitations

Our study has several limitations. Firstly, we had strict exclusion criteria, which may limit the generalizability of edoxaban's effect on MPV to populations beyond AF patients. Secondly, we did not investigate the underlying mechanisms of the observed increase in MPV, which could provide valuable information about the pleiotropic effects of edoxaban. The use of tests such as platelet aggregation could provide more precise data on the clinical significance of the MPV increase. Thirdly, our study patients were receiving treatments for other comorbidities that may affect MPV, and the results may not reflect isolated changes in MPV due to edoxaban. Lastly, we only evaluated the platelet indices at a single time point (6 months after starting edoxaban therapy) and did not assess changes in these indices over time.

Conclusion

Edoxaban treatment led to an increase in MPV levels in anticoagulant OAC naïve AF patients, particularly in those receiving a daily dose of 60 mg, without significant alterations in other platelet indices. This increase in MPV may potentially be attributed to one of the unknown pleiotropic effects of edoxaban. These findings highlight the need for further research to explore the pleiotropic effects of edoxaban and the possible clinical implications of increased MPV levels in patients receiving edoxaban therapy.

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