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Comparison of Clinical and Biochemical Parameters in Atrial Fibrillation Patients Using Dabigatran and Rivoraxaban and Their Relationship with Complications

Acil Serviste Yeni Nesil Oral Antikoagülan Kullanan Hastaların Trombotik Komplikasyon Belirleyicilerinin Değerlendirilmesi

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ABSTRACT

Introduction: Atrial fibrillation (AF) is a common disease that increases mortality and morbidity. New generation oral anticoagulants (NOACs) are agents that reduce ischemic events in patients with AF. In this study, we aim to compare biochemical and clinical parameters and examine the risk factors for thrombotic complications (such as stroke, myocardial infarction, systemic embolization) in patients using NOACs (dabigatran and rivaroxaban).

Methods: This study was designed as a retrospective, method development study. The study included 205 patients who were admitted to Emergency Service, Adıyaman University Training and Research Hospital, from January 2013 to December 2014. The patients were divided into two groups as rivaroxaban users and dabigatran users. The differences of laboratory parameters of patients before drug intake and during their emergency department visits were analyzed. [Δwhite blood cells, Δhemoglobin, Δhematocrit, Δplatelet, Δplatecrit, Δplatelet distribution width, mean platelet volume (ΔMPV)].

Results: There were no major differences between two groups in terms of CHA_2DS_2-VASc scores, complications and duration of drug intake. There was statistically significant decrease with regard to MPV ($p<0.001$), in both of the groups with the usage of NOACs. The optimal threshold point of ΔMPV in the prediction of the thrombotic complications was ≤0.7 fL, with 91.7% sensitivity and 62.2% specificity [area under the curve: 0.805, 95% confidence interval: 0.744-0.857, $p<0.001$).

Conclusion: As a result, the detection of high CHA_2DS_2-VASc score for the patients with AF using NOACs and visiting emergency department and less volume decline in previous MPV value are simple parameters to be used for predicting thrombotic cases and will be clinically useful.

Keywords: Atrial fibrillation, dabigatran, rivaroxaban

ÖZ

Amaç: Atriyal fibrilasyon (AF), mortalite ve morbiditeyi artıran yaygın bir hastalıktır. Yeni nesil oral antikoagülanlar, atriyal fibrilasyonu olan hastalarda iskemik olayları azaltan ajanlardır. Biz bu çalışmada yeni nesil oral antikoagülan (dabigatran ve rivaroksaban) kullanan ve acil servise gelen hastalarda trombotik komplikasyon risk faktörlerini (inme, miyokard infarktüsü, sistemik embolizasyon) incelemeyi amaçladık.

Yöntemler: Bu çalışma retrospektif olarak yöntem geliştirme çalışması olarak tasarlanmıştır. Çalışmaya Ocak 2013-Aralık 2014 yılları arasında Adıyaman Üniversitesi Eğitim ve Araştırma Hastanesi Acil Tıp Kliniği'ne başvuran 205 hasta dahil edilmiştir. Hastalar rivaroksaban kullanan ve dabigatran kullananlar olarak iki gruba ayrılmıştır. İlaç kullanımına başlamadan önceki laboratuvar parametreleri ile ilaç kullanırken acil servise başvuru esnasındaki laboratuvar parametreleri arasındaki farklılıklar analiz edildi. [Δbeyaz kan hücreleri, Δhemoglobin, Δhematokrit, Δtrombosit, Δplatecrit, Δtrombosit dağılım genişliği, ortalama trombosit hacmi (ΔMPV)].

Bulgular: İki grup arasında CHA_2DS_2-VASc skorları, komplikasyonlar ve ilaç alım süresi açısından anlamlı fark yoktu. Yeni nesil oral antikoagülan kullanan her iki grupta da MPV değeri ($p<0.001$) açısından istatistiksel olarak anlamlı bir azalma vardı. Trombotik komplikasyonların öngörülmesinde ΔMPV optimum eşik noktası 910,7 fL, %91,7 duyarlılık ve %62,2 özgüllükte saptandı (eğri altında kalan alan: 0,805, %95 güven aralığı: 0,744-0,857, $p<0,001$).

Sonuç: Sonuç olarak, acil servise başvuran ve yeni nesil oral antikoagülan kullanan atriyal fibrilasyonlu hastalar için yüksek CHA_2DS_2-VASc skoru ve önceki MPV değerinde beklenen düşüşün olmaması, trombotik olguları öngörmede kullanılacak basit parametreler olup klinik olarak kullanışlı olacağı düşünülmektedir.

Anahtar Kelimeler: Atrial fibrilasyon, dabigatran, rivaroxaban

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Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia and related to serious morbidity and mortality (1). AF is a chronic disease which increases the formation of thrombosis in the left atrium and a significant risk factor in terms of stroke recurrence (2). One of the main aims of long-term anticoagulants treatment for patients with AF is to prevent thromboembolism attack and to reduce stroke risk (1).

New generation oral anticoagulants (NOAC) are agents that reduce stroke and systemic embolization in patients with nonvalvular AF (3). Dabigatran is direct thrombin inhibitor which is as efficient as vitamin K antagonist for reducing stroke risk without increasing bleeding risk in AF (4). In addition, dabigatran has been shown to be superior to warfarin in primary and secondary prevention of AF patients from ischemic events (5). Rivaroxaban is a factor Xa inhibitor which is as efficient as warfarin for preventing stroke without bleeding increase in AF patients (6). NOAC was found to be safer and more effective than warfarin to reduce the risk of thrombosis and complications in patients with non-valvular AF (7).

The international normalized ratio (INR) is the value of the warfarin level. In clinical practice, it is not possible to follow the NOAC level. In this study, we aimed to examine the risk factors and laboratory findings of the patients with AF who applied to emergency service with thrombosis related to the use of NOAC (dabigatran and rivaroxaban). We have investigated the availability of a simple usable parameter indicating NOAC activity. Besides, biochemical and clinical parameters were compared in the patients who used dabigatran and rivaroxaban.

Methods

The study included 205 consecutive patients who visited emergency department with chronic nonvalvular AF and were treated with rivaroxaban (15-20 mg) or dabigatran (110-150 mg) between the dates of 01.01.2013 and 31.12.2014. The patients were divided into two groups; group 1 using dabigatran and group 2 using rivaroxaban. The variation between laboratory parameters of patients existing before drug intake and acquired during their emergency department visits was also analyzed. Thrombotic cases were assessed according to type of thrombotic events such as myocardial infarction (MI), stroke, and systemic embolization. CHA_2DS_2-VASc scores were calculated for each patient and shown in Table 1 (8).

Table 1. CHA_2DS_2-VASc score

C	Congestive heart failure	1 point
H	Hypertension	1 point
A_2	Age (≥75 years)	2 point
D	Diabetes mellitus	1 point
S_2	Stroke/ TIA/ systemic embolization	2 point
V	Vascular disease (Old MI, PAH, aortic plaque)	1 point
A	Age (between 65-74 years)	1 point
Sc	Sexuality (Female gender)	1 point

MI: myocardial infarction, PAH: pulmonary arterial hypertension, TIA: transient ischemic attack

Patient Selection

The patients who were prescribed NOAC by the cardiologist and who had been using it for at least three months (dabigatran and rivaroxaban) were included in the study. Blood analyses of the patients before using dabigatran and rivaroxaban and during the emergency department visits were compared. The patients who had different risk factors which could cause thrombosis, such as hematologic diseases, chronic renal failure, hepatic failure, hyper- or hypothyroidism, active infection and malignancy, and who had been using NOAC irregularly or using for less than three months and the ones with missing data were excluded. The study was approved by Adıyaman University Faculty of Medicine Presidency of Ethics Committee of Biomedical Researches on 22.11.2016 with the decision number of 2016/7-1.

Data Collection

Age, gender, smoking status (Smoking +/-), chronic obstructive pulmonary disease (COPD) status (COPD +/-), white blood cells (WBC), hemoglobin (Hb), hematocrit (HTC), INR, prothrombin time (PT), activated partial thromboplastin time (aPTT), C-reactive protein (CRP), platelet (PLT), plateletcrit (PCT), platelet distribution width (PDW), mean platelet volume (MPV), CHA_2DS_2-VASc score, and time of used NOAC results were recorded from the patients' digital hospital files. ΔWBC, ΔHb, ΔHTC, ΔINR, ΔPT, ΔaPTT, ΔCRP, ΔPLT, ΔPCT, ΔPDW, and ΔMPV were calculated from the laboratory values.

Statistical Analysis

Collected data analysis was performed by using SPSS software (version 20.0, SPSS Inc., Chicago, Illinois). The Kolmogorov-Smirnov test was used to evaluate the distribution of continuous variables. Normally distributed continuous variables were compared with the Student's t-test while non-normally distributed continuous variables were compared with the Mann-Whitney U test. Categorical variables compared with the $\chi 2$ or Fisher's exact tests were summarized as percentages. Laboratory parameters of patient population before and three months after the emergency department visit were compared with paired t-test and/or Wilcoxon tests. Correlation analysis was performed using the Pearson's or Spearman's tests. Univariate analyses of all the parameters that might affect the thrombotic complications (age, gender, smoking status, COPD, CHA_2DS_2-VASc score, time of used NOAC, ΔWBC, ΔHb, ΔHTC, ΔINR, ΔPT, ΔaPTT, ΔCRP, ΔPLT, ΔPCT, ΔPDW, ΔMPV) were performed. Parameters having p values of <0.2 were included in the multivariate regression model. As the ΔHTC was highly correlated with ΔHb and ΔMPV with ΔPDW, ΔHTC and ΔPDW were excluded from the multivariate regression model although they both had p values of <0.2. Finally, multivariate regression analyses were performed on the parameters of CHA_2DS_2-VASc score, time of used NOAC, ΔMPV, ΔPT, ΔWBC, ΔHb, ΔPCT and ΔPLT. The fit of the multi regression analysis model was found good according to the Omnibus test. A value of $p<0.05$ was accepted as statistically significant.

Results

Demographic parameters of population included in the study are shown in Table 2. There is no significant difference between the groups with

respect to age, gender, diabetes mellitus, hypertension, cerebrovascular stroke, vascular disease, chronic obstructive pulmonary disease, CHA_2DS_2-VASc score and duration of drug usage. Congestive heart failure rate was higher in group 2 (p=0.006), whereas smoking rate was higher in group 1 (p=0.042).

The laboratory parameters of patient population are shown in Table 3. While the number of platelets was statistically reduced in the group using dabigatran in comparison with pre-treatment (p=0.001), there was no significant difference in the group using rivaroxaban (p>0.05).

Table 2. Basal demographic data of study population

	Group 1 (dabigatran)	Group 2 (rivoraxaban)	p
	(n=68)	(n=137)	
Age (years)	72 (67-77)	75 (65-83)	0.429
Gender (Male, %)	22 (32.4%)	58 (42.3%)	0.168
DM (n, %)	14 (20.6%)	16 (11.7%)	0.089
HT (n, %)	31 (45.6%)	74 (54.0%)	0.256
CHF (n, %)	16 (23.5%)	59 (43.1%)	0.006
CvS (n, %)	28 (41.2%)	43 (31.4%)	0.165
Vascular disease (n, %)	29 (42.6%)	59 (43.1%)	0.955
Smoke (n, %)	19 (27.9%)	19 (13.9%)	0.042
COPD (n, %)	14 (20.6%)	15 (10.9%)	0.062
CHA_2DS_2-VASc score	3.3±1.2	3.2±1.4	0.635
Duration of use (month)	66.4 (1-188)	59.4 (0-192)	0.306

DM: diabetes mellitus, HT: hypertension, CHF: congestive heart failure, CvS: cerebrovascular stroke, COPD: chronic obstructive pulmonary disease

*For categoric parameters $\chi 2$, student's t-test and Mann-Whitney U test were used

There is a statistically significant decrease with regard to MPV (p<0.001, for both group) and PCT (p=0.024, p=0.038, respectively), on the other side a significant increase in PDW value (p<0.001, for both group) in both groups taking NOACs.

As mentioned in Table 3 in detail, Hb, HCT, pentylenetetrazole and CRP did not show significant results in both groups. PCT, PDW and MPV were significantly different in both group 1 and group 2. PLT and aPTT were significant only in group 1 and WBC and INR were significant only in group 2.

In the univariate analysis performed to identify the complications cause p values of variables of <0.20 were included in the multivariate analysis (Table 4). In the logistic multiple regression analysis ΔWBC [odds ratio (OR)=1.163, confidence interval (CI) %95=1.005-1.346, p=0.043, CHA_2DS_2-VASc score (OR=2.195, CI %95=1.157-4.167, p=0.016) and ΔMPV (OR=0.235, CI %95=0.086-0.644, p=0.005)] were the independent predictors of the complications of NOACs (Table 5).

The optimal threshold point of ΔMPV in the prediction of the thrombotic complications was ≤0.7 fL, with 91.7% sensitivity and 62.2% specificity [area under the curve (AUC): 0.805, 95% CI: 0.744-0.857, p<0.001]. The optimal threshold point of CHA_2DS_2-VASc score in the prediction of the thrombotic complications was >3, with 83.3% sensitivity and 56.5% specificity (AUC: 0.731, CI: 0.701-0.857; p<0.001).

Discussion

According to the results of this study, ΔWBC, CHA_2DS_2-VASc score and ΔMPV predict the thrombotic complications which are seen during the process of total population of patients with nonvalvular AF using dabigatran and rivaroxaban (NOACs).

AF is the most common arrhythmia with continuity and its rate rapidly increases with the world-wide age average (9). Nowadays, atrial thrombosis and stroke are the most common reasons for mortality and

Table 3. Laboratory parameters of patient population

	Group 1 (dabigatran)			Group 2 (rivoraxaban)		
	(n=68)			(n=137)		
	Before	After	p	Before	After	p
WBC	8.6±2.4	8.9±3.1	0.313	8.4 (3.4-16.8)	9.6 (3.6-34.8)	0.001
Hb	13.3±1.7	13.1±1.9	0.292	13.4±2.0	13.2±2.2	0.189
HCT	40.9±5.1	39.7±7.1	0.130	41.5±6.1	41.2±6.1	0.562
INR	1.5±0.8	1.5±0.5	0.484	1.7±1.2	2.0±1.5	0.028
PTZ	17.6±7.0	17.4±4.5	0.826	18.7±9.7	20.7±11.9	0.063
aPTT	33.6±7.8	36.7±9.1	0.017	35.5±11.8	38.3±16.2	0.104
CRP	0.5 (0.1-6.6)	0.6 (0.2-10.2)	0.549	0.6 (0.1-19.4)	0.6 (0.1-33.1)	0.485
Plt	262.3±72.1	236.2±68.1	0.001	244.2±67.1	234.9±71.4	0.113
PCT	0.21±0.05	0.19±0.06	0.024	0.20 (0.06-0.37)	0.19 (0.05-0.36)	0.038
PDW	17.4 (10.1-24.8)	19.3 (10.2-23.4)	<0.001	18.5 (10.2-24.1)	20.1 (12.3-24.3)	<0.001
MPV	8.5±1.5	7.0±1.1	<0.001	8.4 (5.6-13.2)	7.1 (4.7-10.0)	<0.001

WBC: white blood cell, Hb: hemoglobin, HCT: hematocrit, INR: international normalized ratio

PT: prothrombin time, APTT: activated partial thromboplastin time, CRP: C-reactive protein, PLT: platelet, PCT: platecrit, PDW: platelet distribution width, MPV: mean platelet volume

*Paired t, t-test and Wilcoxon test were used

Table 4. Univariate regression analysis of parameters that may be associated with thrombotic complications

	p	OR	95% CI	
			Lower	Upper
NOAC type	0.990	0.992	0.288	3.419
Age (years)	0.438	0.983	0.941	1.027
Gender	0.847	0.890	0.272	2.906
Smoke	0.830	0.843	0.177	4.012
COPD	0.998	0.000	0.000	-
ΔWBC	0.101	1.102	0.981	1.237
ΔHb	0.099	0.801	0.616	1.043
ΔHCT	0.088	0.939	0.874	1.009
ΔINR	0.236	0.751	0.467	1.206
ΔPT	0.144	0.960	0.908	1.014
ΔAPTT	0.461	0.987	0.952	1.022
ΔCRP	0.461	0.934	0.780	1.119
ΔPLT	0.176	0.994	0.986	1.002
ΔPCT	0.026	0.000	0.000	0.232
ΔPDW	0.015	1.227	1.041	1.446
ΔMPV	0.004	0.380	0.196	0.736
CHA_2DS_2-VASc score	0.008	1.957	1.194	3.208
Time of use of NOAC	0.080	1.012	0.999	1.025

NOACs: new oral anticoagulants, COPD: chronic obstructive pulmonary disease, ΔWBC: magnitude of change in the white blood cell count, ΔHb: Magnitude of change in the Hemoglobin count, ΔHCT: magnitude of change in the hematocrit count, ΔINR: magnitude of change in the international normalized ratio count, ΔPT: magnitude of change in the prothrombin time count, ΔAPTT: magnitude of change in the activated partial thromboplastin time count, ΔCRP: magnitude of change in the C-reactive protein count, ΔPLT: magnitude of change in the platelet count, ΔPCT: magnitude of change in the platecrit count, ΔPDW: magnitude of change in the platelet distribution width count, ΔMPV: magnitude of change in the mean platelet volume count, CI: confidence interval, OR: odds ratio

Table 5. Multivariate regression analysis of parameters that may be associated with thrombotic complications

	p	OR	95% CI	
			Lower	Upper
CHA_2DS_2-VASc score	0.016	2.195	1.157	4.167
Time of use of NOAC	0.404	1.007	0.991	1.023
Δ MPV	0.005	0.235	0.086	0.644
Δ PT	0.429	0.974	0.914	1.039
Δ WBC	0.043	1.163	1.005	1.346
Δ Hb	0.293	0.847	0.623	1.154
Δ PCT	0.057	0.000	0.000	1.631
Δ PLT	0.456	1.005	0.992	1.018

NOACs: new oral anticoagulants, ΔWBC: magnitude of change in the white blood cell count, ΔHb: magnitude of change in the hemoglobin count, ΔPT: magnitude of change in the prothrombin time count, ΔPLT: magnitude of change in the platelet count, ΔPCT: magnitude of change in the platecrit count, ΔMPV: magnitude of change in the mean platelet volume count, CI: confidence interval, OR: odds ratio

morbidity (10). There are oral (warfarin and other vitamin K antagonists) and parenteral (unfractionated heparin, low molecular weight heparin, hirudin and argatroban) anticoagulant drugs with license to prevent systemic embolism in patients with non-valvular AF (11). Recently, NOACs which can be an alternative way of these treatment options are used. Among these drugs, dabigatran and rivaroxaban are two most frequently used agents (4,6). The measurement of thrombosis activation in patients with AF is significant because PLTs have an important role in thromboembolic cases (12). Many safe indicators have been recently examined to evaluate coagulation and PLT activation such as thrombin/antithrombin complex, b-thromboglobulin and soluble PLT P-selectin. However, these markers are not routine laboratory measurements and it is expensive to calculate the index. PLT index such as PCT, PDW, and MPV are routinely measured with complete blood cell count (CBC) without incremental cost (13).

AF increases the risk of thrombosis and causes platelet activation because of stasis in the left atrium and this is related to the risk of stroke and thromboembolic cases (9). MPV is an easy-measured marker that reflects platelet activation and reactivity. MPV is a significant predictive and prognostic marker in cardiovascular diseases (14). Large PLTs have higher thrombosis potential. Increasing MPV value is approved as an independent risk factor for MI and stroke (15). In another study, MPV has been shown to be increased in AF patients with stroke compared to those without stroke (16). In addition, increasing MPV is related to recurrent ischemia and mortality (17). Recent surveys have investigated the effects of some drugs on MPV. It is stated that the use of acetylsalicylic acid (ASA) for paroxysmal AF cases and dual antithrombocyte treatment for coronary artery disease has no significant effect on MPV (18). In the study conducted by Colkesen et al. (19), the effect of ASA on MPV value in paroxysmal AF patients was investigated and it was stated that MPV was not affected by ASA usage in these patients (19). In a different study, it is pointed that patients with MI that are cured with GP IIb/IIIa inhibitor abciximab and percutaneous coronary have lower MPV values (20). Unlike these studies, the effect of NOAC was evaluated in this study, and it was found that MPV was decreased in both groups using rivaroxaban and dabigatran during the process. However, to use MPV as a predictive factor for thrombotic effects of NOAC, prospective studies with wider populations are needed.

It is known that PLT activation causes morphological changes. PLTs with a bigger volume are more aggregate and active because of having increased the expression of PLT surface receptor (21). Also, larger platelets gather quicker than smaller PLTs. Therefore, higher MPV values are correlated with platelet activation and thrombosis tendency (22). That MPV decrease is lower in the patients with AF using NOAC refers that there is an independent predictor parameter of thrombotic cases, which supports the data in our study.

In a study, WBC has been shown to be a predictor of mortality in patients with stroke and the increase in WBC was found to be associated with high mortality (23). In a different study in which patients with cardiac pathology were followed, high WBC values were shown to be associated with higher rates of stroke (24).

In our study, it was observed that WBC increased significantly in the group using rivaroxaban unlike the group using dabigatran. This may

depend on different efficacy of the agents. However, it is necessary to investigate this with comprehensive studies.

Previous studies indicate that CHA_2DS_2-VASc score is a parameter that predicts hospitalization due to AF, and cardiovascular mortality. Many recent studies indicate that CHA_2DS_2-VASc score is an important parameter that helps to prevent stroke and also shows mortality and morbidity after stroke (8). Likewise, other studies mentioned in this study present that CHA_2DS_2-VASc score is a parameter that predicts the course of events in thrombotic cases in AF patients using NOAC (25).

Study Limitation

Relatively low number of the patients may be considered as a limitation. Another limitation is the inability of the patient to access the CBC before using NOAC. ΔWBC and ΔMPV cannot be calculated if patient's WBC and MPV values cannot be found before using NOAC. However, if the physician notes the WBC and MPV values before using NOAC, ΔWBC and ΔMPV can be used to predict the risk of thrombosis and complications due to use of NOAC drugs.

Conclusion

In conclusion, we found in this study that CHA_2DS_2-VASc score, ΔWBC and ΔMPV values predict the thrombotic complications in patients using NOAC. The results show that MPV change can be considered as an additional marker in the follow-up of patients with AF using NOAC in predicting thrombotic complications. In the follow-up with non-valvular AF patients visiting emergency department, we think it might be useful to evaluate these parameters in terms of the development of thrombotic complications.

Ethics

Ethics Committee Approval: The study was approved by Adıyaman University Faculty of Medicine Presidency of Ethics Committee of Biomedical Researches on 22.11.2016 with the decision number of 2016/7-1.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - İ.A., M.K.P., A.A., G.A., S.E.E.; Concept - G.A.; Design - M.K.P., S.E.E.; Data Collection or Processing - İ.A., M.K.P.; Analysis or Interpretation - A.A., G.A.; Literature Search - A.A.; Writing - A.A.

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