The Effect of Contrast Agents on the Anticoagulant Properties of Oral Factor Xa Inhibitors

Burcu TUNCAY
Bursa Postgraduate Hospital
Selma Ari
Bursa Postgraduate Hospital
Hasan Ari (hasanari03@yahoo.com)
Bursa Postgraduate Hospital https://orcid.org/0000-0002-9681-2374
Sencer CAMCI
Bursa Postgraduate Hospital
Mehmet MELEK
Bursa Postgraduate Hospital
Tahsin BOZAT
Bursa Postgraduate Hospital

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Abstract

Objective: The aim of this study is to evaluate the effect of iohexol as a contrast agent on the anticoagulant activity of oral factor Xa inhibitors.

Methods:The study included 65 people who underwent contrast computerized tomography (CT). Patients in group 1 were using rivaroxaban (20 patients), patients in group 2 were using apixaban (20 patients), patients in group 3 were using edoxaban (20 patients), and group 4 was the control group (5 volunteers). Iohexol (60ml) was used as a contrast agent. Two tubes were used to collect 2 ml of blood from the patients at 4 hours after the drug dose (rivaroxaban, apixaban, or edoxaban) and 1 hour after the contrast CT (CT was performed 3 hours after the drug was taken). In the control group, at any time and 1 hour after contrast CT, 2 tubes of 2 ml of blood were collected. The anticoagulant properties of rivaroxaban, apixaban, and edoxaban were evaluated using anti-factor Xa levels.

Results:The anti-factor Xa level was increased after using the contrast agent in the rivaroxaban group (0.66±0.32U/ml vs. 0.67±0.32U/ml; p=0.01) and the edoxaban group (0.74±0.35 U/ml vs. 0.76±0.36 U/ml; p=0.006). However, there was no significant difference in the apixaban group (0.66±0.33U/ml vs. 0.66±0.32U/ml; p=0.21) and control group (0.02±0.01U/ml vs. 0.03±0.01U/ml; p=0.33).

Conclusion:The anticoagulant properties of rivaroxaban and edoxaban tended to increase significantly, but there was no statistically significant difference in the anticoagulant properties of apixaban with contrast agent. The increasing is too small so that these laboratory results need to validate with larger clinical trials(NCT04611386).

Introduction

Atrial fibrillation (AF) is the most common type of sustained cardiac arrhythmia. The prevalence of AF increases with age by up to 14% [1, 2]. AF increases the risk of ischemic stroke by 5 times [3]. Approximately one-third of patients with ischemic stroke have AF [4]. Vitamin K antagonists (VKA) reduce the incidence of stroke by 64% and 39% compared to any treatment and antiplatelet therapy [5]. However, the quality of anticoagulation control is a challenging process and should be maintained in the therapeutic range (TTR) of > 70% to improve the results [6]. Novel oral anticoagulants (NOAC) are now widely used in patients with non-valvular AF, such as dabigatran, rivaroxaban, apixaban, and edoxaban. Rivaroxaban, apixaban, and edoxaban are factor Xa inhibitors.

Contrast computerized tomography (CT) examinations are frequently performed on patients who are using oral factor Xa inhibitors. Contrast agents have different properties that are based on their osmolarities, chemical structures, and ionization statuses [7]. Previous studies have shown that contrast agents have anticoagulant and antiaggregant effects [8, 9]. However, there are no data in the literature showing whether the contrast agents affect the efficacy of oral factor Xa inhibitors. Thus, the aim of this study is to evaluate the effect of contrast agents on the anticoagulant activity of the oral factor Xa inhibitors rivaroxaban, apixaban, and edoxaban.

Materials And Methods

The study began after approval was obtained from the local ethics committee. The study prospectively included 65 people who underwent contrast computerized tomography (CT). The CT indications were thoracic aortic dilatation, chronic obstructive pulmonary disease, abdominal aortic dilatation, chronic abdominal pain. The subjects comprised 60 patients who were using oral factor Xa inhibitors (20 using rivaroxaban 20 mg OAD, 20 using apixaban 5 mg BID, and 20 using edoxaban 60 mg OAD) and 5 volunteers who did not use oral factor Xa inhibitors between January 2019 and August 2019. Written informed consent was obtained from the study population in accordance with the study protocol. Patients using rivaroxaban were considered as Group 1 (20 patients), patients using apixaban were considered as Group 2 (20 patients), patients using edoxaban were considered as Group 3 (20 patients), and volunteers (control) were considered as group 4.

The inclusion criteria were 1) the use of oral factor Xa inhibitors (patients with nonvalvular AF and CHA2DS2-VASc Score ≥ 2), 2) age of 21–80 years, 3) no contraindications for anticoagulation use, 4) GFR greater than 30, 5) volunteering to participate in the study, and 6) patients who needed to use contrast agent (iohexol) for CT examination. The exclusion criteria were 1) coagulopathy, 2) severe hepatic insufficiency, 3) chronic systemic or inflammatory diseases, 4) patients lighter than 60 kg, 5) malignancy, 6) creatinine value above 1.5 mg/dl, and 7) not providing consent to participate in the study.

Study Protocol

The demographic characteristics of the patients were recorded, and physical examinations were performed. The baseline biochemical values and risk factors were recorded, and blood pressure (BP) was measured before the procedures. Patients were defined as hypertensive if they had a systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg or if they were taking antihypertensive drugs. Patients were defined as diabetic if their fasting blood glucose levels were ≥ 126 mg/dL in two consecutive measurements or if they were using oral antidiabetics or insulin. The body mass index (BMI) was calculated using the following formula: weight (kg)/square of the height (m^2). GFR was calculated using the Cockcroft-Gault formula: [(140 - age) x patient weight (kg)]/[72 x serum creatinine value] (x 0.85 for women) [10].

Four hours after taking the medication (oral factor Xa inhibitor), 2 tubes of 2 ml of blood were taken from the forearm from 60 patients (20 rivaroxaban, 20 apixaban, and 20 edoxaban patients). The blood was taken from the forearm between 12 and 13 o'clock from all patients and volunteers. The anti-factor Xa, PT, INR and aPTT levels were measured from the blood samples. The levels were also measured in the control group. Three days after the first evaluation of the levels, contrast CT was performed. Contrast CT examination was performed 3 hours after taking the oral factor Xa inhibitor for the 60 patients. The second measurement of the anti-factor Xa, PT, INR and aPTT levels was performed 1 hour after the contrast CT evaluation for 60 patients and 5 volunteers (control group) (Fig. 1). The blood was taken from the forearm between 12 and 13 o'clock from all patients and volunteers. Sixty ml iohexol (350 mg I/ml) was use as a contrast agent for all patients and volunteers. BUN and creatinine values were checked at 48–72 hours after the contrast CT for contrast-induced nephropathy (CIN).

Anti-factor Xa Level And Coagulation Parameters Measurement

The 2-ml blood samples were centrifuged immediately in the biochemistry laboratory at 5000 g for 10 minutes. The plasma samples were put into one Eppendorf tube using a plastic pipe and stored in a deep freezer at -20^{o}C until analysis. The anti-factor Xa level was measured from the obtained plasma samples with a Berichrom Heparin kit in a Sysmex cs 5100 device in the biochemistry laboratory. The Berichrom Heparin kit is a chromogenic test (Berichrom heparin, Siemens Healthineers, Marburg, Germany). The kit contains AT III reagent. Berichrom Low Molecular Weight Heparin calibrator was used to calibrate the anti-factor Xa measurement. INR, PT, and aPTT were measured as coagulation parameters. Venous blood samples in coagulation tubes were centrifuged at 5000 rpm for 10 minutes, and the INR, PT, and aPTT levels were measured in the biochemistry laboratory using a Sysmex cs 5100 device, Dade Actin FS, Activated PTT reagent, and thromborel S reagent. Researchers evaluating Anti-Fax level are blind about which patient is taking which medicine.

Statistical Analyses

Statistical analyses were performed by using the program SPSS (Statistical Package for the Social Sciences version. 23, SPSS Inc., Chicago, Illinois, USA). The continuous variables are reported as the means ± standard deviations, and categorical variables are reported as percentages. A Kruskal-Wallis test was used for comparison of the continuous variables among the baseline characteristics of the four groups. A chi-squared test or a Fisher's exact test was used for the comparison of categorical variables. A Wilcoxon Sign Rank test was used to evaluate repeated measurements. In a standard statistical analysis, $p < 0.05$ was accepted as significant. Intra and inter assay coefficient of variation were calculated for anti-factor Xa level measurements.

Results

Patient characteristics

A total of 65 patients were included in the study, and the mean age was 66.4 years. Of these patients, 41.5% (27) were male, and 58.5% (38) were female. The mean BMI was 27.4 (kg/m^2). Hypertension was present in 78.4% (51) of the patients, 27.6% (18) of the patients were hyperlipidaemic, and 26.1% (17) were diabetic. 53.8% of the patients were smokers. The average CHA2DS2-VASc score was 3 ± 1. The demographic and laboratory characteristics of the groups are shown in Table 1. All of the groups' demographic and laboratory characteristics were similar.

Table 1
Baseline Demographic and Laboratory Characteristics of the Patients.

Variable	Rivaroxaban (n = 20)	Apixaban (n = 20)	Edoxaban (n = 20)	Control (n = 5)	P Value
Age, (year)	66.30 ± 10.10	67.20 ± 6.83	67.65 ± 6.12	59.00 ± 16.55	0.88
Gender, n (%)	8 (40)	11 (55)	6 (30)	2 (40)	0.45
Male	12 (60)	9 (45)	14 (70)	3 (60)	
Female					
Body Mass Index, (kg/m^2)	26.90 ± 2.05	27.46 ± 2,82	27.90 ± 3.15	27.30 ± 2.43	0.79
GFR (ml/min)	83.10 ± 31.40	74.84 ± 18.03	79.65 ± 21.04	93.87 ± 32.62	0.78
Hypertension, n (%)	16 (80)	15 (75)	16 (80)	4 (80)	0.97
Diabetes Mellitus, n (%)	5 (25)	8 (40)	3 (15)	1 (20)	0.33
Hyperlipidemia, n (%)	4 (20)	7 (35)	4 (20)	3 (60)	0.22
Smoking, n (%)	10 (50)	8 (40)	13 (65)	4 (80)	0.25
CHA_2DS_2VASc score	3.05 ± 1.23	3.10 ± 0.85	2.85 ± 0.93	3.00 ± 1.03	0.81
EF, %	49.25 ± 14.62	47.00 ± 16.25	53.00 ± 10.56	49.00 ± 11.40	0.79
Hemoglobin (gr/dl)	13.40 ± 1.56	12.82 ± 1.67	12.87 ± 1.64	13.04 ± 1.33	0.65
Platelet (10^3/uL)	246.30 ± 71.80	238.26 ± 77.03	236.25 ± 65.22	254.20 ± 46.97	0.86
BUN (mg/dl)	18.47 ± 7.00	20.99 ± 10.04	19.61 ± 8.19	14.46 ± 4.68	0.56
Creatinine (mg/dl)	0.86 ± 0.17	0.99 ± 0.22	0.89 ± 0.18	0.92 ± 0.41	0.43
Na (mmol/L)	138.05 ± 4.53	138.25 ± 3.36	138.20 ± 4.93	137.60 ± 2.88	0.83
K (mEq/L)	4.41 ± 0,49	4.62 ± 0.51	4.64 ± 0.34	4.62 ± 0.67	0.28
AST (U/L)	22.15 ± 16.32	19.70 ± 5.46	19.80 ± 8.58	24.60 ± 7.66	0.48
ALT (U/L)	23.35 ± 13.53	19.45 ± 8.64	21.20 ± 11.71	19.40 ± 10.64	0.69
Total Bilirubin (mg/dl)	0.63 ± 0.32	0.73 ± 0.35	0.70 ± 0.62	0.45 ± 0.16	0.16
Direct Bilirubin (mg/dl)	0.21 ± 0.20	0.22 ± 0.13	0.19 ± 0.18	0.15 ± 0.08	0.36

BUN: Blood Urea Nitrogen, GFR: Glomerülar filtration rate, EF: Ejection fraction, Na: Sodium, K: Potassium, AST: Aspartate Transaminase, ALT: Alanine Aminotransferase, ACEİ= Angiotensin-Converting Enzyme Inhibitor, ARB: Angiotensin Receptor Inhibitor, CCB DHP: Calcium Channel Blocker Dihydropyridine group, CCB NDHP: Calcium Channel Blocker Non-Dihydropyridine group, OAD: Oral antidiabetic

Variable	Rivaroxaban (n = 20)	Apixaban (n = 20)	Edoxaban (n = 20)	Control (n = 5)	P Value
Medication, n (%)	2 (10)	0 (0)	1 (5)	2 (40)	0.056
Aspirin	3 (15)	7 (35)	4 (20)	3 (60)	0.16
Statin	11 (55)	13 (65)	12 (60)	3 (60)	0.93
Beta blocker	7 (35)	9 (45)	6 (30)	3 (60)	0.56
ACEI	7 (35)	1 (5)	7 (35)	1 (20)	0.089
ARB	5 (25)	2 (10)	2 (10)	1 (20)	0.49
CCB (DHP)	4 (20)	4 (20)	1 (5)	1 (20)	0.49
CCB (NDHP)	5 (25)	5 (25)	2 (10)	1 (20)	0.59
OAD	0 (0)	3 (15)	1 (5)	1 (20)	0.21
Insülin					

BUN: Blood Urea Nitrogen, GFR: Glomerülar filtration rate, EF: Ejection fraction, Na: Sodium, K: Potassium, AST: Aspartate Transaminase, ALT: Alanine Aminotransferase, ACEİ= Angiotensin-Converting Enzyme Inhibitor, ARB: Angiotensin Receptor Inhibitor, CCB DHP: Calcium Channel Blocker Dihydropyridine group, CCB NDHP: Calcium Channel Blocker Non-Dihydropyridine group, OAD: Oral antidiabetic

Anti-factor Xa Level And Coagulation Parameters

The anti-factor Xa level was increased after contrast agent use in the rivaroxaban group (0.66 ± 0.32 vs. 0.67 ± 0.32: p = 0.01) and edoxaban group (0.74 ± 0.35 vs. 0.76 ± 0.36: p = 0.006). However, there was no significant difference in the apixaban group (0.66 ± 0.33 vs. 0.66 ± 0.32: p = 0.21) and control group (0.02 ± 0.01 vs. 0.03 ± 0.01: p = 0.33) (Table 2, Fig. 2). The INR level was increased after contrast agent use in the rivaroxaban group (1.20 ± 0.2 vs. 1.22 ± 0.2: p = 0.01) and edoxaban group (1.33 ± 0.3 vs. 1.34 ± 0.3: p = 0.03). However, there was no significant difference in the apixaban group (1.20 ± 0.1 vs. 1.21 ± 0.1: p = 0.23) and control group (0.85 ± 0.05 vs. 0.87 ± 0.06: p = 0.13) (Table 3). Anti-factor Xa intra assay coefficient of variation was 2.0 %. Anti-factor Xa inter assay coefficient of variation was 3.9 %.

Table 2
Anti Factor Xa Level Before and After Contrast Agent Using

	Contrast Agent		P Value
	Before	After	
	Anti-Factor Xa (U/ml)	Anti-Factor Xa (U/ml)	
Rivaroxaban	0.66 ± 0.32	0.67 ± 0.32	**0.01**
Apixaban	0.66 ± 0.33	0.66 ± 0.32	0.21
Edoxaban	0.74 ± 0.35	0.76 ± 0.36	**0.006**
Control	0.02 ± 0.01	0.03 ± 0.01	0.33

Table 3: PT, aPTT and INR level Before and After Contrast Agent Using

	Contrast Agent						P Value		
	Before			After					
	PT (Sec)	aPTT (Sec)	INR	PT (Sec)	aPTT (Sec)	INR	PT	aPTT	INR
Rivaroxaban	16.23 ± 3.6	30.15±4.6	1.20± 0.2	16.85± 4.1	30.36±4.4	1.22± 0.2	**0.03**	0.82	**0.01**
Apixaban	16.51± 2.7	30.31 ± 5.1	1.20± 0.1	16.86± 2.7	30.42± 4.5	1.21± 0.1	0.10	0.79	0.23
Edoxaban	18.19±5.4	33.25±4.4	1.33±0.3	18.87±5.4	33.52± 3.4	1.34± 0.3	**0.004**	0.73	**0.03**
Control	11.26± 0.9	19.84±1.0	0.85±0.05	11.62± 0.9	19.48±0.83	0.87± 0.06	**0.03**	0.07	0.13

PT: Prothrombin Time, aPTT: Activated Partial Thromboplastin Time, INR: International Normalized Ratio

The INR results were parallel to the anti-factor Xa level results (Table 3). When aPTT values were compared, there was no statistically significant difference between the groups before and after contrast agent use (Table 3). With contrast agent, PT values were increased in the rivaroxaban group (16.23 ± 3.6 vs. 16.85 ± 4.1: p = 0.03), edoxaban group (18.19 ± 5.4 vs. 18.87 ± 5.4: p = 0.004), and control group (11.26 ± 0.9 vs. 11.62 ± 0.9: p = 0.03). However, there was no significant difference in the apixaban group (16.51 ± 2.7 vs. 16.86 ± 2.7: p = 0.10) (Table 3). BUN, creatinine, and GFR values did not change significantly before and after the contrast agent use (Table 4). CIN did not develop in any patients. In this study period, we did not see any clinically significant bleeding with these oral factor Xa inhibitors in our study population.

Table 4: BUN and Creatinine Level Before and After Contrast Agent Using

	Contrast Agent						P Value		
	Before			After					
	BUN (mg/dl)	Creatinine (mg/dl)	GFR (ml/min)	BUN (mg/dl)	Creatinine (mg/dl)	GFR (ml/min)	BUN	Creatinine	GFR
Rivaroxaban	18.47 ± 7.00	0.86±0.17	83.10±31.40	22.69± 8.51	0.98±0.19	70.22±19.67	0.61	0.09	0.12
Apixaban	20.99± 10.04	0.99± 0.22	74.84±18.03	25.83± 11.64	1.06± 0.26	69.14±17.70	0.75	0.34	0.35
Edoxaban	19.61±8.19	0.89±0.18	79.65±21.04	25.94±10.08	0.98± 0.36	77.36±37.64	0.35	0.71	0.71
Control	14.46± 4.68	0.92±0.41	93.87±32.62	18.69± 2.91	1.00±0.41	84.75±25.16	0.28	0.068	0.07

BUN: Blood Urea Nitrogen, GFR: Glomerülar filtration rate.

Discussion

The main results of our study are as follows. a) The anti-factor Xa level increased with contrast agent use (iohexol) in patients with rivaroxaban and edoxaban treatment. b) The PT level increased with contrast agent use in patients with rivaroxaban and edoxaban treatment and the control group. c) The INR level increased with contrast agent use in patients with rivaroxaban and edoxaban treatment. d) The coagulation parameters did not change with contrast agent use in the apixaban group.

AF-related complications (stroke) and venous thromboembolic complications lead to cardiovascular mortality and morbidity [11, 12]. For these reasons, the use of an effective level of oral factor Xa inhibitors is very important. Contrast agents interact with the coagulation mechanism because they are ionic and nonionic [8, 9]. Ionic contrast agents inhibit both intrinsic and extrinsic coagulation cascades at various stages. They act as a direct inhibitor of thrombin production. They also inhibit both platelet activation and aggregation, lead to increased bleeding time, and inhibit fibrinolysis enzymes [8, 9, 13].

Ionic contrast agents increase clotting time by 4-fold compared to nonionic ones [14]. Nonionic contrast agents interact with the coagulation mechanism, although less than ionic contrast agents, by inhibiting the coagulation cascade after thrombin formation in the fibrin monomer polymerization step [15, 16]. Therefore, both ionic and nonionic contrast agents can prolong clotting time and increase the effects of anticoagulant and antiplatelet drugs [13, 14].

In our study, we used iohexol (60 ml for all patients and volunteer), which is a nonionic and water-soluble contrast agent. Iohexol is excreted through the kidneys. Studies have shown that iohexol is freely filtered and does not cause glomerular damage. However, as it dissolves in water, it has been shown that it can be absorbed easily from the proximal tubule and cause cellular damage in the glomerulus [17]. In CIN studies, it was observed that every patient receiving iodine-containing contrast agents developed subclinical CIN, but it did not create apparent CIN clinic since healthy individuals had tubular repair mechanisms [18].

The oral bioavailability of oral factor Xa inhibitors is around 60–80% for rivaroxaban, 50% for apixaban, and 62% for edoxaban [19]. While the absorption of rivaroxaban and edoxaban is increased with food, apixaban absorption does not change [19]. These three drugs reach maximum plasma concentration approximately 3 hours after oral intake [19]. Renal elimination is 35% for rivaroxaban, 27% for apixaban and 50% for edoxaban [19, 20].

The increasing anti-factor Xa level with iohexol in the rivaroxaban and edoxaban groups may be related to the renal elimination ratio of these agents. The little anti-factor Xa level increasing with 60 ml contrast, may much more increase with more contrast using. The anti-factor Xa level was not changed in the apixaban group, and the renal elimination ratio was 27%. The renal elimination ratio is higher for rivaroxaban and edoxaban than apixaban. Both anti-factor Xa levels and PT and INR levels increased significantly after the contrast in the rivaroxaban and edoxaban group, but there was no significant change in the apixaban group. However, aPTT values did not differ significantly in any group after contrast medium use.

Rivaroxaban and edoxaban are used once a day and at a high dose. Drugs given at higher doses also have higher concentrations in the blood in an early period. The elimination rate of these drugs, which have a higher renal elimination rate and blood concentration, decrease because the elimination of the kidneys decreases, which is affected by the contrast agent. Due to this decreased elimination, high blood concentration causes an increase in the anti-factor Xa level.

Apixaban is taken at a lower dose and twice daily. Therefore, the blood concentration of apixaban is lower. Apixaban has the lowest renal elimination rate and is minimally affected by the loss of renal function caused by the contrast agent. The increase in anti-factor Xa levels was higher in the edoxaban group with a renal elimination rate of 50% compared to the rivaroxaban group, which had a renal elimination rate of 35% [19, 20]. This supports the idea that the increase in anti-factor Xa levels may be related to the renal elimination of drugs. Recent studies were evaluated the NOACs on patients with hemodialysis, that showed, apixaban treatment was similar to warfarin treatment [21, 22]. These studies result may support our results.

Oral factor Xa inhibitors do not require routine monitoring as they are taken at a specific dose and have a predictable anticoagulant effect. However, routine coagulation tests have been conducted to determine the patients who have complications such as bleeding and to determine drug doses. In studies performed with standard coagulation tests such as PT, aPTT, and INR tests, it was concluded that these tests are not suitable for use in evaluating oral factor Xa inhibitors because there is no clear correlation between drug doses and these tests [23, 24, 25]. However, studies have shown the presence of PT values within normal limits within the therapeutic limits of oral factor Xa inhibitors [23, 24, 25].

In our study, consistent with the anti-factor Xa test, PT values increased in the rivaroxaban and edoxaban groups after contrast agent use. There was also a significant increase in the INR value calculated with PT values in the rivaroxaban and edoxaban groups. There was no change in aPTT values before and after contrast use. The slight increase in PT values in the control group can also be explained by the effect of contrast agents on PT. In a previous study, a significant increase in PT values was found with nonionic low osmolar iopamidol [26, 27].

Clinical Implications

The decreased renal function may effect the anticoagulant properties of especially rivaroxaban or edoxaban. In such acute events if the patients on NOAC treatment, we should be careful about the complications in these patients. Future studies should evaluate this hypothesis.

Limitations Of The Study

An important limitation is that our study was performed with a single center and limited number of patients. Another limitation is that the drugs' blood concentrations were not examined before and after the use of contrast media. We used low molecular weight heparin evaluation kit for evaluation to oral factor Xa inhibitors anti-factor Xa activity. Studies showed that the kit (we used) can use for evaluating the oral factor Xa inhibitors anti-factor Xa activity (28,29). There was strong correlation between oral factor Xa inhibitors levels and anti–factor Xa activity with Berichrom kit using (28,29). The use of higher doses of contrast agent (iohexol) and the effects of different contrast agents have not been evaluated. In addition, our study results could be test in patients with CIN. We found that very small differences between the oral factor Xa inhibitors anti-factor Xa activity, on the other hand, our study intra and inter-assay coefficient variation were small. However, our study is the first to investigate the effects of contrast agents on the anticoagulant properties of oral factor Xa inhibitors and could guide large-scale studies.

Conclusion

The anticoagulant activity of rivaroxaban and edoxaban tended to be increased by contrast agent use, while the anticoagulant activity of apixaban was not changed The increasing is too small so that these laboratory results need to validate with larger clinical trials. Large-scale studies are needed to find out whether we need dose adjustment for oral factor Xa inhibitors while using contrast agents.

Declarations

Funding

There were no external funding sources for this study.

Conflict of Interest

Author Burcu TUNCAY declares that she has no conflict of interest. Author Selma ARI declares that she has no conflict of interest. Author Hasan ARI declares that he has no conflict of interest. Author Sencer CAMCI declares that he has no conflict of interest. Author Mehmet MELEK declares that he has no conflict of interest. Author Tahsin BOZAT declares that he has no conflict of interest.

Availability of data and material:

This study data submited as supplemantary material with this article.

Authors' contributions:

BT and HA conceived and designed research. BT, SA and HA conducted study analysis. MM, HA and TB analyzed data. BT, HA and SÇ wrote the manuscript. All authors read and approved the manuscript.

The authors declare that all data were generated in-house and that no paper mill was used.

Ethical approval

All procedures performed in studies involving human partic-ipants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. We performed the study after the local ethical committee (Ethic committee approval number: 2019/01-01) approval.

Informed consent

Informed consent was obtained from all individual partici-pants included in the study.

Consent for publication

Consent for publication was obtained from all individual participants included in the study.

References

1. Fuster V, Rydén LE, Cannom DS, et al. Task Force on Practice Guidelines, American College of Cardiology/American Heart Association; Committee for Practice Guidelines, European Society of Cardiology; European Heart Rhythm Association; Heart Rhythm Society, ACC/AHA/ESC 2006 Guidelines for the Management of Patients With Atrial Fibrillation—executive summary : A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation). J Am Coll Cardiol. 2006; 48: 854-906.

2. Go AS, Hylek EM, Phillips KA, et al. Prevalence of Diagnosed Atrial Fibrillation in Adults National Implications for Rhythm Management and Stroke Prevention: the Anticoagulation and Risk Factors In Atrial Fibrillation (ATRIA) Study. JAMA 2001; 285: 2370-2375.

3. Henninger N, Goddeau RP Jr, Karmarkar A, et al. Atrial fibrillation is associated with a worse 90-day outcome than other cardioembolic stroke subtypes. Stroke 2016; 47: 1486–1492.

4. Freedman B. Major progress in anticoagulant uptake for atrial fibrillation at last: does it translate into stroke prevention. European Heart Journal 2018; 39: 2984–2986.

5. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med 2007; 146: 857–867.

6. Hylek EM. Vitamin K antagonists and time in the therapeutic range: implications, challenges, and strategies for improvement. J Thromb Thrombolysis. 2013; 35(3): 333-335.

7. P.B. Persson, P. Hansell, P. Liss. Pathophysiology of contrast medium–induced nephropathy, Kidney Int. 2005; 68: 14–22.

8. S. Heptinstall, A. White, N. Edwards, J. Pascoe. Differential effects of three radiographic contrast media on platelet aggregation and degranulation: implications for clinical practice? Br J Haematol. 1998; 103: 1020–1030.

9. Laura G. Melton, Gregory J. Dehmer, David A. Tate, et al. Variable Influence Of Heparin and Contrast Agents On Platelet Function As Assessed By The In Vitro Bleeding Time. Thrombosis Research 1996; Vol.83 No.3: 265-277.

10. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16: 31-41.

11. Kirchhof P, Benussi S, Kotecha D, et al. ESC Scientific Document Group 2016 ESC Guidelines for the management of atrial fibrillition developed in collaboration with EACTS . European Heart Journal 2016; 37: 2893–2962.

12. Raskob GE, Angchaisuksiri P, Blanco AN, et al. ISTH Steering Committee for World Thrombosis Day, Thrombosis: a major contributor to global disease burden. Arterioscler Thromb Vasc Biol 2014; 34: 2363-2371.

13. Uğuz B, Ari S, Çamci S, Ari H. In vitro analysis of the effect of contrast agents on the antiaggregant effects of P2Y12 inhibitors. Thrombosis Research 2019; 183: 91–97.

14. Frohlich J. Systematic survey of interactions between contrast media and other drugs. Special edition by Guerbet Switzerland 2001.

15. Massee DR, Smith DC, Westengard JC, Bull BS. Heparin supplementation of nonionic contrast agents, Journal of Vascular and Interventional Radiology 1991; 2: 209-213.

16. Parvez Z, Moncada R, Messmore H, Fareed J. Ionic and non-ionic contrast media interaction with anticoagulant drugs, Acta Radiologica Diagnosis 1982; 23: 401-404.

17. McCullough P.A, Choi J.P, Feghali G.A, et al. Contrast-Induced Acute Kidney Injury. Journal of the American College of Cardiology 2016; 68 (13): 1465-1473.

18. Akrawinthawong K, Ricci J, Cannon L, et al. Subclinical and clinical contrast-induced acute kidney injury: data from a novel blood marker for determining the risk of developing contrastinduced nephropathy (ENCINO), a prospective study Ren Fail 2015; 37: 187–191.

19. Heidbuchel H, Verhamme P, Alings M, et al. Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. Europace 2015; 17(10): 1467-1507.

20. Ogata K, Mendell-Harary J, Tachibana M, et al. Clinical safety, tolerability, pharmacokinetics, and pharmacodynamics of the novel factor Xa inhibitor edoxaban in healthy volunteers. J Clin Pharmacol 2010; 50(7): 743-753.

21. Pokorney SD, RENal hemodialysis patients ALlocated apixaban versus warfarin in Atrial Fibrillation - RENAL-AF. At the American Heart Association Annual Scientific Sessions (AHA 2019), Philadelphia, PA, 2019;November 16.

22. Kuno T, Takagi H, Ando T, et al. Oral Anticoagulation for Patients With Atrial Fibrillation on Long-Term Hemodialysis J Am Coll Cardiol. 2020; 28;75(3): 273-285.

23. Sikorska J and Uprichard J, Direct Oral Anticoagulants: A Quick Guide. European Cardiology Review 2017; 12(1): 40–45.

24. Cuker A, Siegal DM, Crowther MA, Garcia DA, Laboratory Measurement of the Anticoagulant Activity of the Non–Vitamin K Oral Anticoagulants. J Am Coll Cardiol 2014; 64: 1128–1139.

25. Kitchen S, Gray E, Mackie I, on behalf of the BCSH committee, Measurement of non-coumarin anticoagulants and their effects on tests of Haemostasis: Guidance from the British Committee for Standards in Haematology. British Journal of Haematology. 2014;166: 830–841.

26. Kilinc Y, Şasmaz I, Bozkurt A, et al, Effect of the Radiographic Contrast Material Iopamidol on Hemostasis: An Observational Study in Thirty Cardiac Patients. Curr Ther Res Clin Exp 2003; 64: 461–472.

27. Hoffmann JJ, Tielbeek AV, Krause W. Haemostatic effects of low osmolar non-ionic and ionic contrast media: a double-blind comparative study. Br J Radiol 2000; 73(867): 248-255.

28. Margetić S, Ćelap I, Brkljačić DD, et al. Chromogenic anti-FXa assay calibrated with low molecular weight heparin in patients treated with rivaroxaban and apixaban: possibilities and limitations. Biochem Med (Zagreb). 2020; 15; 30 (1) : 010702.

29. Gosselin RC, Francart SJ, Hawes EM, et al. Annals of Pharmacotherapy. 2015, Vol. 49(7) 777–783.

Figures

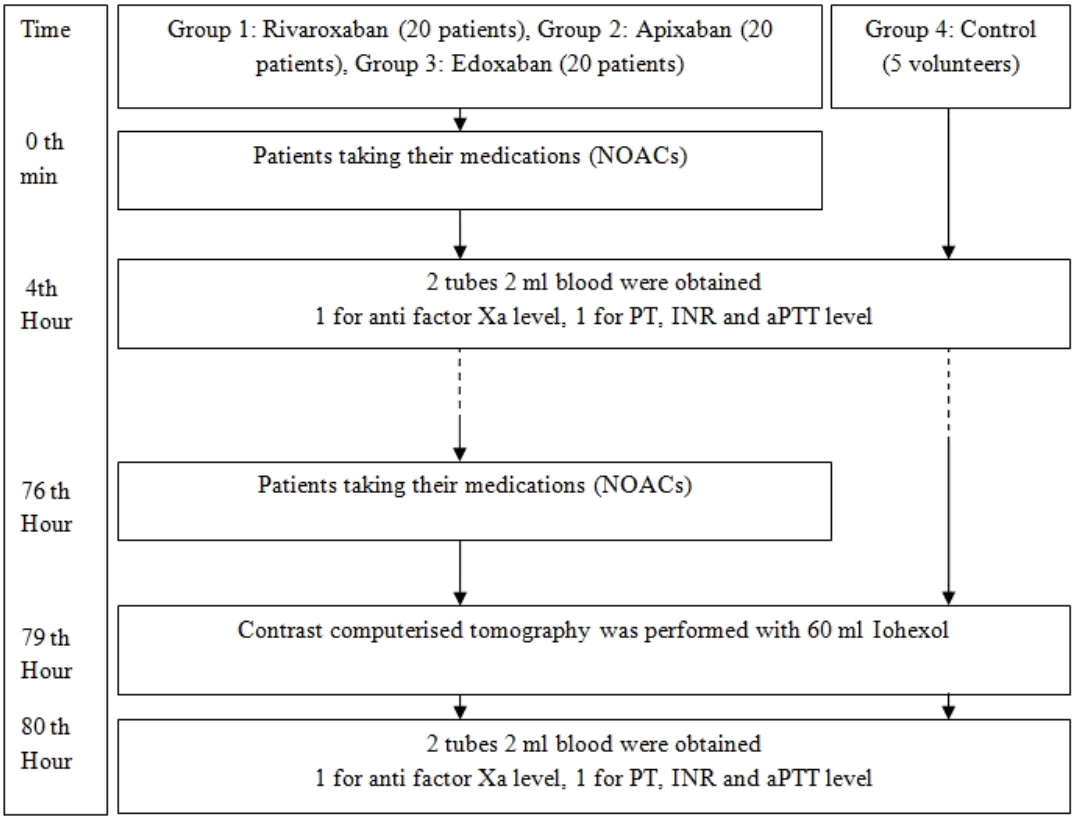

Figure 1

Study design.

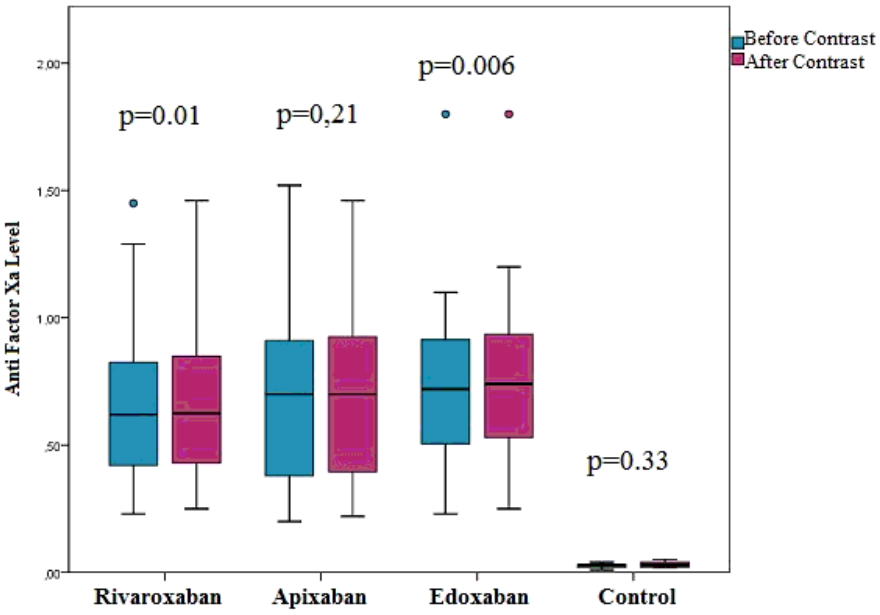

Figure 2

Anti factor Xa level before and after contrast agent.

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