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RESEARCH

Protectıve Effects Of Dırect Oral Antıcoagulants In An Experimental Ischemıa-Reperfusıon Model

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Abstract

Objective The aim of this study was to investigate the protective effect of direct oral anticoagulants on skeletal muscle reperfusion injury in an experimental ischemia–reperfusion (IR) model.
Methods 40 female Wistar albino rats were randomly divided into five groups: control, sham, apixaban, rivaroxaban and dabigatran. Sham group underwent only anesthesia and median laparotomy. Control group underwent the IR procedure. Apixaban group received 10 mg/kg twice daily, dabigatran group received 15 mg/kg once daily and rivaroxaban group received 3 mg/kg once daily by oral gavage for one week. IR procedure was performed as infrarenal aorta clamping for 60 min followed by 120 min of reperfusion. After the procedure, 2–3 cc intracardiac blood and bilateral gastrocnemius muscle samples were obtained from each group. Biochemical markers TAC,TOS,IL-1,IL-6 and TNF-α levels were analyzed in muscle tissue and blood. Histopathologically, inflammation, necrosis,congestion,fibrosis and atrophy levels in muscle tissue were examined.
Results IL-6 levels were significantly lower in muscle and serum samples in the dabigatran group ($p<0.001$). In addition, TNF-a levels were significantly lower in the dabigatran group ($p=0.003$). Inflammation was also reduced in the rivaroxaban and apixaban groups, but not as markedly as in the dabigatran group. In histopathologic evaluations, muscle tissue damage was found to be the lowest in the dabigatran group. Antioxidant capacity (TAC) was higher in the dabigatran group ($p=0.009$), but there was no significant difference in TOS levels between the groups.
Conclusion Direct oral anticoagulants showed anti-inflammatory and antioxidant effects against IR injury. In particular, dabigatran offered a more pronounced protective effect compared to other drugs with its effects on inflammation and oxidative stress.

Keywords Ischemia–Reperfusion Injury · Apixaban · Dabigatran · Rivaroxaban

1 Introduction

Ischemia–reperfusion injury (IRI) is the pathological damage to the structure and function of tissues that occurs as a result of the restoration of blood flow after an ischemic process caused by impaired blood supply to tissues and organs [1]. Acute limb ischemia (ALI) is a critical ischemic disease that can cause irreversible damage and can progress to limb amputation. Tissue damage that begins with limb ischemia continues and may even worsen during reperfusion [2]. Reactive oxygen species (ROS) are the main mechanism of ischemia-reperfusion [3]. Therefore, various antioxidants have been tried to reduce ROS to prevent ischemia–reperfusion injury [4].

Direct oral anticoagulants (DOACs) are popular anticoagulant drugs used to prevent thrombosis in cardiovascular diseases [5]. DOACs are divided into two groups: direct factor Xa inhibitors (rivaroxaban, apixaban, edoxaban and betrixaban) and direct thrombin inhibitors (dabigatran). In addition the antioxidant effects of direct oral anticoagulants have been investigated and it has been reported that they have antioxidant effects by reducing the release of reactive oxygen species in experimental studies [6]. DOACs also

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have pleiotropic effects including the anti-inflammatory, anti-atherosclerotic and anti-fibrotic effects on endothelial cells [7].

In this study, the protective effects of rivaroxaban, apixaban and dabigatran, which are direct oral anticoagulants, in ischemia reperfusion injury model were investigated through muscle tissue damage and inflammatory markers.

2 Method

Aydın Adnan Menderes University Animal Experiments Local Ethics Committee (ADÜ-HADYEK) approved this study (Protocol no: 2018/082). Forty WistarAlbino rats (210–300 g) were used in the study. Free access to dry pellet feed and tap water was provided under standard maintenance conditions (temperature: $23 \pm 1C^{o}$, humidity: $55\% \pm 10\%$, 12:12-h reverse light cycle). Animals were equally divided into five groups:

Sham group (n:8), Distilled water was given by oral gavage. No ischemia–reperfusion(IR) procedure was performed.

Control group (n:8), No drug administration. IR procedure was performed.

Rivaroxaban group (n:8), Rivaroxaban (3 mg/kg) was given for one week and IR procedure was performed.

Dabigatran group (n:8), Dabigatran (15 mg/kg) was given for one week IR procedure was performed.

Apixaban group (n:8), Apixaban (10 mg/kg) was administered for one week and IR procedure was performed. (Since the dose of Apixaban was twice a day, each group received equal amount of distilled water by gavage twice a day).

2.1 Surgery and Ischemia–Reperfusion Model

Rats were fasted for 12 h before the study. They were allowed to drink water during this period. For induction of anesthesia, a mixture of ketamine (90 mg/kg) (Ketalar®, Parker-Dawis, Pfizer, Istanbul, Turkey) and xylazine (10 mg/kg) (Rompun®, Bayer AG, Leverkusen, Germany) was administered by intraperitoneal injection. The surgical fields were shaved under a heating lamp while the rats were in supine position. A midline laparotomy was performed in accordance with asepsis rules. The intestines were retracted superiorly and covered with wet gauze and the abdominal aorta was explored. An atraumatic microvascular clamp was placed on the abdominal aorta and ischemia was performed for 60 min. At 120 min after unclamping, 1 cc blood sample was obtained from all rats by intracardiac puncture. The gastrocnemius muscle was then removed as a block. Decapitation was performed under anesthesia. The removed tissues were stored in an eppendorf tube in a deep freezer at $-80C^{o}$ (SANYO MDF-U2086S®).

2.2 Determination of TAC and TOS Levels in Serum and Tissue Samples

Realassay colorimetric kit (Rel Assay Diagnostics; Mega Tıp, Gaziantep, Turkey) was used for Total Antioxidant Capacity (TAC) and Total Oxidant Status (TOS) measurements. ELISA was measured spectrophotometrically with a microplate reader (DAR 800, Diagnostic Automation, CA, USA).

2.3 Determination of TNF-a, IL-1, IL-6 levels in Blood and Muscle Tissue Samples

Interleukin-1β (IL-1), Interleukin-6 (IL-6), Tumor Necrosis Factor-alpha (TNF-α), levels were determined by Elabscience rat ELISA kit (catalog. No: EE-EL-R0019, E-EL-R0012, EL-R0015 Elabscience Biotechnology Co. Wuhan, PRC). Microplates were counted at 450 nm using an ELISA (DAR 800, Diagnostic Automation, CA, USA) microplate reader.

2.4 Histopathologic Examination of Muscle Tissues

For histopathologic examinations, tissue samples were fixed in 10% buffered formaldehyde solution. Then, all sections taken at a thickness of 5 µm from paraffin blocks prepared by passing through alcohol and xylol series in an automatic tissue tracking device (Leica TP1020, Leica Microsystems, Nussloch, Germany) were stained with Hematoxylin–Eosin (HE). Stained slides were examined under a binocular light microscope (Olympus BX51, Tokyo, Japan). Muscle tissue samples were analyzed using the semi-quantitative method described by Bilgiç et al [8]. Histopathologic evaluation of muscle tissue samples was performed by looking for congestion, necrosis, atrophy, fibrosis and inflammation. Each parameter was scored between 0 and 3. Scoring values; 0: None, 1: Mild, 2: Moderate, 3: Severe.

2.5 Statistical Analysis

The data of this study were analyzed with SPSS 26.0 MacOS version package program. The normality of the variables was assessed visually using the Shapiro–Wilk test. Descriptive statistics of the study were presented as mean ± standard deviation (SD), median (minimum, maximum), number (n), percentage (%). One-way analysis of variance (ANOVA, Analysis of Variance) was used for data fitting the normal distribution, and Tamhane's T2 test was used for post-hoc evaluation for pairwise comparison of statistically significant data because the variances were not homogeneous (Levene's statistic). The Kruskal–Wallis test was applied to data that

did not follow a normal distribution. Mann–Whitney U test was used for paired analysis of groups and Bonferroni correction was used for multiple comparisons using an ap value of 0.005. For statistical analysis, an a *p* value of < 0.05 was considered statistically significant.

3 Results

The difference between IL-1, IL-6, TNF-a, TAC and TOS levels of serum samples is shown in Table 1. No statistically significant difference was found in serum IL-1 levels among the groups ($p = 0.926$). The difference in IL-6 levels was statistically significant ($p < 0.001$) and this difference was found to be control-rivaroxaban ($p = 0.003$), control-dabigatran ($p < 0.001$), dabigatran-rivaroxaban ($p = 0.002$) and $p < 0.001$ in all other pairwise comparisons in the matched subgroup analysis. The difference between serum TNF-α levels was statistically significant ($p = 0.010$) and this difference was found to be between the control-dabigatran ($p = 0.011$) groups in binary subgroup analysis. The difference between serum TAC levels was statistically significant ($p = 0.009$).In the binary subgroup analysis, this difference was found to be between the apixaban-dabigatran ($p = 0.002$) groups.There was no statistically significant difference in serum TOS levels ($p = 0.341$).

The difference between IL-1, IL-6, TNF-a, TAC and TOS levels of muscle tissue is shown in Table 2. The difference between IL-1 levels in muscle samples was found to be statistically significant ($p = 0.001$) and this difference was found to be between control and dabigatran ($p = 0.002$) and sham and dabigatran ($p = 0.007$) in pairwise subgroup analyses. The difference between IL-6 levels in muscle samples was statistically significant ($p < 0.001$). In paired subgroup analysis, this difference was found between control-dabigatran ($p = 0.004$), dabigatran-apixaban ($p < 0.001$) and dabigatran-rivaroxaban ($p = 0.002$) groups. The difference between TNF-α levels in muscle tissue samples was statistically significant ($p = 0.003$). Paired subgroup analysis showed that this difference was between sham-dabigatran ($p = 0.009$) and

Table 1 IL-1, IL-6, TNF-a, TAC and TOS levels of blood samples

Parameter	Group	Mean ± SS	Median (min—max)	*p*-value
IL-1	Sham	42,43 ± 6,11	44,10 (33,10—49,10)	0.926*
	Control	40,41 ± 6,20	42,45 (33,00—47,40)	
	Apixaban	43,45 ± 2,44	42,60 (40,50—47,70)	
	Dabigatran	41,68 ± 6,13	44,90 (33,00—47,60)	
	Rivaroxaban	41,12 ± 6,45	43,55 (33,00—48,80)	
IL-6	Sham	109,73 ± 14,28	104,45 (91,40—132,70)	**< 0.001****
	Control	162,28 ± 28,50	153,10 (135,20—206,20)	
	Apixaban	288,71 ± 55,39	289,05 (225,20—391,70)	
	Dabigatran	61,28 ± 6,09	63,10 (50,50—66,80)	
	Rivaroxaban	79,43 ± 7,88	79,90 (70,40—89,90)	
TNF-α	Sham	823,55 ± 675,85	635,75 (274,10—1946,70)	**0.010***
	Control	1953,06 ± 3088,31	645,45 (216,80—9391,50)	
	Apixaban	264,63 ± 206,23	203,65 (157,00—771,70)	
	Dabigatran	191,90 ± 120,46	149,40 (79,00—427,00)	
	Rivaroxaban	526,28 ± 711,50	243,05 (95,90—2243,90)	
TAC	Sham	1,22 ± 0,22	1,23 (0,88—1,57)	**0.009****
	Control	1,33 ± 0,09	1,33 (1,16—1,45)	
	Apixaban	1,24 ± 0,05	1,24 (1,15—1,33)	
	Dabigatran	1,47 ± 0,10	1,46 (1,29—1,61)	
	Rivaroxaban	1,31 ± 0,15	1,33 (1,06—1,49)	
TOS	Sham	18,87 ± 10,96	17,51 (5,52—38,62)	0.341**
	Control	26,39 ± 18,36	18,41 (5,38—60,55)	
	Apixaban	30,11 ± 7,05	29,33 (20,22—41,25)	
	Dabigatran	23,13 ± 8,55	26,48 (6,62—32,00)	
	Rivaroxaban	21,74 ± 7,91	21,10 (8,55—32,55)	

*Kruskal–Wallis Test

**ANOVA Test, IL-1:Interleukin-1, IL-6:Interleukin-6, TNF-a:Tumor Necrosis Factor alpha, TAC:Total Antioxidant Capacity, TOS:Total Oxidant Status

Table 2 IL-1, IL-6, TNF-a, TAC and TOS levels of muscle tissue samples

Parameter	Group	Mean ± SS	Median (min—max)	*p*-Value
IL-1	Sham	7,57 ± 2,57	7,13 (4,91—11,13)	**0,001***
	Control	10,45 ± 8,62	6,64 (4,18—30,20)	
	Apixaban	16,91 ± 15,26	9,08 (4,81—45,48)	
	Dabigatran	73,01 ± 34,95	82,83 (6,22—117,88)	
	Rivaroxaban	24,27 ± 12,86	24,70 (9,40—41,49)	
IL-6	Sham	3,32 ± 0,74	3,16 (2,58—4,87)	**< 0,001****
	Control	5,09 ± 1,00	5,10 (3,33—6,92)	
	Apixaban	2,60 ± 0,31	2,51 (2,27—3,08)	
	Dabigatran	1,66 ± 0,11	1,71 (1,51—1,81)	
	Rivaroxaban	2,45 ± 0,33	2,35 (2,11—2,93)	
TNF-α	Sham	24,47 ± 10,90	23,69 (12,99—45,64)	**0,003***
	Control	19,93 ± 3,87	20,12 (13,23—25,25)	
	Apixaban	221,67 ± 473,90	27,57 (15,25—1378,43)	
	Dabigatran	173,59 ± 167,99	119,04 (23,49—450,08)	
	Rivaroxaban	207,84 ± 347,19	64,90 (20,99—1030,85)	
TAC	Sham	0,30 ± 0,11	0,28 (0,19—0,55)	0,245*
	Control	0,28 ± 0,09	0,27 (0,18—0,43)	
	Apixaban	0,23 ± 0,05	0,24 (0,17—0,30)	
	Dabigatran	0,22 ± 0,04	0,20 (0,19—0,31)	
	Rivaroxaban	0,27 ± 0,03	0,27 (0,22—0,31)	
TOS	Sham	1,29 ± 0,31	1,34 (0,83—1,81)	0,694**
	Control	1,42 ± 0,46	1,43 (0,80—2,05)	
	Apixaban	1,40 ± 0,41	1,25 (1,00—2,05)	
	Dabigatran	1,10 ± 0,66	0,90 (0,08—2,11)	
	Rivaroxaban	1,20 ± 0,60	1,27 (0,11—2,02)	

*Kruskal–Wallis Test

**ANOVA Test, IL-1:Interleukin-1, IL-6:Interleukin-6, TNF-a:Tumor Necrosis Factor alpha, TAC:Total Antioxidant Capacity, TOS:Total Oxidant Status

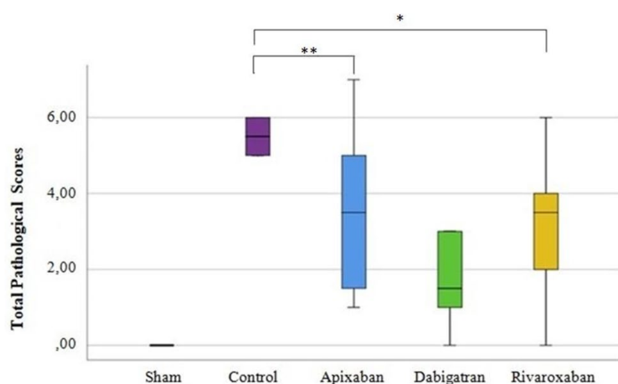

Fig. 1 Total pathologic score values according to groups. The horizontal lines in the middle of each box indicate the median; the top and bottom borders of the box mark the 25th and 75th percentiles, respectively. The whiskers above and below the box correspond to the maximum and minimum values

sham-rivaroxaban ($p = 0.039$) groups. There was no statistically significant difference in muscle tissue TAC and TOS levels between the experimental groups.

Total pathologic score values are shown in Fig. 1. The difference between the total score between the experimental groups was statistically significant ($p < 0.001$). In paired subgroup analyses, this difference was found to be between control-sham ($p < 0.001$), control-apixaban ($p = 0.008$), control-rivaroxaban ($p = 0.025$) and sham-dabigatran ($p = 0.047$) groups.

4 Discussion

This is the first study to comparatively evaluate the effects of direct oral anticoagulants rivaroxaban, apixaban and dabigatran on lower extremity ischemia–reperfusion injury.

Our findings showed that there were significant differences in proinflammatory markers and antioxidant capacity between the study groups.

IL-1, IL-6 and TNF-α levels in serum and muscle tissue are critical biomarkers in determining the degree of inflammation.In our study, a significant decrease in inflammatory markers was observed especially in the dabigatran group.

The decrease in inflammatory cytokines such as TNF-α and IL-6 indicates the anti-inflammatory activity of dabigatran. Similarly, the inflammatory response was suppressed in the rivaroxaban and apixaban groups, but was less pronounced than in the dabigatran group.

In the evaluation of muscle tissue damage, the total pathologic score was not statistically significantly different in the rivaroxaban and apixaban groups, but a statistically significant protective effect was observed in the dabigatran group. IRH studies of different tissues in the literature include studies with and without beneficial effects on the relationship between thrombin inhibition and the degree of IRH. The difference of dabigatran from rivaroxaban and apixaban in our experiment is its direct thrombin inhibition effect and it is thought that its pathologic benefit may be related to this [9].

TNF-α, IL-1 and IL-6 levels, which are inflammation markers involved in the pathogenesis of IRH, are valuable in terms of showing the response of the tissue against ischemia-reperfusion [10, 11]. A significant difference was observed between the groups in terms of TAC levels in both muscle tissue and serum of direct oral anticoagulants only in the subgroup analysis of dabigatran and apixaban and TAC level was found to be higher in the dabigatran group. When the literature is examined, it is seen that dabigatran has high antioxidant activity [12]. When the values of TAC levels in muscle tissue are examined, the lack of significant statistical difference between the groups may be related to the fact that muscle is more resistant to ischemia reperfusion damage than other tissues.

Oxidative stress causes varying degrees of tissue damage at every stage of the ischemia–reperfusion process. When we examined the TOS level of direct oral anticoagulants in both serum and muscle tissue, it was observed that TOS values increased in the sham group compared to the control group. However, there was no statistically significant difference between the groups. However, TNF-α, IL-1 and IL-6 levels, which are proinflammatory cytokines, are widely examined in experimental studies. When the results of these experimental studies are evaluated, it is seen that inflammatory responses are quite variable. Active coagulation factors are the driving forces of inflammation formation [13, 14]. Under physiologic conditions, coagulation and inflammation work in homeostatic balance, but dysregulation of this interaction probably contributes to cellular damage. To prevent this, anticoagulant therapy is often used in clinical practice.

Comparative analysis of muscle tissue TNF-α levels showed that TNF-α levels were lower in the sham group than in the control group. This was contrary to what was expected. When histopathologic examination and other inflammation markers were examined in our study, it was observed that there were variations in muscle tissue TNF-α results and extreme values between the results. Therefore, it was interpreted as a limitation in our study. In the comparative analysis of serum TNF-α levels between the control and experimental groups, a statistically significant difference was found only between the sham and dabigatran groups. Similar to our study, it has been shown that treatment with dabigatran significantly inhibited the P65 activities of IL-1β, IL-6 and TNF-α in an acute myocardial infarction model in rabbits [15]. It was thought that this effect may be due to the direct thrombin inhibition effect of dabigatran, unlike other anticoagulant agents.

When serum levels of IL-1 and IL-6, another marker of inflammation, were analyzed, IL-6 levels were significantly lower in all groups except apixaban, suggesting that rivaroxaban and dabigatran reduced the systemic effects of inflammation. The significant statistical difference in muscle tissue IL-6 levels between the apixaban, rivaroxaban and dabigatran groups and the sham group suggests that they may have local anti-inflammatory effects. In a study conducted on humans with abdominal aortic aneurysm, lower IL-6 levels were found in abdominal aortic tissues containing mural thrombus with riveroxaban use [16]. However, similar results were not found when IL-1 levels were analyzed.

This study has two important limitations. Firstly, it was performed in an experimental animal model and may not fully reflect the complexity of ischemic-reperfusion injury in humans. therefore, the results need to be validated in humans under clinical conditions. secondly, although inflammatory markers such as IL-1, IL-6 and TNF-α were analyzed, other potential mechanisms involved in ischemic-reperfusion injury such as apoptotic and endothelial dysfunction markers were not examined.

5 Conclusıon

In conclusion, DOACs were found to have anti-inflammatory and antioxidant effects in an experimental ischemic muscle injury model.These effects were most pronounced in the dabigatran group and were also found to be significant in the apixaban and rivaroxaban groups. Histopathologic evaluation also showed less damage to muscle tissue, especially in the dabigatran group, in agreement with the biochemical findings. These results suggest that DOACs may have potential therapeutic roles in ischemic muscle injury.

Author contribution EB: Conceptualization, Investigation, Supervision, Writing – original draft, Writing – review & editing. MHE: Writing – original draft, Writing – review & editing. ÖFR: Investigation, Methodology. SD: Conceptualization, Supervision, Project administration, Writing – review & editing.

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Data Availability No datasets were generated or analysed during the current study.

Declarations

Conflict of Interest The authors declare no competing interests.

Ethics Approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Aydın Adnan Menderes University Animal Experiments Local Ethics Committee (ADÜ-HADYEK) (No:2018/082). Clinical Trial Number: Not applicable.

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