

Effect of systemic anticoagulants on fracture healing in rats tibia

Efecto de los anticoagulantes sistémicos en la consolidación de fracturas en la tibia de ratas

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ABSTRACT

This study aimed to evaluate the effects of the systemic anticoagulants Apixaban, Rivaroxaban, Edoxaban, and Dabigatran on fracture healing. 48 female Sprague Dawley rats were divided into 6 groups with 8 rats in each group. Healthy Control group (n=8): no procedure was applied during the four-week experimental setup. Sham group (n=8): fractures were created in the right tibias of the subjects by surgical methods and the fractures were fixed with Kirshner wires in this group and all anticoagulant groups. No additional procedure was applied during the four (4) week to the sham group experimental setup. Throughout the 4-week experimental period, the animals were administered the following treatments via oral gavage three times per week: the Apixaban Group (n=8) received 5 mg/kg of apixaban; the Rivaroxaban Group (n=8) received 3 mg/kg of rivaroxaban; the Edoxaban Group (n=8) received 3 mg/kg of edoxaban; and the Dabigatran Group (n=8) received 10 mg/kg of dabigatran. At the end of the four-week experimental period, all rats were euthanized. Bone tissues were harvested, decalcified, and processed for histological analysis. A statistically significant difference was observed among the groups ($P < 0.05$). Post hoc analysis revealed that the Apixaban group ($M = 55.75$, $SD = 3.41$) and the Rivaroxaban group ($M = 55.38$, $SD = 3.89$) had significantly higher mean values compared to the Control group ($M = 41.75$, $SD = 5.57$) ($P < 0.05$). Additionally, the Dabigatran group ($M = 44.00$, $SD = 4.66$) and the Edoxaban group ($M = 48.63$, $SD = 5.55$) also differed significantly from the Control, with Edoxaban showing a statistically significant difference compared to Dabigatran ($P < 0.05$). No significant difference was observed between Apixaban and Rivaroxaban. The histopathological evaluations revealed that the administration of these anticoagulants had statistically significant effects on new bone formation compared to the control group.

Key words: Apixaban; rivaroxaban; edoxaban; dabigatran; bone healing

RESUMEN

Este estudio tuvo como objetivo evaluar los efectos de los anticoagulantes sistémicos Apixabán, Rivaroxabán, Edoxabán y Dabigatrán en la consolidación de fracturas. Se conformaron 6 grupos de ratas hembra Sprague Dawley de 8 ejemplares cada uno. Grupo control sano (n=8): no se aplicó ningún procedimiento durante las cuatro semanas de duración del experimento. En el resto de los grupos, se crearon fracturas en las tibias derechas mediante métodos quirúrgicos y se fijaron con agujas de Kirshner. Grupo simulado (n=8): no recibió tratamiento con anticoagulantes. El resto de los grupos recibieron las siguientes dosis de los fármacos correspondientes mediante sonda oral tres veces por semana: grupo apixabán (n=8) recibió 5 mg/kg; grupo rivaroxabán (n=8) recibió 3 mg/kg; grupo edoxabán (n=8) recibió 3 mg/kg; y el grupo dabigatrán (n=8) recibió 10 mg/kg. Al final del período experimental de cuatro semanas, todas las ratas fueron eutanasia. Se extrajo tejido óseo, se descalcificó y se procesó para análisis histológico. Se observó una diferencia estadísticamente significativa entre los grupos ($P < 0,05$). El análisis post hoc reveló que el grupo Apixabán ($M = 55,75$, $DE = 3,41$) y el grupo Rivaroxabán ($M = 55,38$, $DE = 3,89$) tuvieron valores medios significativamente más altos en comparación con el grupo Control ($M = 41,75$, $DE = 5,57$) ($P < 0,05$). Además, el grupo Dabigatrán ($M = 44,00$, $DE = 4,66$) y el grupo Edoxabán ($M = 48,63$, $DE = 5,55$) también difirieron significativamente del Control, con Edoxabán mostrando una diferencia estadísticamente significativa en comparación con Dabigatrán ($P < 0,05$). No se observó una diferencia significativa entre Apixabán y Rivaroxabán. Las evaluaciones histopatológicas revelaron que la administración de estos anticoagulantes tuvo efectos estadísticamente significativos en la formación de hueso nuevo en comparación con el grupo control.

Palabras clave: Apixabán, rivaroxabán, edoxabán, dabigatrán, consolidación ósea

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INTRODUCTION

Unlike muscle and skin tissues, which typically heal through the formation of scar tissue, bone possesses a unique regenerative capacity whereby fracture healing restores both the original structure and function of the tissue. Effective fracture repair requires accurate reduction and adequate immobilization to facilitate optimal bone healing. These objectives are achieved through the application of surgical instruments, orthopedic implants and specialized reduction techniques [1].

Accurate alignment of fracture fragments is crucial to enable the continuous progression of secondary osteons across the fracture interface. Although minor bone defects often undergo spontaneous healing without the need for supplementary bone regeneration strategies, larger defects—especially those identified as critical-sized—represent a substantial challenge in both human and veterinary orthopaedics due to their limited intrinsic regenerative capacity, necessitating additional therapeutic interventions to achieve bone union [2, 3].

Bone healing proceeds through a series of sequential and overlapping regenerative stages, beginning with the hematoma and inflammatory phase, followed by callus formation and the development of woven bone, ultimately culminating in the remodeling phase that restores the bone's original structure and function [4, 5].

However, this depiction of fracture healing serves as a simplified overview of a multifaceted physiological process. The inflammatory phase, for instance, is activated by a pro-inflammatory signaling cascade that is critical for the initiation of the tissue repair process. The initial pro-inflammatory reaction shares a phylogenetic connection with the coagulation cascade initiated in the course of hematoma development. Subsequent suppression of the inflammatory response is essential to facilitate revascularization, which is vital for re-establishing blood flow to the injury site [5, 6, 7].

The process of bone tissue formation and destruction, also known as remodeling, continues throughout life. Certain medications used for various diseases can directly affect the quality of bone tissue and the process of formation and destruction. For example, bisphosphonates, used in the treatment of some types of cancer that cause bone metastases and metabolic bone diseases, are examples of such drugs. Bisphosphonates exert a relative osteoblastic effect on bone tissue while suppressing the osteoclastogenesis step of the bone formation and destruction process [8].

Various medications used for systemic conditions and diseases can affect bone healing. Anticoagulant therapies are commonly employed in the management of coronary artery disease (CAD) and related conditions, including stroke, ischemia, and myocardial infarction. Rivaroxaban is an oral direct Factor Xa (FXa) inhibitor, approved for both the prevention and treatment of thromboembolic conditions [9]. Rivaroxaban has more recently gained approval in select countries for prophylactic use against venous thromboembolism in patients undergoing elective hip or knee arthroplasty [9].

Rivaroxaban exerts selective inhibition not only on free Factor Xa ($K_i = 0.4 \text{ nM}$), but also on Factor Xa associated with the prothrombinase complex and fibrin-bound forms. In vitro studies have shown that rivaroxaban inhibits thrombin generation and

prolongs clotting times, while in vivo experiments demonstrate its potent antithrombotic efficacy in multiple animal models of arterial and venous thrombosis [9].

Apixaban is a potent, orally administered, and highly selective direct Factor Xa inhibitor indicated for the treatment and prevention of venous and arterial thromboembolic disorders. Apixaban reversibly inhibits the activity of Factor Xa in both its free form and when bound within the prothrombinase complex. In addition, apixaban is indicated for both the prophylaxis and management of venous thrombosis in clinical settings [10, 11].

As a reversible, selective thrombin inhibitor with oral bioavailability, Dabigatran is experiencing growing utilization in complex clinical scenarios [12, 13]. Edoxaban, a recently developed oral Factor Xa inhibitor, demonstrates reversible activity and has an elimination half-life of approximately 10 to 14 hours. Clinical studies have shown that it is non-inferior to warfarin for the prevention of stroke and systemic embolism in individuals with atrial fibrillation [14, 15].

The purpose of this investigation was to evaluate how systemic anticoagulants, including rivaroxaban, apixaban, dabigatran and edoxaban, influence the fracture healing process.

MATERIAL AND METHODS

Study design and animals

This study was approved by the Firat University Animal Experiments Local Ethics Committee (Approval No: 21318, Date: 12 January 2024) and was conducted at the Firat University Experimental Research Center. The principles outlined in the Declaration of Helsinki were rigorously adhered to throughout the experimental procedures. For the standardization of this animal study, 48 female Sprague Dawley rats (*Rattus norvegicus*) that were determined to be in the same estrus period after vaginal swabs were included in the study due to the possibility that female hormones could affect bone healing.

The rats were obtained from the Firat University Experimental Research Center. The rats were housed in plastic cages, with the room temperature consistently maintained at 22 °C each day. Throughout the experimental period, the rats were housed under a 12-hour light/12-hour dark cycle and provided with ad libitum access to food and water.

The subjects were divided into 6 groups with 8 rats in each group.

Healthy Control group (n=8): no procedure was applied during the four-week experimental setup.

Sham group (n=8): fractures were created in the right tibias of the subjects by surgical methods and the fractures were fixed with Kirshner wires. No additional procedure was applied during the four (4) week experimental setup.

Apixaban Group (n=8): fractures were created in the right tibias of the subjects by surgical methods and the fractures were fixed with Kirshner wires. 5 mg/kg Apixaban (Eliquis 2,5

mg, Pfizer, Germany) was administered to the subjects by oral gavage 3 times a week during the 4-week experimental setup.

Rivaroxaban Group (n=8): fractures were created in the right tibias of the subjects by surgical methods and the fractures were fixed with Kirshner wires. 3 mg/kg rivaroxaban (Xarelto 10 mg, Bayer, Germany) was administered to the subjects by oral gavage 3 times a week during the 4-week experimental setup.

Edoxaban Group (n=8): fractures were surgically created in the right tibias of the subjects, and the fractures were fixed with Kirshner wires. 3 mg/kg edoxaban (Lixiana 30 mg, Daiichi Sankyo, Germany) was administered to the subjects via oral gavage, 3 times a week, for a 4-week experimental setup.

Dabigatran Group (n=8): fractures were surgically created in the right tibias of the subjects, and the fractures were fixed with Kirshner wires. 10 mg/kg dabigatran (Pradaxa 110 mg, Boehringer, Germany) was administered to the subjects via oral gavage, 3 times a week, for a 4-week experimental setup.

Surgical Procedures

All surgical procedures were performed under sterile conditions. General anesthesia was induced by intramuscular administration of Xylazine (10 mg/kg; Rompun, Bayer, Germany) and Ketamine (40 mg/kg; Ketazol, Richter Pharma, Wels, Austria). Prior to the incision, the surgical site was shaved and disinfected with a povidone-iodine solution. In accordance with standard aseptic and antiseptic protocols, an approximately 5 mm longitudinal incision was made along the tibial crest using a no. 22 scalpel blade. After elevation of the soft tissues and periosteum, the diaphyseal region of the tibia was exposed. A bicortical osteotomy was then performed using a rotary disk under continuous saline irrigation (FIG. 1). The resulting bone fragments were stabilized with Kirschner wires (FIG. 2), and the surrounding soft tissues were anatomically repositioned and sutured. No intraoperative or postoperative complications, either fatal or non-fatal, were observed.

Postoperatively, rats were administered intramuscular antibiotics 40 mg/kg Cefazolin sodium (Iespor, I.E. Ulagay, Turkiye) and analgesics Tramadol hydrochloride, 0.1 mg/kg (Contramal, Mefar, Turkiye). At the conclusion of the four-week experimental period, all rats were euthanized. Bone specimens were harvested, decalcified, and processed for histological analysis.



FIGURE 1. Rats Tibia bone undergoing bicortical osteotomy using a rotating disc

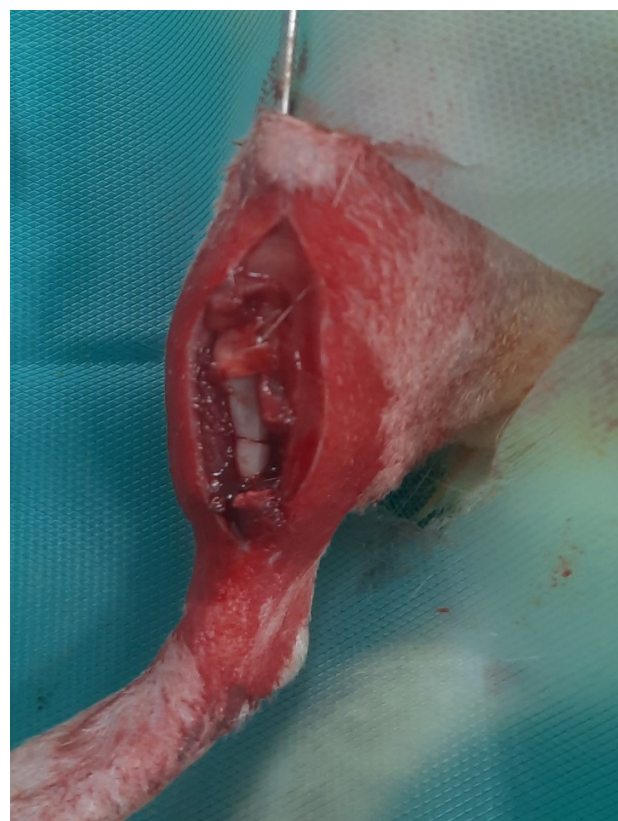


FIGURE 2. Fixation of Rats bone fragments with Kirschner wire

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Histopathological analysis

Tibias obtained from euthanasia procedures were stored in a 10% neutral formalin solution for 3 days (d). They were then cleared of surrounding soft tissues such as muscle, tendon, and fascia and decalcified in a 10% formic acid solution for approximately one week. They were then processed through ascending alcohol, xylene, and paraffin series using an automatic tissue processing device (Leica TP 1020, Germany) and embedded longitudinally in paraffin (Leica EG1150 H-C, Germany). 3-micron-thick sections were cut using a rotary microtome (Leica RM2125 RTS, Germany) and stained with hematoxylin and eosin (H&E) (Leica Autostainer XL).

The examination was performed under a standard light microscope (Olympus BX42, Japan). New bone formation was used to assess healing. For this purpose, the entire healing tissue area at the fracture site was measured. The area of new bone formation was then measured and compared to the total area. This gave the rate of new bone formation at the healing site for each sample.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics version 23. Data normality was evaluated with the Shapiro–Wilk and Kolmogorov–Smirnov tests. Given that the data satisfied the normality assumptions, group differences were assessed using one-way analysis of variance (ANOVA), followed by Tukey's Honestly Significant Difference (HSD) post hoc test for pairwise comparisons. Results are expressed as mean $\pm$ standard deviation, with statistical significance defined as $P < 0.05$. All analyses were conducted by a blinded investigator, who was unaware of the group assignments.

RESULTS AND DISCUSSION

In both the control and experimental groups, callus tissue was observed at the fracture site, covering the defect in most samples. New bone formation (NBF) within the healing callus was more pronounced in the A, D, E, and R experimental groups. In contrast, some animals in the control group exhibited incomplete filling of the fracture area with healing tissue, and one animal showed a notably irregular and excessive healing tissue. Additionally, the control group displayed a higher density of fibrous connective tissue (F) in the healing region, with most samples being at the stage of fibrous callus formation. In groups A and R, the areas of new bone and cartilage formation (CF) within the healing region were more prominent, whereas groups D and E demonstrated a greater extent of fibrous tissue (FIGS. 3 and 4).

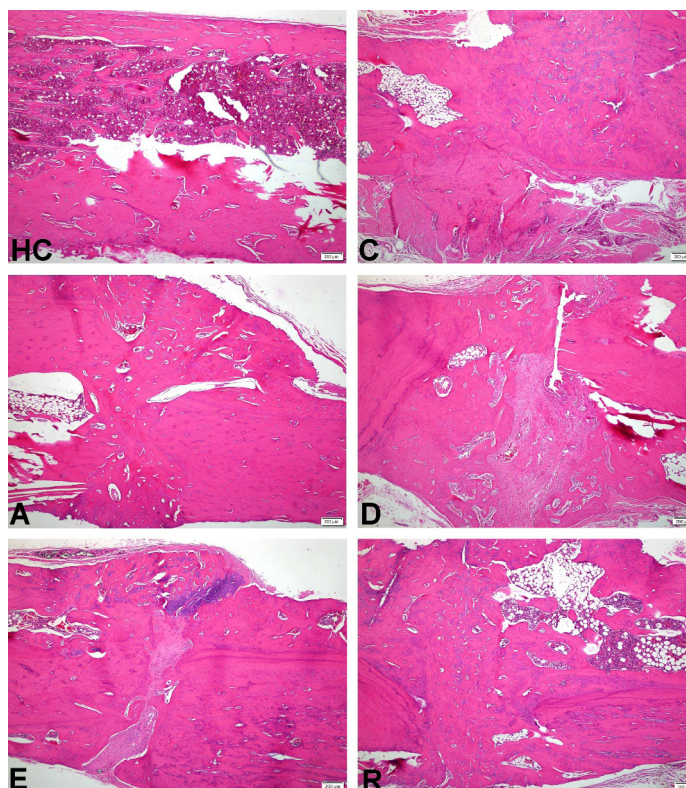


FIGURE 3. General view of the healing area at the fracture site in the Control (C) and treatment groups (A, D, E, and R), excluding the Healthy Control (HC). Magnification 4 $\times$, H&E staining

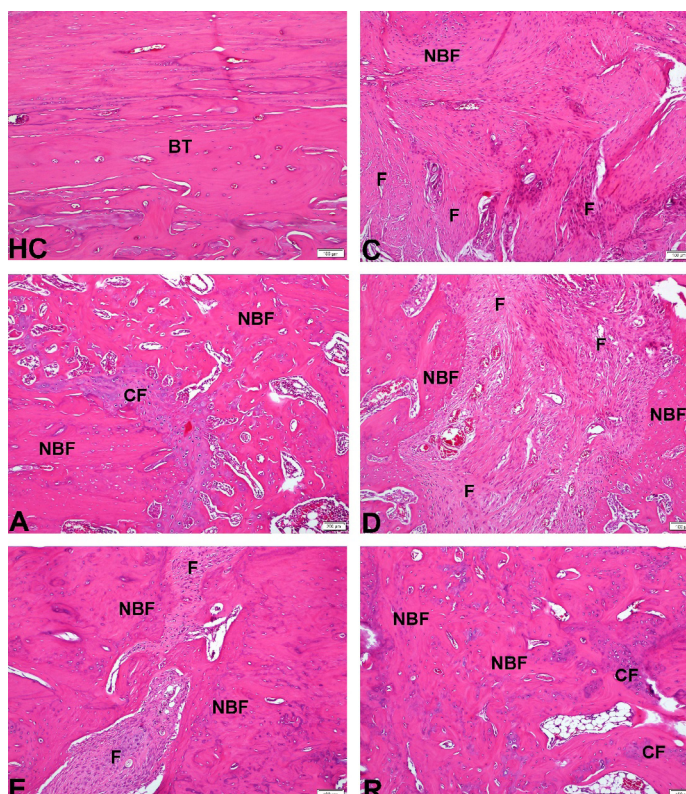


FIGURE 4. Normal bone tissue (BT) in the Healthy Control (HC) group, and areas of new bone formation (NBF), fibrosis or fibrous callus (F), and cartilage formation (CF) in the experimental groups. Magnification 10 $\times$, H&E staining

Fracture healing in the apixaban, edoxaban, and rivaroxaban groups was significantly greater compared to the control group. Moreover, healing in the apixaban group was significantly greater than that observed in both the dabigatran and edoxaban groups. Fracture healing in the rivaroxaban group was also significantly greater than in the dabigatran group (TABLE I). Although not statistically significant, there was a trend toward significance in the comparison between the edoxaban and rivaroxaban groups ($P = 0.05$).

TABLE I New Bone Formation (NBF) Ratios Across Experimental Groups				
Groups	N	Mean	Std. Deviation	P*
Control	8	41,75	5,57	0,000 ($P < 0,05$)
Apixaban ^{a1}	8	55,75	3,41	
Dabigatran ^{b1}	8	44,00	4,66	
Edoxaban ^{a2, b2}	8	48,63	5,55	
Rivaroxaban ^{a3, c}	8	55,38	3,89	

One Way Anova. $P = 0,000$. ^{a1}: 0,000, ^{a2}: 0,044, ^{a3}: 0,000. ^{a1,2,3}: Different compared with the controls. ^{b1}: 0,000, ^{b2}: 0,034, ^{b1,b2}: Different compared with the apixaban. ^c: Different compared with the dabigatran. $\dagger$: 0,000. ^{a1,2,3, b1,2, c}: Tukey HSD.

The mechanism of how anticoagulant medication interfere with bone healing was still unclear. In this study, it was investigated whether apixaban, edoxaban, rivaroxaban and dabigatran used as anticoagulants have any effects on fracture bone healing.

Prodingar *et al.* [16] investigated the effects of rivaroxaban on fracture healing and evaluated it biomechanically. They also examined callus formation and found that more callus formation occurred compared to the control group.

In a study conducted by Klüter *et al.* [17], after creating fractures in the femurs of rats and fixing them with Krishner wires, they reported a larger callus and a marginal increase in tissue mineral density in the rivaroxaban group compared to the control group. Histopathological evaluation of rivaroxaban, one of the anticoagulant agents used in this study, revealed significantly higher new bone (callus) formation compared to the control group. The studies appear to be parallel.

Namba *et al.* [18] reported that transitioning patients with atrial fibrillation from warfarin to rivaroxaban was associated with increased markers of bone formation and decreased markers of bone resorption. These findings are consistent with the results of the present study, which demonstrated improved bone healing parameters in rats treated with rivaroxaban.

Lau *et al.* [19] reported a lower risk of hip and vertebral fractures in dabigatran users compared to warfarin. In a similar study, Norby *et al.* [20] demonstrated a lower risk of hip and pelvic fractures in rivaroxaban users compared to warfarin. In this study, bone healing data in the rivaroxaban and dabigatran group were found to be higher compared to controls.

Kyriakaki *et al.* [21] reported in a study that dabigatran did not produce a significant difference in early bone defect healing compared to controls. A literature review did not reveal

sufficient studies on the subject. However, this study observed a slight difference in callus formation compared to the control group. Consequently, this study is not consistent with the current study. This difference may be due to the two studies being evaluated at different stages of healing.

Butler *et al.* [22] noted in a review that some limited studies suggested that anticoagulants may be effective in enhancing bone healing. Gómez-Outes *et al.* [23] evaluated apixaban, dabigatran, and rivaroxaban for thromboprophylaxis after total hip or knee arthroplasty and reported no significant difference in efficacy or safety among these new anticoagulants. In this study, no lesions were encountered in terms of thromboprophylaxis after the use of these new anticoagulants.

Fusaro *et al.* [24] investigated the effects of dabigatran and warfarin on bone volume and architecture, suggesting that treatment with dabigatran may be associated with a reduced incidence of fractures.

CONCLUSION

There is very little literature demonstrating the effects of the new anticoagulant apixaban, edoxaban, rivaroxaban, and dabigatran on fracture healing. In this study, histopathological analyses demonstrated statistically significant effects of these anticoagulants on new bone formation compared to the control group.

Conflicts of interest

The authors declare that there are no known conflicts of interest.

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