ACTA ORTHOPAEDICA et TRAUMATOLOGICA TURCICA

www.aott.org.tr

Research Article

Effects of repeated intravenous doses of tranexamic acid on closed tibial fracture healing: Experimental study based on the rat model

Ibrahim Doğan[1], Fevzi Birişik[2], Yücel Bilgin[3], Ahmet Sinan Kalyenci[2], Erol Rüştü Bozkurt[4], Yusuf Öztürkmen[2]

[1]*Department of Orthopedics and Traumatology, Erzincan University, Faculty of Medicine, Erzincan, Turkey*
[2]*Department of Orthopedics and Traumatology, İstanbul Research and Training Hospital, İstanbul, Turkey*
[3]*Department of Orthopedics and Traumatology, Uludağ University, Bursa, Turkey*
[4]*Department of Pathology, İstanbul Research and Training Hospital, İstanbul, Turkey*

ARTICLE INFO

Article history:
Submitted June 29, 2022
Received in revised form March 17, 2023
Accepted June 20, 2023
Publication Date September 22, 2023

Keywords:
Tranexamic acid
Closed Fracture
Rat model
Fracture Healing
Intramedullary Nailing

ORCID iDs of the authors:
I.D. 0000-0003-4183-7993;
F.B. 0000-0003-3274-6096;
Y.B. 0000-0003-0433-1918;
A.S.K. 0000-0001-7586-4370;
E.R.B. 0000-0002-1349-2206;
Y.Ö. 0000-0002-2199-2411.

Corresponding author:
Ibrahim Doğan
ibrahimdogan2424@gmail.com

ABSTRACT

Objective: The aim of this study was to assess the effects of tranexamic acid on fracture healing in the rat tibia closed fracture model.

Methods: Sixty-four male Sprague–Dawley rats were included in this study, where closed fracture and intramedullary nailing were performed on their right tibial diaphyses. They were divided into 2 main groups, the experimental group, which was given weekly tranexamic acid injections, and the control group, which received no additional treatment. Eight rats from each group were sacrificed and evaluated for fracture healing at the first experimental group and control group, second experimental group and control group, third experimental group and control group, and fourth experimental group and control group weeks. Fracture healing was radiologically assessed according to the "Spencer Index" and "Lane and Sandhu Scoring System," and histologically evaluated according to the scoring system devised by Huo et al.

Results: According to the Spencer Index, the mean union score was statistically significantly higher in the E3 group than in the third control group ($P = .014$). Furthermore, the mean union score was statistically significantly higher in the fourth experimental group compared to the fourth control group ($P = .047$). According to the Lane and Sandhu Scoring System, only the mean union scores of the E3-4 groups were statistically significantly higher than the mean union scores of the C3-4 groups ($P = .048$). There was no histological difference between groups in terms of union, according to the criteria defined by Huo et al ($P > .05$).

Conclusion: This study showed us that repeated intravenous administrations of tranexamic acid had no negative effect on fracture healing in the rat tibia fracture model. Although tranexamic acid demonstrated better radiological healing in the late period, it had no effect on histological union.

Introduction

Fracture is the deterioration of the structural integrity of the bone due to external or internal forces. Fracture healing is affected by many physiological, biological, and mechanical factors. Today, many biological factors and mechanisms effective on fracture healing have been elucidated. Undoubtedly, all these studies are for understanding the physiology and aiding in fracture healing. Supporting fracture healing medically will reduce the morbidity of the patients as well as reduce the costs of health expenditures.

Tranexamic acid (TXA) is a synthetic lysine amino acid derivative. Tranexamic acid binds to the active site on plasminogen, reversibly inhibits its conversion to its active molecule, plasmin, and indirectly inhibits fibrin degradation.[1,2]

Although fracture hematoma is known to be essential for fracture, the extent to which it affects fracture healing has not been fully demonstrated. Although complete removal of the fracture hematoma has been shown to negatively affect fracture healing in rat studies, it is not known whether reducing bleeding reduces fracture healing.[3-6] It is not known whether TXA will reduce callus quality while reducing bleeding.

Our hypothesis in this study is that TXA will not have adverse effects on fracture healing. In this study, we aimed to investigate the potential effects of TXA on fracture healing with the closed fracture model of rat tibia and intramedullary nailing (IMN) technique.

Materials and methods

Ethics committee approval dated 24.01.2019 and numbered 2019/03 was obtained from Bezmialem Vakıf University Experimental Animals Local Ethics Committee for this experimental study. All experimental stages of the study were carried out in Istanbul University Experimental Animals Department Laboratories.

In the study, 64 male Sprague–Dawley rats aged 2.5-3.5 months and weighing 300-350 grams were used. Four experimental groups defined as "E1 (experimental

Cite this article as: *Doğan I, Birişik F, Bilgin Y, Kalyenci AS, Bozkurt ER, Öztürkmen Y. Effects of repeated intravenous doses of tranexamic acid on closed tibial fracture healing: Experimental study based on the rat model. Acta Orthop Traumatol Turc., 2023;57(5):204-208.*

DOI: 10.5152/j.aott.2023.22132

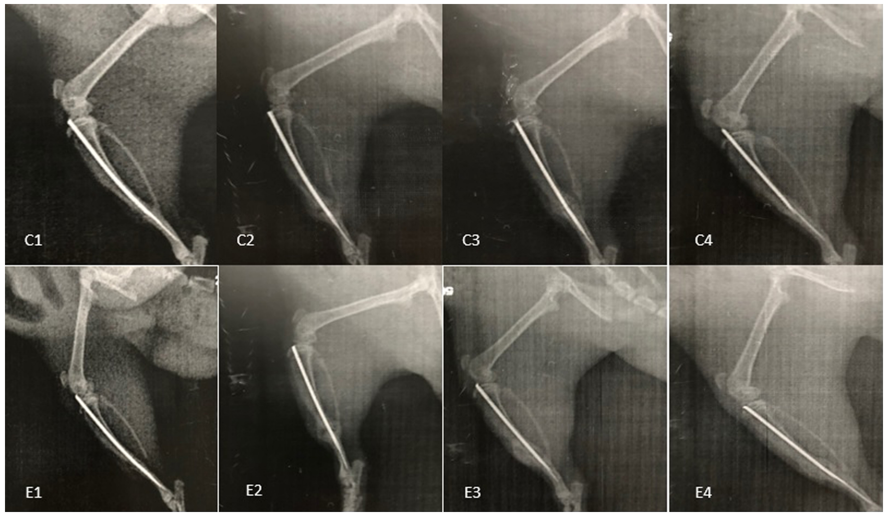

Figure 1. C1—control group right tibia lateral radiograph of the sacrificed rat at week 1, C2—control group right tibia lateral radiograph of the sacrificed rat at week 2, C3—control group right tibia lateral radiograph of the sacrificed rat at week 3, C4—control group right tibia lateral radiograph of the sacrificed rat at week 4. E1—experimental group right tibia lateral radiograph of the sacrificed rat at week 1, E2—experimental group right tibia lateral radiograph of the sacrificed rat at week 2, E3—experimental group right tibia lateral radiograph of the sacrificed rat at week 3, E4—experimental group right tibia lateral radiograph of the sacrificed rat at week 4.

group sacrificed at end of the first week)," "E2 (experimental group sacrificed at end of the second week)," "E3 (experimental group sacrificed at end of the third week)," "E4 (experimental group sacrificed at end of the fourth week)," and 4 control groups defined as "C1 (control group sacrificed at end of the first week)," "C2 (control group sacrificed at end of the second week)," "C3 (control group sacrificed at end of the third week)," and "C4 (control group sacrificed at end of the fourth week)" were formed. Eight rats were included in each group. Closed fracture and IMN model was created to the right tibial diaphysis of rats in all groups. The rats in the experimental group were injected with 10 mg/kg/day TXA as a single daily dose intravenously through the tail vein for 1 week. No additional treatment was applied to the rats in the control group. During the study, rats were given standard rodent chow (ad libitum) and no water restriction was applied. The rats were followed at a room temperature of 22°C with a rhythm of 12 hours during the day and 12 hours at night. Rats were followed in isolated cages for 1 postoperative day. Then, the social cage system was started and allowed to bear weight. Rats were followed with 4 rats in a cage.

The E1 and C1 group was sacrificed at the end of the first week, the E2 and C2 group at the end of the second week, the E3 and C3 group at the end of the third week, and the E4 and C4 group at the end of the fourth week. Cervical dislocation was used as the sacrification method. After sacrification, anteroposterior (AP) and lateral (LAT) x-rays were taken on the right tibia of all rats (Figure 1). Union scores were calculated using the "Spencer Index"[7] and the "Lane and Sandhu Scoring System."[8] Then the right tibia was separated from the soft tissues and fixed in 10% formaldehyde solution. Bone structures were decalcified in 10% hydrochloric acid solution after fixation. Afterward, longitudinal sections of 5 μm thickness were taken using a microtome and stained with hematoxylin–eosin and examined under a light microscope. Olympus BX51 light microscope was used in the examination. Scoring was done according to the criteria system described by Huo et al.[9]

HIGHLIGHTS

- Fracture hematoma formation is known to be essential for fracture healing. It is not known whether Tranexamic acid (TXA) will reduce callus quality while reducing bleeding. This study was aimed to investigate the potential effects of TXA on fracture healing with the closed fracture model of rat tibia and intramedullary nailing technique.
- Radiological results showed that the mean union score was significantly higher in the TXA groups at the third and fourth weeks, compared to the control group. However, histologic examination revealed no significant difference between the groups.
- The results from this study indicate that repeated TXA can be a possible option to enhance fracture healing in closed tibial diaphyseal fractures treated with intramedullary nailing, however prospective randomised studies in humans are needed.

Surgical technique

About 5 mg/kg xylazine hydrochloride (Rompun; Bayer Healthcare, Leverkusen, Germany) and 50 mg/kg ketamine hydrochloride (Ketalar; Pfizer, Turkey) were administered intraperitoneally as preoperative anesthesia. The right hind limbs of the animals were then shaved in the supine position. Surgical site preparation was performed with 10% povidone iodine (Batticon; Adeka, Turkey). The closed tibia fracture model was created by the guillotine method. A 1 cm longitudinal incision was made over the patellar tendon. The patellar tendon was retracted laterally. The intramedullary nail insertion site was opened using a high-speed burr. Using the 27G needle as the guide wire, the 21G needle was sent as an intramedullary nail up to the distal tibia, entering the medullary cavity. Detection was checked with pathological movement control. It was determined that there was no pathological movement after fixation in all rats. The skin incision was closed with 3.0 prolene. After awakening, the experimental animals were allowed to load and move freely in the cage. Daily wound follow-up and pain follow-up were performed.

Statistical analysis

Statistical analyses were performed with Statistical Package for Social Sciences (SPSS) version 17.0 program (SPSS Inc.; Chicago, IL, USA). The conformity of the variables to the normal distribution was examined by histogram graphics and the Kolmogorov–Smirnov test. Mean, SD, and median values were used when presenting descriptive analyses. Categorical variables were compared with the Pearson chi-square test. The Mann–Whitney *U* test was used when evaluating non-normally distributed (nonparametric) variables between 2 groups. *P* value < .05 was considered statistically significant.

Table 1. Spencer Index Averages

	Groups							
	E1	C1	E2	C2	E3	C3	E4	C4
Mean	1.446	1.595	1.825	1.988	2.067	1.760	2.147	1.644
SD (±)	0.25	0.33	0.33	0.38	0.20	0.23	0.57	0.31
*P**	.322		.375		.014		.047*	

*Significant value ($P < 0.05$).

Results

Radiological findings

The union scores calculated using the "Spencer Index" on x-rays were compared separately between the experimental and control groups sacrificed in the same week. There was no statistical difference between the C1-E1 and C2-E2 groups ($P = .322$ and $P = .375$, respectively). The mean union score was statistically significantly higher in the E3 group than C3 group ($P = .014$) and also the mean union score was statistically significantly higher in the E4 group than C4 group ($P = .047$) (Table 1). In addition, rats sacrificed at the end of the first week and at the end of the second week were defined as the early period of fracture healing, and the rats sacrificed at the end of the third week and at the end of the fourth week were defined as the late period of fracture healing. In this way, when the mean union scores of the E1-2 groups were compared with the mean union scores of the C1-2 groups, no statistically significant difference was found ($P = .244$). When the mean union scores of the E3-4 groups were compared with the mean union scores of the C3-4 groups, it was found that the mean union scores of the E3-4 groups were statistically significantly higher ($P = .003$).

In addition, union scores calculated using the "Lane and Sandhu Scoring System" on x-rays were compared separately between the experimental and control groups sacrificed in the same week. The mean union score was 3.00 ± 2.27 in the E1 group, while the mean union score was 1.63 ± 2.56 in the C1 group. The mean union score was 6.63 ± 2.39 in the E2 group, while the mean union score was 6.38 ± 3.02 in the C2 group. The mean union score was 9.13 ± 2.10 in the E3 group, while the mean union score was 7.88 ± 2.30 in the C3 group. While the mean union score was 8.75 ± 2.05 in the E4 group, the mean union score was calculated as 7.25 ± 2.87 in the C4 group. There was no statistical difference between the all control and experimental groups (Table 2). When the mean union scores of the E1-2 groups were compared with the mean union scores of the C1-2 groups, no statistically significant difference was found ($P = .490$). When the mean union scores of the E3-4 groups were compared with the mean union scores of the C3-4 groups, it was found that the mean union scores of the E3-4 groups were statistically significantly higher ($P = .048$).

Histological findings

Histological evaluation scores made according to the criteria defined by Huo et al[9] were compared between the experimental and control groups who were sacrificed in the same week. When the histological scores of the E1 group was compared with the histological scores of the C1 group, no statistically significant difference was found ($P = 1.000$). When the histological scores of the E2 group were compared with the histological scores of the C2 group, no statistically significant difference was found ($P = .602$). When the histological scores of the E3 group were compared with the histological scores of the C3 group, no statistically significant difference was found ($P = .680$). When the histological scores of the E4 group were compared with the histological scores of the C4 group, no statistically significant difference was found ($P = 1.000$). When the histological scores of the E1-2 groups were compared with the histological scores of the C1-2 groups, no statistically significant difference was found ($P = .869$). When the histological scores of the E3-4 groups were compared with the histological scores of the C3-4 groups, no statistically significant difference was found ($P = .891$).

Discussion

Our most valuable finding in this study is that TXA does not negatively affect fracture healing but also has a positive effect on long-term fracture healing.

Fracture occurs when the structural integrity of the bone is disrupted by external or internal forces. Fracture healing starts from the moment of the fracture and continues until mature, organized bone tissue and bone ends are integrated. In order to clarify the biochemical and cellular processes of these periods, many factors that will affect fracture healing have been investigated.[10]

The effects of drugs that affect bleeding and vascular permeability due to the hematoma stage in the inflammation period of fracture healing have been continuously investigated in the literature. Malekigorji et al[11] found that pentoxifylline and sildenafil (phosphodiesterase inhibitor), which are agents that increase vascular permeability, have a positive effect on bone healing in an experimental maxillofacial fracture model performed on rats. In an experimental study on nitric oxide, that increases vascular permeability, in a rat model, Diwan et al.[12] They showed that fracture healing was delayed after nitric oxide inhibition. In an in vivo study showing the effect of aprotinin, an antifibrinolytic agent such as TXA, on bone colonization, Le Guehennec et al[13] showed low bone levels at low aprotinin and calcium chloride levels. Studies have been conducted to examine the effects of agents that prevent intravascular coagulation on fracture healing. In an experimental study on rat femur fondaparinux was shown to have possitive effect of healing, Say et all.[14]

Tranexamic acid, as a lysine amino acid derivative, binds to the active site on plasminogen, reversibly inhibits its conversion to its

Table 2. Lane and Sandhu Scores

	Groups							
	E1	C1	E2	C2	E3	C3	E4	C4
Mean	3.00	1.63	6.63	6.38	9.13	7.88	8.75	7.25
SD (±)	2.27	2.56	2.38	3.02	2.10	2.30	2.05	2.87
P	.214		.914		.071		.295	

active molecule, plasmin, and indirectly inhibits fibrin degradation.[1,2] Although TXA is used in many other medical fields, it has been used frequently in orthopedic surgery in the last 10 years.[15-19] It has been shown that TXA reduces the amount of bleeding and the need for transfusion in many areas of orthopedic surgery and has positive effects on patient morbidity. Although complete removal of the fracture hematoma has been shown to negatively affect fracture healing in experimental studies in the literature, it is not known whether reducing bleeding reduces fracture healing.[3-6] Therefore, in our study, we aimed to determine the possible effects of TXA on fracture healing.

In our study, we chose the rat as the experimental animal. We preferred the rat because it is easy to care for, easy to apply fracture modeling, less in-experimental animal loss, resistance to infection and other comorbidities, and it has been frequently experienced in similar studies in the literature. Since long bone fractures are mostly closed fractures, we applied the closed fracture model. We thought that we could better detect its effect on the union by reducing the amount of bleeding without affecting the fracture hematoma that occurs immediately after the fracture. In addition, we preferred the closed IMN technique because it is a method that is used more frequently in closed fractures of long bones. In our study, we chose IV administration via the tail vein as the drug administration route. The reason we chose this route was that no invasive procedure was applied directly to the fracture line. As the dose, we chose 10-15 mg/kg/day, which is more frequently used in experimental models in the literature and more frequently used as the application dose in humans.[20,21] Considering the rat bone healing as the sacrification time, we planned sacrification in the first week showing the hematoma and inflammation period, the second week showing the soft callus formation, the third week showing the hard callus period, and the fourth week showing the maturation period. We considered first and second weeks as early period, third and fourth weeks as late recovery.

Although we did not find a significant effect of TXA on fracture healing histologically in our study, we found that rats sacrificed at the end of the third and fourth weeks in the radiological evaluation had better union scores than the control group. There were limited experimental studies on this subject in the literature. Çevik et al[22] in their study, the effects of local and systemic TXA on fracture healing after open femur fracture in rats were investigated. Lane and Sandhu scoring system was used for radiological evaluation and the scoring system defined by Huo et al was used for histological evaluation. While a positive effect was observed on fracture healing after local application and systemic application, they stated that local application increased fracture healing more than systemic application.[22] In another study, Balkanlı et al[23] in their experimental animal model study, 42 rats were used. The effect of local and systemic application of TXA on bone healing after the rat tibia open fracture model was evaluated. The local application was made as 1.5-3 g, and IV as 10-15 mg/kg. In addition, in this study, the amount of hematoma between the experimental and control groups was evaluated by ultrasonography on the first and third days. Although there was a decrease in the amount of hematoma after local application, no statistically significant difference was found between the groups. When fracture healing was evaluated, no significant difference was found again.[23] In another study, a single dose of 30 mg/kg IV administration of TXA was compared with the control group in 36 rats who underwent IMN after the femoral closed fracture created in the study by Karaduman et al.[24] The rats were sacrificed on the 15th, 30th, and 45th days. It was observed that the recovery was significantly better in the group sacrificed in 15 days. No difference was found between the other groups.[24]

The most important difference in our study compared to other studies in the literature is that TXA was administered at repeated doses for 7 days. Bleeding after fracture is usually not instantaneous, and bleeding complications may develop within the first 7 days. For this reason, repeated doses of TXA may be required. Despite 7 days of application, we did not detect any negative effects on fracture healing, both radiologically and histologically, due to TXA. Another difference is that we use the tibia closed fracture model. Closed tibia fractures are fractures with a high risk of bleeding complications. Soft tissue problems and compartment syndromes may develop after bleeding. We think that the use of this fracture model is more clinically meaningful.

The main limitations of our study are that only x-ray was used in the radiological examination and no biomechanical examination was performed. If micro CT could be used in addition to x-ray in imaging, more detailed radiological evaluation could be made. In addition, the biomechanics of the union tissue is an important parameter as well as the radiological and histological examination in the post-union evaluation. In addition, we did not use any parameter showing the effect of TXA on bleeding when evaluating the effect on union. We could have provided more detailed information if we had added a radiological imaging method that quantifies the hematoma.

Repeated intravenous administration of TXA has no negative effect on fracture healing in closed tibial diaphysis fractures treated with IMN in experimental rat model. While radiological healing is better in the late period of fracture healing, there is no histological difference. Repeated doses of systemic TXA can be safely used for union in closed tibial diaphyseal fractures treated with IMN.

Availability of Data: Data are stored by the corresponding author of this manuscript and will be shared whenever required.

Ethics Committee Approval: This study was approved by the Bezmialem Vakıf University Experimental Animals Department Laboratories (Registration number: 2019/03).

Informed Consent: N/A.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – I.D., F.B.; Design – I.D., F.B.; Supervision – Y.O., F.B.; Resources – I.D., A.S.K.; Materials – I.D., Y.B.; Data Collection and/or Processing– I.D., A.S.K.; Analysis and/or Interpretation – I.D., E.R.B.; Literature Search – I.D., A.S.K.; Writing – I.D., Y.B.; Critical Review – Y.O., I.D.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: The authors declared that this study has received no financial support.

References

1. Hardy JF, Desroches J. Natural and synthetic antifibrinolytics in cardiac surgery. *Can J Anaesth.* 1992;39(4):353-365. [CrossRef]
2. Samama CM. A direct antifibrinolytic agent in major orthopedic surgery. *Orthopedics.* 2004;27(6):s675-s680. [CrossRef]
3. Xing Z, Lu C, Hu D, Miclau T, Marcucio RS. Rejuvenation of the inflammatory system stimulates fracture repair in aged mice. *J Orthop Res.* 2010;28(8):1000-1006. [CrossRef]
4. Grundnes O, Reikerås O. The importance of the hematoma for fracture healing in rats. *Acta Orthop Scand.* 1993;64(3):340-342. [CrossRef]
5. Kolar P, Schmidt-Bleek K, Schell H, et al. The early fracture hematoma and its potential role in fracture healing. *Tissue Eng Part B Rev.* 2010;16(4):427-434. [CrossRef]
6. Mountziaris PM, Mikos AG. Modulation of the inflammatory response for enhanced bone tissue regeneration. *Tissue Eng Part B Rev.* 2008;14(2):179-186. [CrossRef]

7. Spencer RF. The effect of head injury on fracture healing. A quantitative assessment. *J Bone Joint Surg Br*. 1987;69(4):525-528. [CrossRef]
8. Lane JM, Sandhu HS. Current approaches to experimental bone grafting. *Orthop Clin North Am*. 1987;18(2):213-225. [CrossRef]
9. Huo MH, Troiano NW, Pelker RR, Gundberg CM, Friedlaender GE. The influence of ibuprofen on fracture repair: biomechanical, biochemical, histologic, and histomorphometric parameters in rats. *J Orthop Res*. 1991;9(3):383-390. [CrossRef]
10. Jensen JE, Jensen TG, Smith TK, Johnston DA, Dudrick SJ. Nutrition in orthopaedic surgery. *J Bone Joint Surg Am*. 1982;64(9):1263-1272. [CrossRef]
11. MalekiGorji M, Golestaneh A, Razavi SM. The effect of two phosphodiesterase inhibitors on bone healing in mandibular fractures (animal study in rats). *J Korean Assoc Oral Maxillofac Surg*. 2020;46(4):258-265. [CrossRef]
12. Diwan AD, Wang MX, Jang D, Zhu W, Murrell GA. Nitric oxide modulates fracture healing. *J Bone Miner Res*. 2000;15(2):342-351. [CrossRef]
13. Le Guehennec L, Goyenvalle E, Aguado E, Pilet P, Spaethe R, Daculsi G. Influence of calcium chloride and aprotinin in the in vivo biological performance of a composite combining biphasic calcium phosphate granules and fibrin sealant. *J Mater Sci Mater Med*. 2007;18(8):1489-1495. [CrossRef]
14. Say F, Iltar S, Alemdaroğlu KB, Ozel I, Aydoğan NH, Gönültaş M. The effect of various types low molecular weight heparins on fracture healing. *Thromb Res*. 2013;131(3):e114-e119. [CrossRef]
15. Gillespie R, Shishani Y, Joseph S, Streit JJ, Gobezie R. Neer Award 2015: A randomized, prospective evaluation on the effectiveness of tranexamic acid in reducing blood loss after total shoulder arthroplasty. *J Shoulder Elb Surg*. 2015;24:1679-1684.
16. Perel P, Ker K, Morales Uribe CH, Roberts I. Tranexamic acid for reducing mortality in emergency and urgent surgery. *Cochrane Database Syst Rev*. 2013;2013(1):CD010245. [CrossRef]
17. Poeran J, Rasul R, Suzuki S, et al. Tranexamic acid use and postoperative outcomes in patients undergoing total hip or knee arthroplasty in the United States: retrospective analysis of effectiveness and safety. *BMJ*. 2014;349:g4829. [CrossRef]
18. Jiménez JJ, Iribarren JL, Brouard M, et al. Safety and Effectiveness of two treatment regimes with tranexamic acid to minimize inflammatory response in elective cardiopulmonary bypass patients: a randomized double-blind, dose-dependent, phase IV clinical trial. *J Cardiothorac Surg*. 2011;6:138. [CrossRef]
19. Yao RZ, Gao WQ, Wang BW, Wang GL, Wu CX, A-Mu YD. Efficacy and safety of tranexamic acid in reducing blood loss of lower extremity osteotomy in peri-acetabulum and high tibia: A systematic review and meta-analysis. *Orthop Surg*. 2019;11(4):545-551. [CrossRef]
20. Barrachina B, Lopez-Picado A, Remon M, et al. Tranexamic acid compared with placebo for reducing total blood loss in hip replacement surgery: A randomized clinical trial. *Anesth Analg*. 2016;122(4):986-995. [CrossRef]
21. Chu C, Yang C, Wang X, et al. Early intravenous administration of tranexamic acid ameliorates intestinal barrier injury induced by neutrophil extracellular traps in a rat model of trauma/hemorrhagic shock. *Surgery*. 2020;167(2):340-351. [CrossRef]
22. Çevik HB, Eceviz E, Çilingir Kaya ÖT, Ercan F, Çeçen GS. The effect of topical and systemic tranexamic acid on fracture healing in rats. *Acta Orthop Traumatol Turc*. 2020;54(2):207-212. [CrossRef]
23. Balkanlı B, Çopuroğlu C, Çopuroğlu E. The effects of intravenous and local tranexamic acid on bone healing: an experimental study in the rat tibia fracture model. *Injury*. 2020;51(12):2840-2845. [CrossRef]
24. Karaduman ZO, Arıcan M, Turhan Y, Turhal O, Orhan Z, Gamsızkan M. Systemic tranexamic acid promotes bone healing in a rat model of femur fracture. *Jt Dis Relat Surg*. 2020;31(3):432-439. [CrossRef]