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ORIGINAL ARTICLE

Topical or intravenous administration of tranexamic acid accelerates wound healing

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Wound healing is still poorly understood, although detailed research methods and tools have been used from the past to the present. Systemic and topical factors affecting the process have been understood in more detail over time, and many growth factors and cytokines affecting healing have been discovered in animal experiments. Growth factors, blood elements, extracellular, and parenchymal agents have been shown to affect healing.[1]

Tranexamic acid (TA) is a synthetic lysine amino acid derivative that reduces fibrin dissolution. Its mechanism of action is to bind to plasminogen and block the association of fibrin and plasmin, which prevents the dissolution of the fibrin plug. It is known to be used in patients prone to bleeding, including abnormal bleeding, local,

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ABSTRACT

Objectives: In this study, we aimed to investigate the morphological and histological effects of tranexamic acid (TA) on wound healing in a rat wound model.

Materials and methods: A total of 24 adult male Wistar Albino rats were used in this study. All rats were simple randomly divided into three groups including eight rats in each group. A full-thickness skin defect was created on the back of the rats in all groups. Serum physiological (2 mL) was instilled saline drops after wound formation (control group). Wound was created and topical TA (0.12 to 0.15 mL [30 mg/kg]) was applied (local group). Intravenous TA (0.12 to 0.15 mL [30 mg/kg]) was applied intravenously before the wound was created (intravenous group). The wound diameters of the groups were photographed and measured on Days 0, 3, 7, 10, 14 and, at the end of Day 14, the rats were sacrificed and their histopathological results and wound diameters were compared.

Results: Fibroblast count values of the control group were found to be significantly lower than the local group (p=0.002), and no significant difference was observed between the local and intravenous groups (p>0.05). The collagen density (%) values of the control group were found to be significantly higher than the local and intravenous groups (p=0.016 and p=0.044). Wound diameter values of the control group on Day 10 day were found to be significantly higher than the local and intravenous groups (p=0.001). In addition, the wound diameter values of the control group on Day 14 were found to be significantly higher than the local and intravenous groups (p=0.001 and p=0.0001). The wound diameter changes of the control group on Days 0-10 were found to be significantly lower than the local and intravenous groups (p=0.001). In addition, the wound diameter changes of the control group on Days 0-14 were found to be lower than those of the local and intravenous groups (p=0.001 and p=0.0001).

Conclusion: The use of local or intravenous TA may have positive effects on the fibroblast count and wound contraction in a rat wound model.

Keywords: Intravenous, local, rat, tranexamic acid, wound healing.

or systemic hyperfibrinolysis.[2] Tranexamic acid is an antifibrinolytic agent that has been widely used for many years in orthopedic, cranial surgery, cardiac surgery, and urological surgery procedures to minimize the intra- and postoperative blood loss and the resulting transfusion requirement.[3,4]

Since TA has a hemostatic effect by inhibiting plasminogen activation and providing fibrin protective activity, in the present study, we hypothesized that it would have a positive effect on the wound healing model in rats. We, therefore, aimed to investigate the morphological and histological effects of TA on wound healing in rats.

MATERIALS AND METHODS

A total of 24 male Wistar Albino rats with an average of 2.5 (2 to 3) months and an average weight of 250 (range, 200 to 300) g were used in this study. All procedures were carried out in the Experimental Animals Breeding and Research Center of the Medical Faculty of Düzce University between 1 March 2019 and 15 July 2019. The subjects were simple randomly divided into three groups and observed for one week preoperatively to kept under standardized conditions in the laboratory with eight rats in each cage. They were identified using a tail-marking counting system to ensure proper matching. During the study, the rats were given unlimited tap water *(ad libitum)* and standard rodent food. The rats were monitored in a cage in a temperature-controlled room (23°-25°) with a 12/12-h light/dark cycle. Antibiotics were not administered in either group before or after surgery. Serum physiological (control group) was instilled saline drops after wound formation. Wound was created and topical TA was applied (local group). Intravenous TA was applied intravenously before the wound was created (intravenous group). The control group received a single dose of 2 mL of saline topical immediately after surgery, the local group received a single dose of 0.12 to 0.15 mL (30 mg/kg) topical immediately after surgery, and the intravenous group received a single dose of 0.12 to 0.15 mL (30 mg/kg) intravenously immediately before surgery.

Surgical technique

The rats, which were monitored and prepared, were taken to the intervention room. The anesthetic dose was calculated by measuring the weight of each rat on an electronic scale. Ketamine (Eczacıbaşı, Istanbul, Türkiye) 50 mg/kg and xylazine (Bayer, Istanbul, Türkiye) 10 mg/kg were used as anesthetics. Anesthesia was administered intraperitoneally from the left inguinal region. The rats were stained with povidone-iodide (Batticon®, ADEKA, Türkiye) after shaving their dorsal regions (Figure 1a, b). The mean wound sizes of 17.93±1.06, 19.26±1.26, and 19.3±1.43 mm were created in each of the control, local, and intravenous groups, respectively. In the control group, using a scalpel, a full-thickness skin defect was created and 2 mL of saline solution was dripped into the wound after surgery. The wound created for local group was coated with oxidized cellulose (Surgicel™; Johnson & Johnson, Piscataway, New Jersey, USA) and sutured to the wound edges so that locally applied substances could be absorbed faster and remain in the wound area longer. Afterwards, TA 0.12 to 0.15 mL (30 mg/kg) (Transamine®, Actavis, Türkiye) was applied topically to the wound. In the intravenous group, a vascular access was opened with a granule through the tail vein, and a single intravenous dose of 0.12 to 0.15 mL (30 mg/kg) of TA was administered before the surgical intervention. A scalpel was, then, used to create a skin defect from an area that was shaved from the back (Figure 2a, b). Then, on Days 0, 3, 7, 10, 14, the diameters of skin lesions of rats of all groups were measured using millimeters (mm) to track contractions, captured, and recorded simultaneously. Diameter measurement on photographs was made using the Autocad software (Autodesk, USA) (Figure 3). The rats were sacrificed at the end of Day 14, the wound scars on their dorsal areas were excised, and they were placed in 10% formaldehyde and examined histopathologically.

Histopathological evaluation

After the usual follow-up procedures, the samples were embedded in paraffin and 7-micron-thick

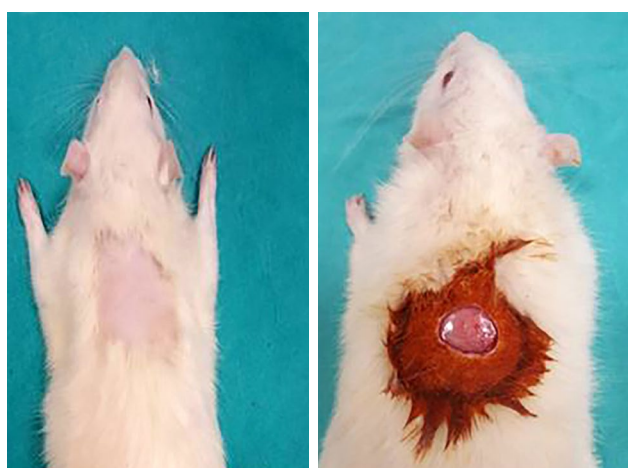

FIGURE 1. (a) Shaving the back of the rat before surgery. **(b)** Creating a full-thickness wound from the back region.

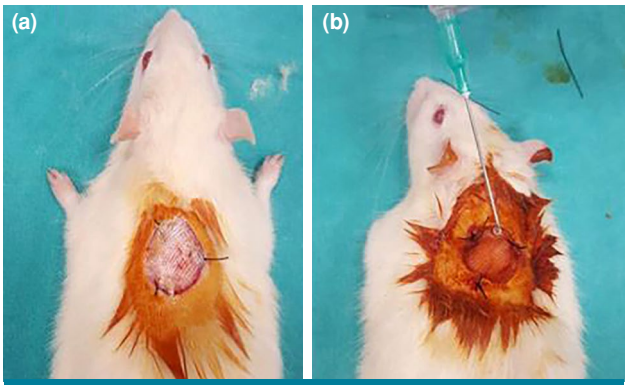

FIGURE 2. (a) Application of absorbable oxidized regenerated cellulose (Surgicel™) to the group applied topical Tranexamic acid (Local group). **(b)** application of local Tranexamic acid.

sections were obtained. Routine hematoxylin-eosin and Masson's trichrome staining were done on the sections. Additionally, immunohistochemical staining was performed with CD31 (Biocare, 1/200) and transforming growth factor-beta (TGF-B1) (Santa Cruz, 1/100) antibodies with the avidin-biotin immunoperoxidase method for vessel density and TGF-B1 (Figure 4a, b).

Lymphocyte density was categorized as mild (1), moderate (2), and severe (3).[5] The number of fibroblasts per square millimeter was also measured. Numerical values were obtained by measuring scar thickness on a computer. Images were taken from Masson's trichromes and converted to black

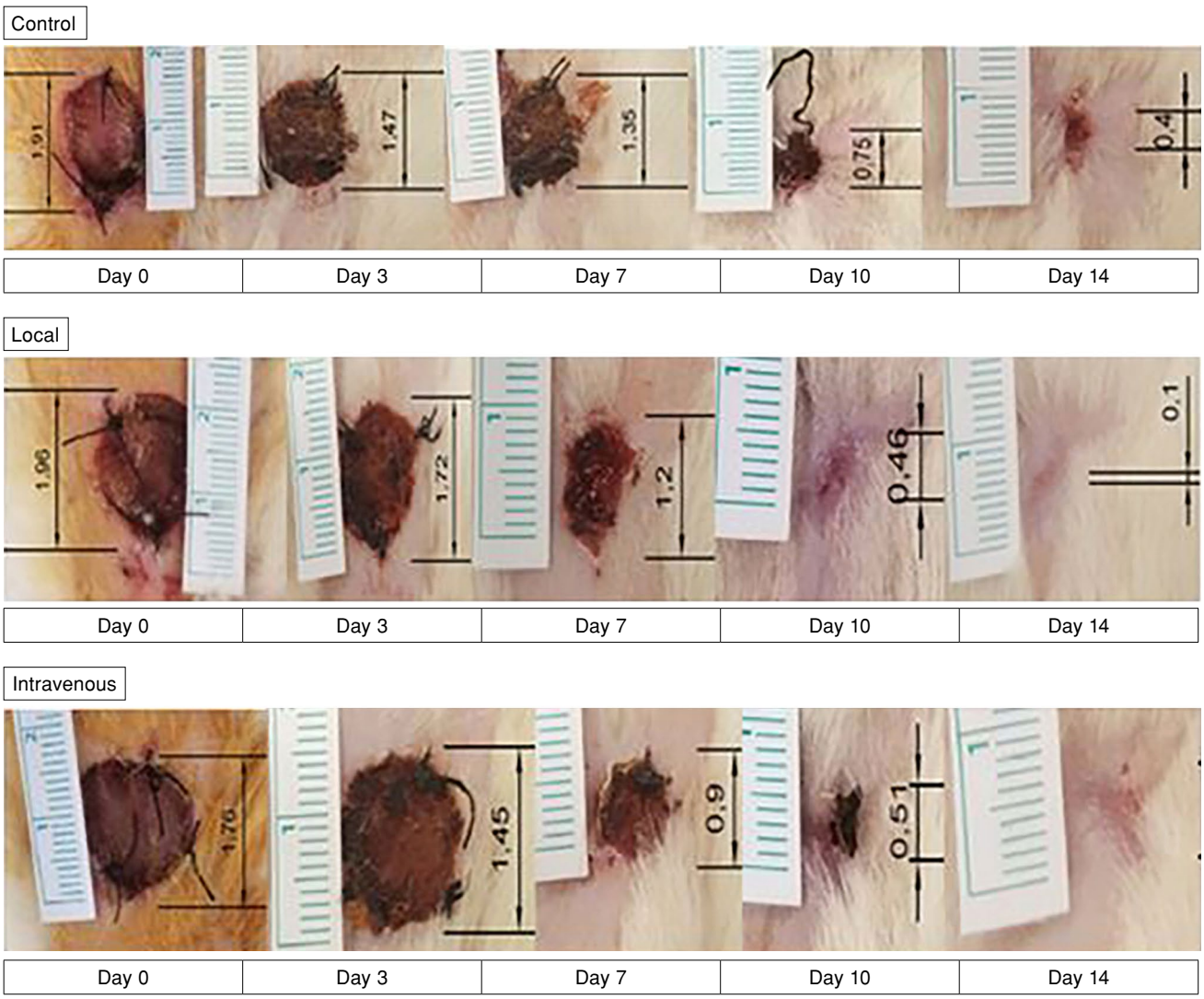

FIGURE 3. Measurement of wound diameters of control, local and intravenous groups with the help of Autocad program on Days 0, 3, 7, 10, 14.

and white format. The density of the scars was, then, measured in the most intense area for each sample using the Image J image processing software (Figure 5a-c and Figure 6a, b). Vessel density per square millimeter was obtained using CD31 dye. If TGF-B1 immune expression was focal (≤10%), the score was 1, if it was between 10 and 25%, the score was 2, and if >25%, the score was 3. Mild intensity score was given as 1, moderate-intensity score as 2, and severe intensity score as 3. The total score was obtained by multiplying these values with each other.[5] The histopathological evaluation was done one time at the end of Day 14 by the same specialist in the Department of Pathology.

Statistical analysis

Statistical analysis was performed using the Number Cruncher Statistical System (NCSS) 2007 Statistical Software (NCSS LLC, Utah, USA). Descriptive data were expressed in mean ± standard deviation (SD), median and interquartile range (IQR) or number and frequency. The distribution of variables was examined with the Shapiro-Wilk normality test, Friedman test was used for time comparisons of

FIGURE 4. CD31-kx10: CD31 immunoexpression in vessels (×100). **(a)** Control, **(b)** local, **(c)** intravenous tranexamic acid.

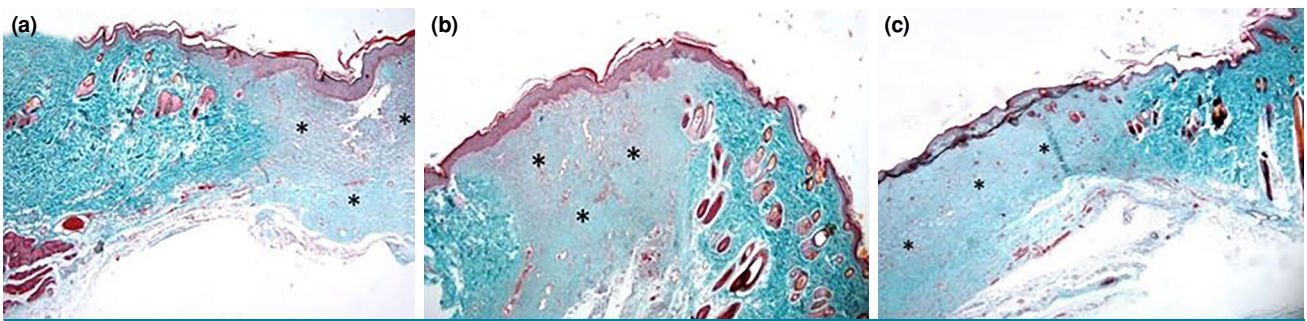

FIGURE 5. Scar development (right, starry part), and normal skin-subcutaneous tissue (Masson-Trichrome, ×40) **(a)** Control, **(b)**local, **(c)** Intravenous.

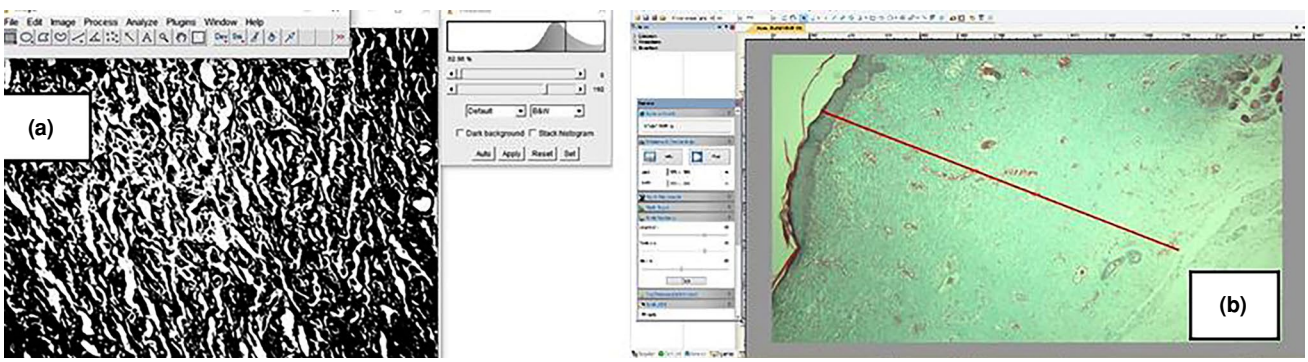

FIGURE 6. (a) Morphometric measurement of collagen density. **(b)** Measurement of scar thickness (Masson-trichrome ×40).

non-normally distributed variables, Dunn's multiple comparison test was used for subgroup comparisons, Kruskal-Wallis test was used for intergroup comparisons, Dunn's multiple comparison test was used for subgroup comparisons, and chi-square test was used for qualitative data comparisons. A p value of <0.05 was considered statistically significant.

RESULTS

There was no statistically significant difference in lymphocyte count, polymorphonuclear leukocyte (PMNL) count, scar thickness, microvascular density values between control, local and intravenous groups (p=0.087, p=0.994, p=0.098, and p=0.315, respectively); however, a statistically significant difference was observed between the fibroblast count values (p=0.018). Fibroblast count values of the control group were found to be statistically significantly lower than the local group (p=0.002), and no statistically significant difference was observed between the local and intravenous groups (p>0.05). In addition, a statistically significant difference was observed between the collagen density (%) values of the control, local and intravenous groups (p=0.049). The collagen density (%) values of the control group were found to be statistically significantly higher than the local and intravenous groups (p=0.016 and p=0.044) (Table I, Figures 7, 8).

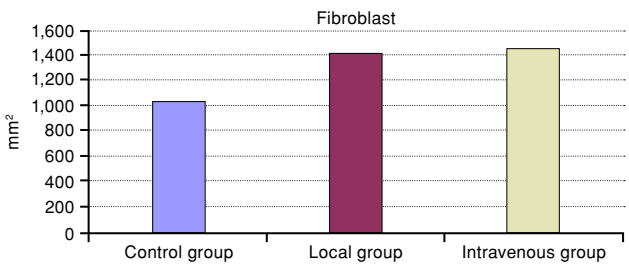

FIGURE 7. Mean fibroblast values of control, local and intravenous groups.

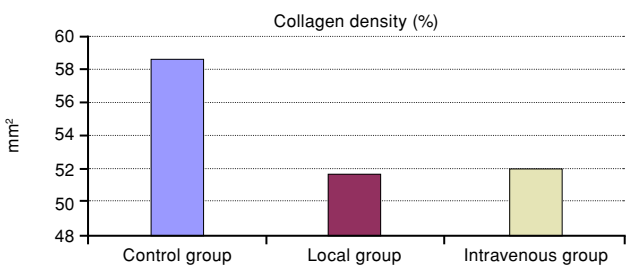

FIGURE 8. Mean collagen density values of control, local and intravenous groups.

TABLE I
Comparison of lymphocyte, PMNL, fibroblast count, scar thickness, collagen density and MVD values of Control, Local, and Intravenous groups

	Control group			Local group			Intravenous group			p
	Mean±SD	Median	IQR	Mean±SD	Median	IQR	Mean±SD	Median	IQR	
Lymphocyte	1.5±0.93	1.5	1-2	0.88±0.64	1	0.25-1	0.63±0.52	1	0-1	0.087
PMNL	0.13±0.35			0.25±0.71			0.13±0.35			0.994
Fibroblast	1167.75±165.66	1161	1048.5-1251	1521±115.46	1530	1404-1597.5	1424.25±318.59	1512	1066.5-1714.5	**0.018**
Scar thickness	1655.38±426.46	1696.5	1591.5-1972.25	1315±343.88	1314	956.5-1667.5	1269.38±538.64	1324.5	951.75-1435.25	0.098
Collagen density (%)	59.55±3.37	59.1	56.13-62.38	52.56±5.61	51.3	48-56.625	52.84±9.57	51.8	43.63-59.65	**0.049**
MVD	53.75±7.15	54	50.25-57	52.25±12.49	51.5	39.75-65	46.88±6.79	46	43-52.25	0.315

Dunn's Multiple Comparison test	Fibroblast	Collagen density (%)
Control group/Local group	**0.002**	0.016
Control group/Intravenous group	0.141	**0.044**
Local group/Intravenous group	0.636	0.999

PMNL: Polymorphonuclear leukocyte; MVD: Microvascular density; SD: Standard deviation; IQR: Interquartile range; Kruskal Wallis test.

TABLE II

Comparison of mean wound diameter values of control, local and intravenous groups on Days 0, 3, 7, 10, 14

	Control group			Local group			Intravenous group			
Wound diameter	Mean±SD	Median	IQR	Mean±SD	Median	IQR	Mean±SD	Median	IQR	*p*
Day 0	17.93±1.06	18	16.93-18.95	19.26±1.26	19.4	18.38-19.58	19.3±1.43	19.1	17.825-20.9	0.057
Day 3	14.05±0.68	14.35	13.35-14.58	15.81±1.42	16.25	14.35-17.08	15.13±1.34	14.8	13.95-16.48	0.074
Day 7	10.48±2.58	9.25	8.25-13.48	10.14±1.59	10	8.48-11.78	9.93±0.99	9.95	9.18-10.43	0.978
Day 10	6.58±0.78	6.2	5.9-7.48	3.94±0.73	4.15	3.13-4.43	4.04±0.5	3.95	3.65-4.25	**0.0001**
Day 14	3.61±0.47	3.5	3.15-4.1	0.26±0.49	0	0-0.75	0±0	0	0-0	**0.0001**
p‡		0.0001			0.0001			0.0001		

Dunn's Multiple Comparison test	10th Day	14th Day
Control group/Local group	0.001	0.001
Control group/Intravenous group	0.001	0.0001
Local group/Intravenous group	0.998	0.144

Dunn's Multiple Comparison test	Control	Local	Intravenous
Day 0 / Day 3	0.044	0.038	0.04
Day 0 / Day 7	0.031	0.025	0.033
Day 0 / Day 10	0.022	0.012	0.022
Day 0 / Day 14	0.012	0.011	0.011
Day 3 / Day 7	0.041	0.034	0.036
Day 3 / Day 10	0.036	0.028	0.016
Day 3 / Day 14	0.014	0.016	0.01
Day 7 / Day 10	0.031	0.029	0.021
Day 7 / Day 14	0.028	0.017	0.011
Day 10 / Day 14	0.011	0.012	0.011

SD: Standard deviation; IQR: Interquartile range; * Kruskal Wallis test; ‡ Friedman test.

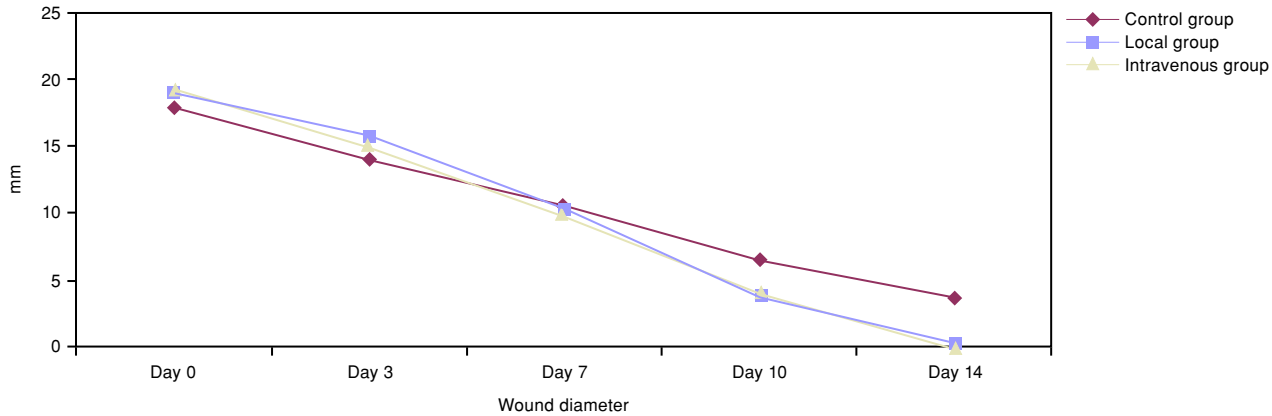

FIGURE 9. Change in wound diameters of control, local and intravenous groups from Day 0 to Day 14.

Wound diameter values of the control group on Day 10 were found to be statistically significantly higher than the local and intravenous groups (p=0.001). In addition, the wound diameter values of the control group on Day 14 were found to be statistically significantly higher than the local and intravenous groups (p=0.001 and p=0.0001) (Table II, Figure 9).

There was no statistically significant difference between the wound diameter on Day 0-3 and on Day 0-7th % change values of the control, local and intravenous groups (p=0.505 and p=0.501); however, a statistically significant difference was observed between the % change values on Day 0-10 and Day 0-14 (p=0.0001 and p=0.0001). Wound diameter changes of the control group on Day 0-10 were found to be statistically significantly lower than the local and intravenous groups (p=0.001). In addition, wound diameter changes of the control group on Day 0-14 were found to be significantly lower than those of the local and intravenous groups (p=0.001 and p=0.0001), and no statistically significant difference was observed between the local and intravenous groups (p=0.146) (Table III, Figure 10). A statistically significant difference was observed between the TGF-B distributions of the control, local and intravenous groups (p=0.0001). The mild presence of TGF-B in the control group was found to be statistically significantly higher than the local and intravenous groups.

None of the subjects died in any group after surgery. Wound infection was not observed in any of the rats during follow-up.

DISCUSSION

Wound healing continues to be an important problem throughout history, both after major traumas and

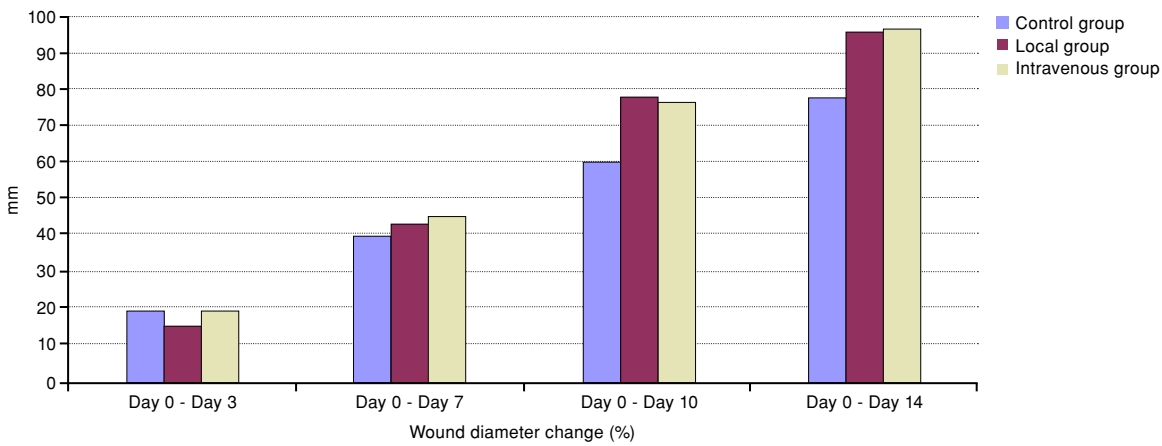

FIGURE 10. Percent change in wound diameter of control, local and intravenous groups.

TABLE III
Comparison of the percentage changes in wound diameter of the control, local and intravenous groups on Days 0, 3, 7, 10, 14

	Control group			Local group			Intravenous group			
Change %	Mean±SD	Median	IQR	Mean±SD	Median	IQR	Mean±SD	Median	IQR	*p*
Day 0-3	21.52±3.26	22.33	18.6-24.46	17.84±6.48	17.44	12-23.86	21.07±10.55	15.91	12.03-33.42	0.505
Day 0-7	42±11.39	46.64	29.09-51.75	47.43±7.19	49.92	39.41-53.36	48.55±3.89	49.31	47.57-51.66	0.501
Day 0-10	63.38±2.9	63.19	60.65-66.08	79.58±3.49	79.6	76.91-82.93	78.88±3.83	78.39	77.98-82.08	**0.0001**
Day 0-14	79.88±1.98	79.73	78.04-81.21	98.65±2.51	100	96.15-100	100±0	100	100-100	**0.0001**

Dunn's Multiple Comparison test	Change (%) Day 10	Change (%) Day 14
Control group/Local group	0.001	0.001
Control group/Local group	0.001	0.0001
Local group/intravenous group	0.834	0.146

SD: Standard deviation; IQR: Interquartile range.

major surgical interventions. Antifibrinolytic drugs and particularly TA are widely used to reduce blood loss both in post-traumatic emergency services and in trauma departments where bleeding operations, such as orthopedics, are performed.[6-8] In a systematic and meta-analysis study of topical and intravenous TA on blood loss and wound healing in bone surgery, Xu et al.[9] reported that it had an equal effect on blood loss after bone surgery and was also beneficial in wound healing. Similarly, in the animal study in which we modeled wound healing, we found that when topical and intravenous TA was applied to the wound area, it has a positive effect on wound healing in the early period compared to the control group.

Tranexamic acid is a drug that has been used for a long time, particularly in orthopedic and cardiovascular surgeries, to stop bleeding.[6,7] In the review of the literature on the use of TA in orthopedic surgery, there have been mostly studies related to intra- and postoperative bleeding.[10,11] Another study showed that TA significantly reduced hemoglobin loss and the number of transfusions in patients who underwent primary unilateral total knee arthroplasty (TKA) compared to the control group, but no significant difference was observed in thromboembolic complications or wound healing.[12] In the English literature, there is a limited number of clinical studies on wound healing of TA and there is no animal study.

Intravenous, topical, and oral routes are available to administer TA; however, the ideal route of TA administration remains unclear and controversial.[13-20] For instance, intravenous administration provides fast and uniform distribution of TA in the knee joint, while locally applied TA quickly reaches the maximum concentration in the knee and does not cause the systemic side effects caused by intravenous TA administration.[15,16] Additionally, Wong et al.[16] reported that locally applied TA in TKA was more effective and caused fewer complications. In the study by Manor and Sadeh,[17] in which water and fat-soluble drugs were injected into the anterior tibial muscles of rats, some amphiphilic and lipid-soluble drugs with heterogeneous pharmacological properties caused acute muscle fiber necrosis while injecting TA, which is one of the water-soluble drugs, caused no tissue damage. This shows that our local application does not cause muscle necrosis. Another study by Reichel et al.[18] showed that TA decreased the migration of inflammatory cells and post-ischemic exaggerated

neutrophilic response in ischemia/reperfusion injury in rats administered *in vivo* TA. Similar to the studies in the literature, there was no additional drug-related inflammation in addition to the surgery-induced inflammation in our study; therefore, it can be speculated that TA application may have an anti-inflammatory effect on wound healing.

Considering the studies on TA in the literature, topically applied TA in rats with Achilles tendon rupture has been found to have a negative effect on tendon healing in the late period, but it has not been reported to have a negative or positive effect on wound healing.[19] In another study, Xie et al.[20] reported a lower incidence of wound complications compared to the control group in their study to evaluate the effect of TA on the reduction of postoperative blood loss in internal fixation and bone graft open reduction applications in calcaneal fractures. In our study, we did not encounter any wound complications, particularly wound infection, in any of the rats during the follow-ups.

Many studies have been conducted showing that TA has an effect on the inflammatory system in addition to its bleeding-reducing feature. In these studies, the authors have mostly advocated the anti-inflammatory effect, but there are also studies showing the pro-inflammatory effect.[21,22] The study of Xie et al.[23] evaluated patients who received intravenous TA at different doses in total hip replacement surgery. The rate of inflammation in the postoperative period in patients who received high doses decreased more than the other groups (lower C-reactive protein and interleukin [IL]-6 levels). On the contrary, in the study of Grant et al.[24] in TKA patients who underwent TA, compared to patients who received TA during surgery and patients who did not receive TA, TA significantly increased monocyte chemoattractant protein-1 (MCP-1), tumor necrosis factor-alpha (TNF-α), IL-1β, and IL-6 levels after surgery compared to patients without TA.[24] In our study, inflammatory parameters were not measured in the blood of rats. This is one of the limitations to our study in terms of inflammation. However, histopathologically, there was no significant difference in the lymphocyte and PMNL values in all three groups in our study.

Wound healing is a process in which three phases: hemostasis-inflammation, proliferation and remodeling follow each other.[25] When we evaluated the inflammation phase of our study, no statistically significant difference was observed between the 14th-day lymphocyte count and PMNL values of the control group, local and intravenous groups. The reason for this may be due to the rapid decrease in PMNL and lymphocyte counts while passing into the proliferation phase, while lymphocyte and PMNL cells are dominant in the hemostasis and inflammation phase, which is the first stage of wound healing. At the end of the inflammation phase, growth factors and cytokines released from platelets attract fibroblasts to the wound and initiate the proliferative phase. In our study, histopathologically, the fibroblast count was statistically significantly higher in those treated with local TA than the control group; however, there was no significant difference between the control and intravenous groups. At the last stage of wound healing, the number of fibroblasts begins to decrease, but the lack of significant difference in the number of fibroblasts between the intravenous and control groups in our study may be due to the measurement made on Day 14. The proliferative phase is characterized by angiogenesis, collagen production and deposition, and wound contraction. In angiogenesis, new blood vessels are formed from epithelial cells, providing nutrients and oxygen for new cells. In epithelialization, epithelial cells proliferate and spread to the wound sites; however, fibroblasts proliferate at the wound site and proliferate by transforming into myofibroblasts.[26] In the current study, the collagen density (%) values of control group on Day 14 were found to be significantly higher than those of local and intravenous group, and no significant difference was observed between local and intravenous group. This is because while the remodeling phase was continuing on Day 14 in local, the wound diameter in local and intravenous group on Day 14 was 0 mm, the wound was completely healed, and the remodeling phase started earlier. In addition, while no significant difference was observed between the control, local and intravenous group wound diameters on Day 0, Day 3, and Day 7, local and intravenous group wound diameters were found to be significantly smaller than local on Day 10 and Day 14. No significant difference was observed between the local and intravenous groups. This result indicates that TA has a positive effect on wound healing and accelerates wound healing compared to local group. However, the fact that there were no significant differences between the wound diameters in local and intravenous did not bring a new perspective to the TA best practice discussion, which is still a controversial issue in the literature.

Various growth factors play a role in wound healing, of which TGF-β is of particular importance for all stages of this process. It has a pleiotropic effect on wound healing by regulating cell proliferation, differentiation, programmed cell death, extracellular matrix production, and modulating the immune response. There are three TGF-β isoforms (TGF-β 1, 2, and 3), each showing a unique expression pattern. There is increasing evidence that TGF-β1 has a profibrotic role both *in vivo* and *in vitro*. The TGF-β3 plays a powerful and specific role in preventing scar formation, while overproduction of TGF-β1 and -β2 isoforms promote scar formation.[26] The TGF-β3 is more common than TGF-β1 in the early stages of wound healing. The TGF-β1 is detected at high levels in wound healing only after epithelialization begins. In particular, recent data have shown that TGF-β1 may have a fibrotic effect, while TGF-β3 may have an anti-fibrotic effect during wound healing and in different tissues (skin, lips, oral and laryngeal mucosa).[27] In our study, TGF-β1 concentration in the local and intravenous groups was found to be statistically significantly higher than the TGF-β1 concentration of the control group. In addition, as the wound diameter on Day 14 was significantly lower in the local and intravenous groups compared to the control group, it can be suggested that TGF-β1 has a profibrotic effect in line with the information in the literature.

The main limitations to our study are that it is an animal study, and an animal model of wound healing can be created with longer follow-up times and more groups for wound healing. In addition, the scaffold (Surgicel™) we used to fix the TA in the wound area in all groups in our study may increase inflammation. Therefore, unused animal model studies should be performed. Furthermore, the level of biochemical indicators in the blood during wound healing can be determined or biomechanical study of resistance to wound tension forces can be conducted.

In conclusion, TA is widely used both topically and intravenously in various doses to reduce the amount of bleeding that can occur after major orthopedic surgery, as well as the amount of blood and blood products that can be used for replacement. As a result of the study we planned, given that when used for this purpose, it may have effects in areas other than its purpose, and TA seems to shorten wound healing time and reduce scarring in rats.

Ethics Committee Approval: Animal care was carried out with the prior approval of the Düzce University Animal Experimental Ethics Committee on 19 February 2019 with approval number 2019/1/7 and was in full compliance with Turkish Law 6343/2, Veterinary Medicine Deontology Regulation 6.7.26, and the Helsinki Declaration of Animal Rights.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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