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ORIGINAL ARTICLE

Histopathological and immunohistochemical investigation of the local and systemic effects of tranexamic acid on the healing of the Achilles tendon in rats

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ABSTRACT

Objectives: This study aims to compare the effects of systemic and local applications of tranexamic acid (TXA) on tendon healing using a rat Achilles tendon injury model.

Patients and methods: Thirty-six adult male albino Wistar rats (aging 3-4 months; weighing 350 to 400 g) were used in this study conducted between December 2019 and January 2020. The Achilles tendon was performed bilateral tenotomy and surgically repaired. Postoperatively, 1 mL of TXA was administered to each leg locally in the local group, whereas 2 mL of TXA was intraperitoneally administered in the systemic group. The control group was left untreated. Half of the rats were sacrificed on Day 15 and the other half on Day 30. Tendon healing was evaluated with the Bonar and the Movin scoring systems and immunohistochemical methods.

Results: The systemic group had the highest Bonar and Movin scores on Day 15. All groups exhibited tendon healing on Day 30, with no significant differences among the groups. The tenocyte morphology was found to be more impaired in both TXA groups on Day 30 (p=0.013). Ground substance scores were lower in the systemic group on Day 30 (p=0.028). The fiber structure and arrangement scores were higher in the systemic group on Day 15 (p=0.007 and p=0.032). Immunohistochemical analyses showed that galectin-3 values exhibited a significant difference in all groups on Day 30 (p=0.020). In all groups, it was determined that type I collagen values showed an increasing trend on Day 30, compared to the values on Day 15, whereas type III collagen values showed a decreasing trend.

Conclusion: Our results demonstrated that local and systemic use of TXA does not impair tendon healing. Although advanced studies are needed, our study suggests that TXA application reduces the development of fibrosis.

Keywords: Achilles tendon, histopathology, immunohistochemical, rat, tranexamic acid.

With its bleeding-reducing feature, tranexamic acid (TXA) is widely used in orthopedic surgeries today.[1] However, there is no current consensus about its optimal dosage, duration of administration and duration of treatment.[1] Although the use of TXA through intravenous (IV) route is an effective and safe way, topical use is particularly recommended for patients with the risk of thromboembolism.[2] In a recent meta-analysis, there was no significant difference between IV and topical administration routes regarding the need for transfusion and postoperative complications.[3]

The tendon is comprised of 95% type I collagen, and a much smaller percentage of type III collagen. The quality of tendon healing is based on the amount and parallel arrangement of the newly formed type I and type III collagen. Type III collagen synthesis begins with angiogenesis and tenocyte proliferation during the inflammatory phase of tendon healing. The second proliferative phase begins 48 h after injury and lasts approximately

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four to six weeks. The synthesis of type III collagen produced by fibroblasts reaches its peak level at this stage. The extracellular matrix synthesized at this stage of recovery consists of type III collagen, with type I collagen being produced in smaller amounts. During this phase, glycosaminoglycan (GAG) content is at its highest level. In the final remodeling phase, collagen fibers are organized, repair tissue changes from cellular to fibrous tissue,[4] and the longitudinal arrangement of fibroblasts and tendon fibers begins. A higher proportion of type I collagen is synthesized, whereas cellularity, and collagen type III and GAG levels decrease.[5] The absence of this reduction results in healing with fibrosis.

Galectin-3 is one of the main molecules of wound healing involved in inflammation, macrophage polarization, angiogenesis, and fibroblast-myofibroblast transition. Its presence in cells such as monocytes, macrophages, neutrophils, and fibroblasts involved in wound healing is known. Galectin-3 has been reported to show different effects in different tissues during the fibrosis process, such as increasing fibrosis in kidney tissue while decreasing it in lung and heart tissues.[6]

The effect of TXA on the surrounding soft tissues is not fully known. Knowing this effect will provide a scientific contribution to the knowledge of tendon healing process in joint surgeries where TXA is used. To the best of our knowledge, there is no study in the literature comparing the effect of systemic and local application of TXA on tendon healing or the effect of the presence of type I or type III collagen on tendon healing through immunohistochemistry. In this study, we aimed to compare the effects of systemic and local applications of TXA on tendon healing using a rat Achilles tendon injury model.

PATIENTS AND METHODS

This study was conducted at Department of Orthopedics and Traumatology, Namık Kemal University, Faculty of Medicine Hospital between December 2019 and January 2020. A total of 36 adult male albino Wistar rats (weighing 350 to 400 g; aging 3-4 months) were used. Rats were separated into three groups, each consisting of 12 rats. The study protocol was approved by the Namık Kemal University Medical Faculty Ethics Committee for Animal Experiments (date: 18 November 2019, no: T2019/365). The study was conducted in accordance with the principles of the Declaration of Helsinki. International guidelines regarding the care and use of laboratory animals were followed.

Following bilateral tenotomy on the Achilles tendons of the rats, 1 mL of TXA (TXA 250 mg/5 mL; Actavis Pharma Inc., Istanbul, Turkey) was administered to each leg locally in the local group. In the systemic group, 2 mL of TXA was intraperitoneally administered after operation for systemic effect. The control group was left untreated. In our study, instead of using the second leg as a control, both legs of the rats were administered TXA and a separate control group was created in

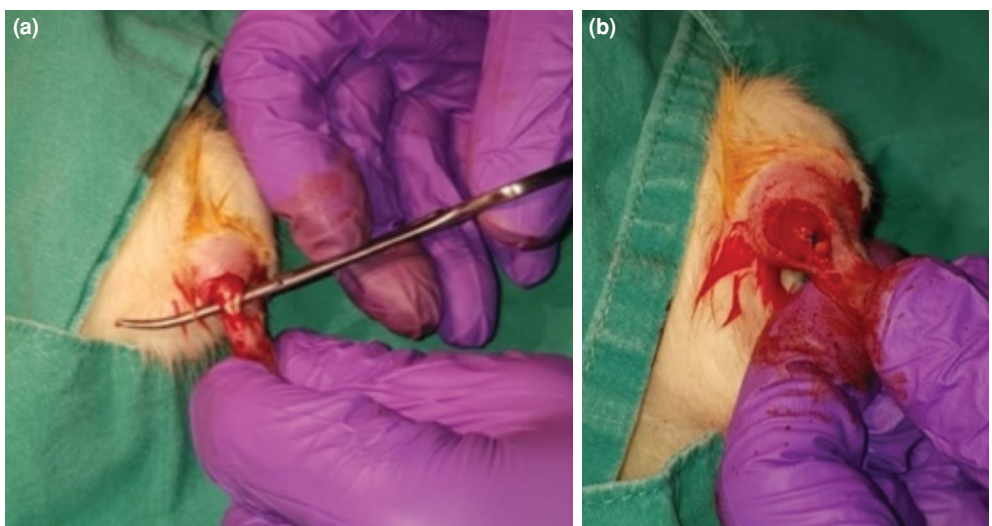

FIGURE 1. (a) Rats were shaved and disinfected with povidone-iodine. Achilles tendon was exposed by an incision through skin and subcutaneous tissue. **(b)** After tenotomy, Achilles tendon was repaired via modified Kessler technique using atraumatic 4-0 polypropylene suture.

order to avoid the possible effect of the drug in the non-injected leg. After the procedure, half of the rats were sacrificed on Day 15 and the other half on Day 30.

Before the operation, gentamicin 8 mg/kg (Genthaver; Osel İlaç Sanayi ve Tic. A.Ş., Istanbul, Turkey) was given for prophylaxis subcutaneously. Surgical procedures were performed under general anesthesia. Inhaler anesthetic drug isoflurane (Forane; Abbott Laboratories Import Export Trade Co. Ltd., Istanbul, Turkey) was administered with 4% dosage for induction and 2% for maintenance. A longitudinal incision of approximately 1 cm was performed on the Achilles tendon. The tendon was exposed and cut transversely from approximately 0.5 cm proximal to the side of Achilles tendon insertion site using a no. 11 scalpel (Plusmed; Trimpeks İth. İhr. Tur. ve Tic. A.Ş., Istanbul, Turkey). The Achilles tendon was then repaired with the Kessler method using an atraumatic 4-0 polypropylene suture (Propilen®; Dogsan Tıbbi Malzeme San. A.Ş., Trabzon, Turkey) and the skin was closed using a 3-0 polypropylene suture (Figure 1).

Postoperative pain management was performed by subcutaneous administration of carprofen 3 to 5 mg/kg (Rimadyl; Pfizer Inc., NY, USA) with 12-h intervals in the first 24 h. No postoperative immobilization method was applied. The rats were fed with standard rodent food (ad libitum) and unlimited water, and were kept under 22°C temperature and 12-h dark-light cycle. During the first 24 h, each cage consisted of one rat; then in the subsequent days, each cage consisted of six rats. In addition to daily wound site assessment, the general condition and the physical activities of the rats were checked and recorded. On Days 15 and 30, euthanasia was performed through high-dose anesthesia (xylazine 10 mg/kg and ketamine hydrochloride 90 mg/kg).

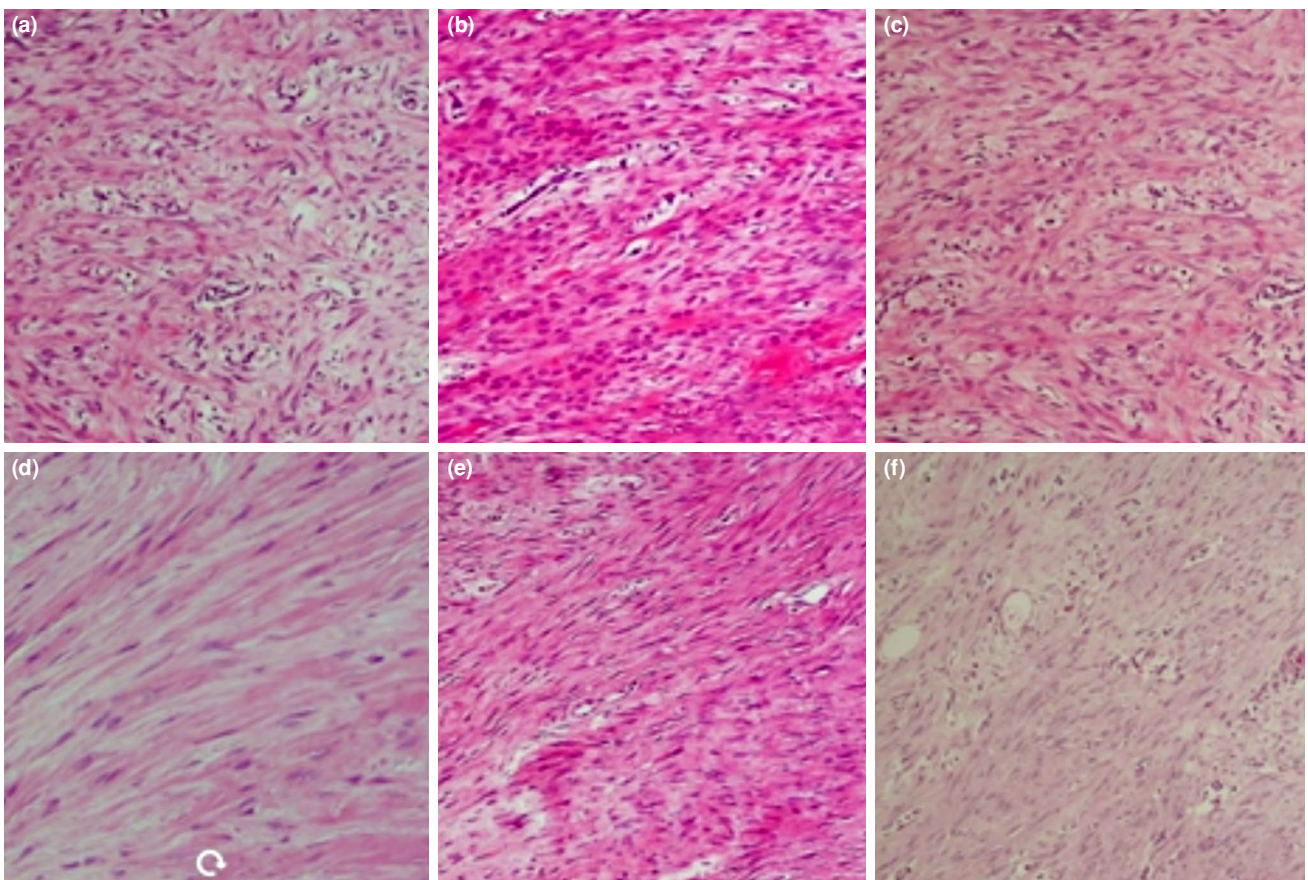

FIGURE 2. **(a)** Tenocyte morphology in control group on Day 15 (hematoxylin and eosin [H-E], ×100). **(b)** Tenocyte morphology in systemic group on Day 15 (H-E, ×100). **(c)** Tenocyte morphology in local group on Day 15 (H-E, ×100). **(d)** Tenocyte morphology in control group on Day 30 (H-E, ×100). **(e)** Tenocyte morphology in systemic group on Day 30 (H-E, ×100). **(f)** Tenocyte morphology in local group on Day 30 (H-E, ×100).

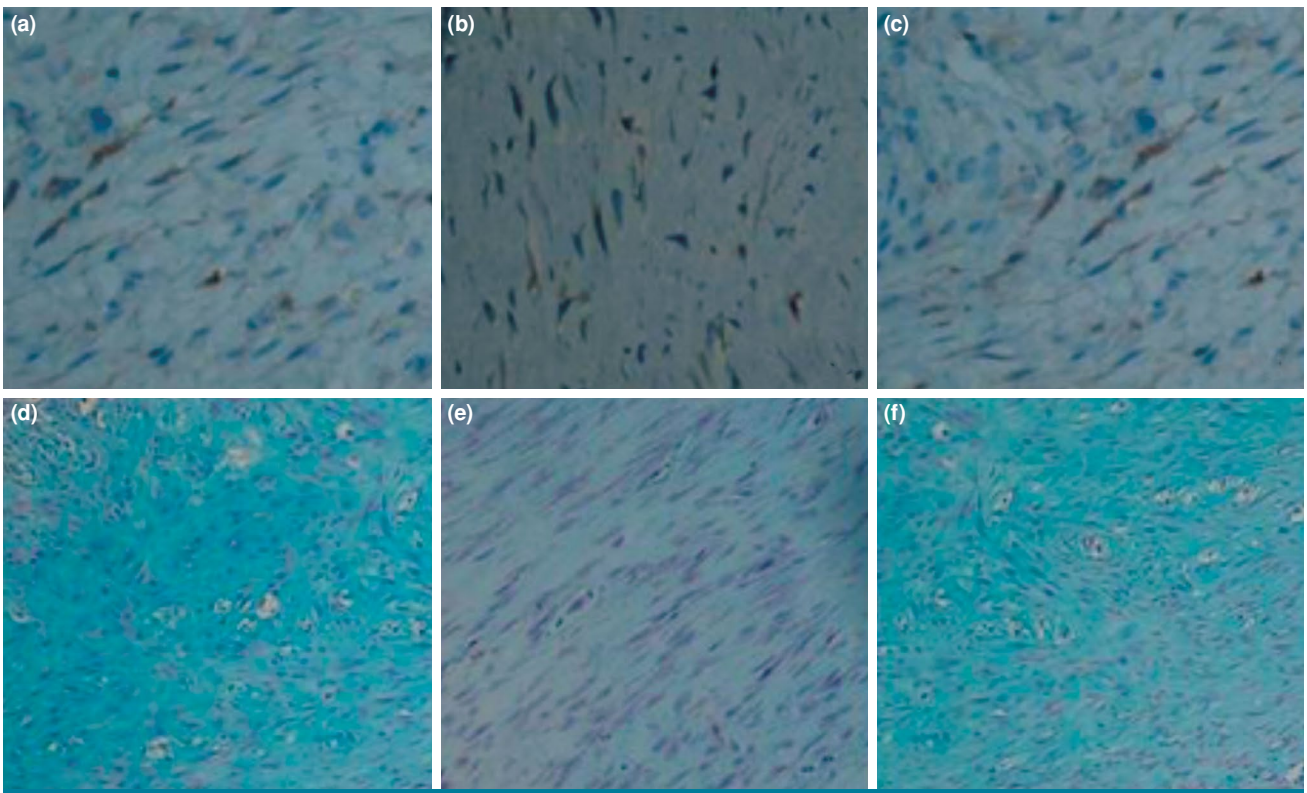

FIGURE 3. (a) Fibroblasts stained with galectin-3 in control group on Day 30 (galectin-3 immunohistochemistry, ×400). **(b)** Fibroblasts stained with galectin-3 in systemic group on Day 30 (galectin-3 immunohistochemistry, ×400). **(c)** Fibroblasts stained with galectin-3 in local group on Day 30 (galectin-3 immunohistochemistry, ×100). **(d)** Glycosaminoglycan content in control group on Day 30 (Alcian blue, ×100). **(e)** Glycosaminoglycan content in systemic group on Day 30 (Alcian blue, ×100). **(f)** Glycosaminoglycan content in local group on Day 30 (Alcian blue, ×100).

Histological analyses were performed by an experienced pathologist who was blinded to the study conditions. For evaluation, tendons were removed with the adjacent bone tissue exposed to the suture area and fixed with a 10% buffered formaldehyde solution. After follow-up and paraffin embedding, 4-micron sections were taken and hematoxylin and eosin staining was performed. The sections taken on the positive charged slides were placed on a BenchMark XT device (Roche Diagnostics Turkey A.S., Istanbul, Turkey) and type I collagen (1:100, Sigma, Saint Louis, USA), type III collagen (1:100, Sigma, Saint Louis, USA), actin alfa smooth muscle type (RTU, Leica, UK) and galectin-3 (RTU, Cell Marque, CA, USA) antibodies were applied and stained with Alcian blue (pH: 2.5) with the VENTANA Benchmark Special Stains immunohistochemistry device (Roche Diagnostics Turkey A.S., Istanbul, Turkey). Results were evaluated using an Olympus CX41 microscope (Olympus Corp., Tokyo, Japan).

Using Bonar scoring, we assessed four variables, namely tenocyte morphology and proliferation, presence or absence of ground substance, collagen bundle characteristics, and vascularity. The numbers ranged from 0 (best) to 3 (worst).[7] In the Movin scale, we assessed eight variables as follows: fiber structure, fiber arrangement, rounding of the nuclei, regional variations in cellularity, increased vascularity, decreased collagen stainability, hyalinization, and GAG content.[8] Each variable was scored from 0 (best) to 3 (worst). Low Movin and Bonar scores indicate sufficient healing, while high scores indicate insufficient healing (Figures 2 and 3).

The amount of type I and type III collagen, the main substance in tendon healing, was evaluated by immunohistochemistry in order to evaluate the healing stages in more detail. Type I collagen, type III collagen and actin alfa smooth mucle type that were applied with immunohistochemistry were scored between 0 and 3 according to the staining intensity

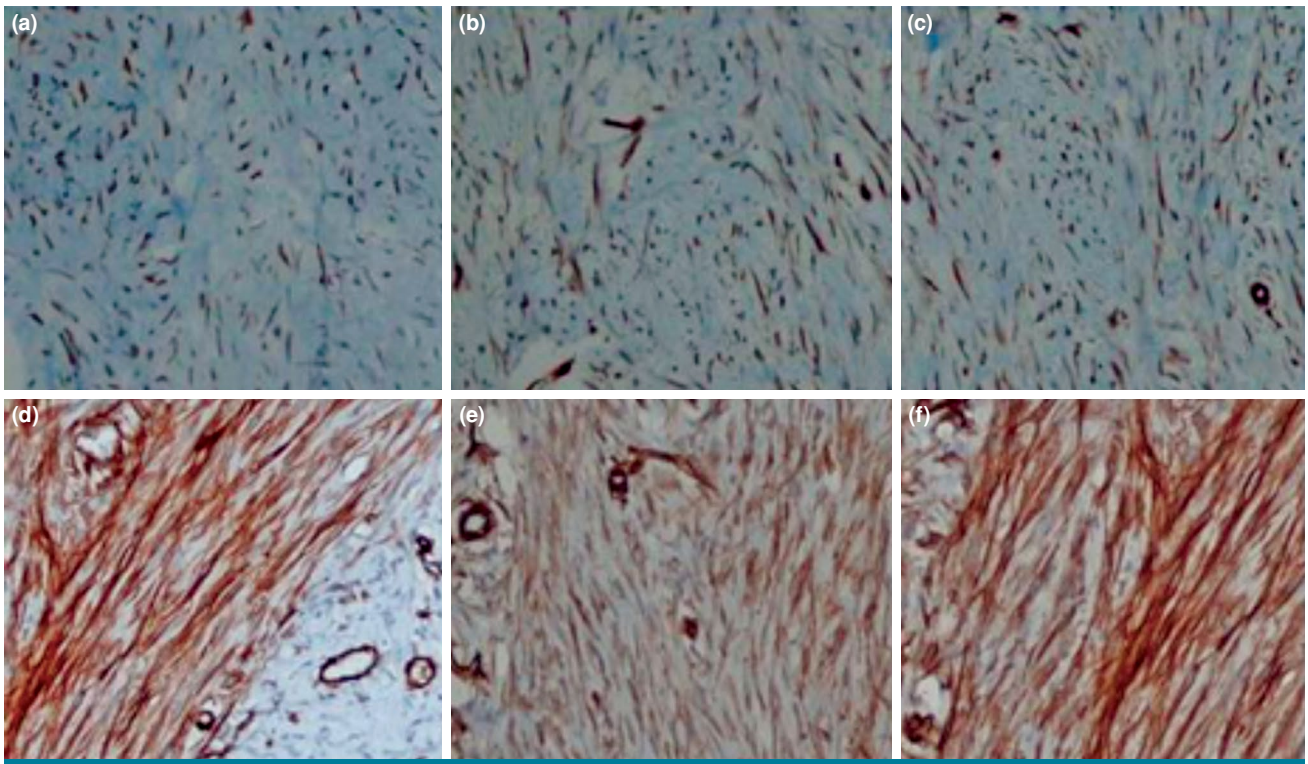

FIGURE 4. (a) Type I collagens in control group on Day 15 (immunohistochemistry, ×100). **(b)** Type I collagens in systemic group on Day 15 (immunohistochemistry, ×100). **(c)** Type I collagens in local group on Day 15 (immunohistochemistry, ×100). **(d)** Type I collagens in control group on Day 30 (immunohistochemistry, ×100). **(e)** Type I collagens in systemic group on Day 30 (immunohistochemistry, ×100). **(f)** Type I collagens in local group on Day 30 (immunohistochemistry, x100).

of tenocytes.[9] In order to evaluate the relationship between galectin-3 and fibrosis, galectin-3 was administered using the immunohistochemical method. In the evaluation of galectin-3, fibroblastic cells stained in a high power field area of ×400 were counted under a light microscope. After fibroblasts were stained with galectin-3, monocytes, macrophages and neutrophil cells were separated and the morphological features of the fibroblasts were analyzed. The area with the highest number of fibroblasts was preferred (Figure 4).

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 23.0 software (IBM Corp., Armonk, NY, USA). The normality of the variables

TABLE I
Statistical analysis of total Bonar and Movin scores

	Local			Systemic			Control			Kruskal-Wallis
	Mean±SD	Median	Min-Max	Mean±SD	Median	Min-Max	Mean±SD	Median	Min-Max	*p*
Total Bonar										
Day 15	8.8±1.3	8.50	7.00-11.00	9.1±1.6	9.00	7.00-12.00	8.8±1.2	8.00	8.00-11.00	0.830
Day 30	8.0±0.6	8.00	7.00-9.00	7.2±1.2	7.00	6.00-9.00	7.2±1.3	7.00	5.00-9.00	0.271
Mann-Whitney U		0.238			**0.026**			**0.031**		
Total Movin										
Day 15	14.6±1.7	14.50	12.00-18.00	16.9±2.4	16.50	13.00-21.00	14.5±2.1	14.50	11.00-18.00	0.054
Day 30	12.0±1.1	12.00	11.00-14.00	12.3±2.4	12.00	9.00-16.00	11.3±1.8	12.00	8.00-13.00	0.850
Mann-Whitney U		**0.008**			**0.007**			**0.013**		

SD: Standard deviation; Significant p values were written in bold.

TABLE II
Histological results according to Bonar histological grading scale

	Local		Systemic		Control		Kruskal-Wallis
	Mean±SD	Median-IQR	Mean±SD	Median-IQR	Mean±SD	Median-IQR	*p*
Tenocyte							
Day 15	2.1±0.6	2.00-0.50	2.5±0.5	2.50-1.00	2.3±0.5	2.00-0.50	0.407
Day 30	2.2±0.4	2.00-0.00	2.3±0.5	2.00-1.00	1.3±0.5	1.00-1.00	0.013
Mann-Whitney U	0.935		0.548		**0.009**		
Ground substance							
Day 15	1.9±0.6	2.00-0.50	1.9±0.8	2.00-1.50	2.1±0.4	2.00-0.00	0.631
Day 30	1.8±0.4	2.00-0.00	1.2±0.4	1.00-0.00	2.2±0.8	2.00-1.00	**0.028**
Mann-Whitney U	0.935		0.082		0.807		
Collagen							
Day 15	1.8±0.7	2.00-1.00	1.8±0.7	2.00-1.00	1.4±0.5	1.00-1.00	0.433
Day 30	1.0±0.0	1.00-0.00	0.7±0.5	1.00-1.00	0.5±0.6	0.50-1.00	0.160
Mann-Whitney U	**0.022**		**0.012**		**0.017**		
Vascularity							
Day 15	3.0±0.0	3.00-0.00	3.0±0.0	3.00-0.00	3.0±0.0	3.00-0.00	1.000
Day 30	3.0±0.0	3.00-0.00	3.0±0.0	3.00-0.00	3.0±0.0	3.00-0.00	1.000
Mann-Whitney U	1.000		1.000		1.000		

SD: Standard deviation; IQR: Interquartile range; IQR: Q3-Q1. Significant p values were written in bold.

was examined by visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov and Shapiro-Wilk tests). Descriptive statistics were presented in mean and standard deviation (SD) for normally distributed variables. In cases where the data did not show normal distribution, the Mann-Whitney U test was used in the comparison of two groups, while the Kruskal-Wallis test was performed in the comparison of more than two groups. A *p* value of <0.05 was considered statistically significant.

RESULTS

The systemic group had the highest Bonar and Movin scores on Day 15 (Bonar score: 9.13±1.55, Movin score: 16.88±2.36). All groups exhibited tendon healing on Day 30 with no significant differences among the groups (Table I). The tenocyte morphology was found to be impaired in both TXA groups on Day 30 (local: 2.17±0.41, systemic: 2.33±0.52, control: 1.33±0.52) (p=0.013) (Table II).

The fiber structure and arrangement scores were higher in the systemic group on Day 15 (p=0.007 and p=0.032). Glycosaminoglycan content scores (1.17±0.41) were lower in the systemic group on Day 30 (p=0.028) (Table III).

Immunohistochemical analyses showed that galectin-3 values exhibited a significant difference among all groups on Day 30 (local: 2.83±2.40, systemic: 1.17±0.41, control: 0.50±0.55) (p=0.020). In accordance with the phases of healing, it was determined that type I collagen values showed an increasing trend on Day 30 compared to the values on Day 15, whereas type III collagen values showed a decreasing trend (Table IV).

DISCUSSION

Our study showed that systemic TXA application partially slowed the tendon healing on Day 15; however, both systemic and local applications of TXA did not have an effect on the tendon healing on Day 30. In addition, TXA application reduced the rate of healing with fibrosis, more commonly in the systemic group.

Tranexamic acid is an antifibrinolytic which prevents the formation of plasmin. With its bleeding-reducing effects, it is used in urological, gynecological, thoracic, and orthopedic surgeries and to prevent post-traumatic hemorrhagic shock.[10,11] For a more effective and safe effect, TXA is used in different forms and combinations (intramuscular, IV, oral or local). It has been reported

TABLE III
Histological results according to Movin histological grading scale

	Local		Systemic		Control		Kruskal-Wallis
	Mean±SD	Median-IQR	Mean±SD	Median-IQR	Mean±SD	Median-IQR	*p*
Fiber structure							
Day 15	1.5±0.5	1.50-1.00	2.1±0.4	2.00-0.00	1.3±0.5	1.00-0.50	**0.007**
Day 30	1.0±0.0	1.00-0.00	1.5±0.6	1.50-1.00	1.2±0.4	1.00-0.00	0.119
Mann-Whitney U		**0.048**		**0.028**		**0.717**	
Fiber arrangement							
Day 15	1.5±0.5	1.50-1.00	2.3±0.7	2.00-1.00	1.4±0.5	1.00-1.00	**0.032**
Day 30	1.2±0.4	1.00-0.00	1.7±0.5	2.00-1.00	1.3±0.5	1.00-1.00	0.213
Mann-Whitney U		0.215		0.112		0.877	
Rounding of the nuclei							
Day 15	2.0±0.5	2.00-0.00	2.4±0.5	2.00-1.00	2.1±0.6	2.00-0.50	0.408
Day 30	1.8±0.4	2.00-0.00	1.8±0.4	2.00-0.00	1.2±0.8	1.00-1.00	0.099
Mann-Whitney U		0.529		0.061		**0.030**	
Regional variations in cellularity							
Day 15	2.5±0.5	2.50-1.00	2.5±0.5	2.50-1.00	2.6±0.5	3.00-1.00	0.851
Day 30	1.3±0.5	1.00-1.00	1.7±0.8	1.50-1.00	1.2±0.4	1.00-0.00	0.423
Mann-Whitney U		**0.006**		0.053		**0.002**	
Increased vascularity							
Day 15	2.5±0.5	2.50-1.00	2.8±0.7	3.00-0.00	2.6±0.5	3.00-1.00	0.418
Day 30	2.7±0.8	3.00-0.00	2.8±0.4	3.00-0.00	2.7±0.5	3.00-1.00	0.803
Mann-Whitney U		0.359		0.916		0.877	
Decreased collagen stainability							
Day 15	1.8±0.7	2.00-1.00	1.8±0.7	2.00-1.00	1.4±0.5	1.00-1.00	0.433
Day 30	1.0±.0	1.00-0.00	0.7±0.5	1.00-1.00	0.5±6	0.50-1.00	0.160
Mann-Whitney U		**0.022**		**0.012**		**0.017**	
Hyalinization							
Day 15	1.0±0.0	1.00-0.00	1.3±0.5	1.00-0.50	1.0±0.0	1.00-0.00	0.124
Day 30	1.2±0.4	1.00-0.00	1.0±0.0	1.00-0.00	1.2±0.4	1.00-0.00	0.588
Mann-Whitney U		0.248		0.202		0.248	
GAG content							
Day 15	1.9±0.6	2.00-0.50	1.9±0.8	2.00-1.50	2.1±0.4	2.00-0.00	0.631
Day 30	1.8±0.4	1.8±0.4	1.2±0.4	1.00-0.00	2.2±0.8	2.00-1.00	**0.028**
Mann-Whitney U		0.935		0.082		0.807	

SD: Standard deviation; IQR: Interquartile range; GAG: Glycosaminoglycan; IQR: Q3-Q1. Significant p values were written in bold.

that the use of TXA on intraarticular joints offers certain advantages, such as low systemic side effects and high concentration in the surgical field.[12] In another study, partial microvascular hemostasis was achieved with topical use.[13] Despite the widespread use of TXA in joint surgeries, our knowledge on its effect on soft tissues is still limited.[12,13] In our study, the well-known Achilles tendon model was used.[14] In our model, the systemic effect was obtained by the administration of TXA through intraperitoneal route, and the local effect through the injection of TXA in the tendon repair site after suturing the skin. In this way, both forms of application of TXA in total knee arthroplasty were simulated.

Review of the literature reveals a limited number of studies investigating the effect of bleeding regulators on tendon healing. Eren et al.[15] showed the positive effect of low-molecular-weight heparin and rivaroxaban on tendon healing in an experimental model in rats. Histopathologically, the authors found

TABLE IV
Statistical analysis of immunohistochemical values

	Local		Systemic		Control		Kruskal-Wallis
	Mean±SD	Median-IQR	Mean±SD	Median-IQR	Mean±SD	Median-IQR	*p*
Galectin-3							
Day 15	3.4±1.9	3.00-3.00	4.0±2.5	4.00-3.50	3.5±2.3	3.00-2.50	0.869
Day 30	2.8±2.4	2.00-3.00	1.2±.4	1.00-0.00	0.5±0.6	0.50-1.00	**0.020**
Mann-Whitney U		**0.019**		0.511		**0.005**	
Alpha-actin							
Day 15	2.0±0.9	2.00-2.00	1.8±0.7	2.00-1.00	1.4±.74	1.00-0.50	0.277
Day 30	1.2±0.4	1.00-0.00	1.2±0.4	1.00-0.00	1.3±0.5	1.00-1.00	0.738
Mann-Whitney U		0.091		0.071		0.871	
Type I collagen							
Day 15	2.7±0.0	3.00-0.00	2.6±0.5	3.00-1.00	2.2±0.5	2.00-1.00	0.055
Day 30	3.0±0.5	3.00-1.00	3.0±0.0	3.00-0.00	2.7±0.5	2.00-1.00	0.059
Mann-Whitney U		0.103		0.089		0.377	
Type III collagen							
Day 15	1.0±0.0	1.00-0.00	1.4±0.5	1.50-1.00	1.1±0.4	1.00-0.00	0.053
Day 30	0.7±0.5	1.00-1.00	0.7±0.4	1.00-0.00	1.0±0.0	1.00-0.00	0.322
Mann-Whitney U		**0.032**		0.089		0.386	

SD: Standard deviation; IQR: Interquartile range; IQR: Q3-Q1. Significant p values were written in bold.

a statistically significant decrease in the Bonar and Movin scores in the study groups ($p<0.05$). Maintenance of microcirculation by preventing clot formation and continued migration of growth factors to the injury site were thought to underlie this positive effect.

In another study, Çıraklı et al.[16] applied TXA locally in an experimental Achilles tendon rupture model and found a negative effect on healing in the long-term. The total Bonar and tenocyte morphology scores also reached higher values in the TXA group at six weeks, compared to the values at three weeks ($p=0.041$ and $p=0.009$, respectively). This effect is associated with angiogenesis in the early period and the decrease in hematoma formation at the later stage. However, the authors observed no significant difference between the control group and the local TXA group in terms of tendon healing scores. Similar to this study, Bonar tenocyte morphology scores on Day 30 of both TXA groups were found to be more impaired than those of the control group in our study.

Based on the tendon healing phases, we found the total Bonar and Movin scores to be higher in the systemic TXA group than in the local and control groups on Day 15. However, this difference was non-significant, indicating that the systemic application of TXA delayed the recovery in the proliferation phase. On Day 30, we observed similar values in all three groups and the recovery was close in each group. Findings of our study support the fact that, although systemic application of TXA delayed the recovery on Day 15, it demonstrated similar outcomes with the local TXA and control groups on Day 30.

Regarding the subgroups of Bonar scoring, the tenocyte scores of the local and systemic groups on Day 30 were significantly higher than the control group, although there was no significant difference between the groups on Day 15. While there was no significant difference in the total Bonar score on Day 30, the difference in the tenocyte score can be explained by the fact that the other parameter in the total score, ground substance values, were lower in both TXA groups on Day 30. The significantly higher ground substance values in the control and local groups on Day 30, while being lower in the systemic group, indicate that systemic TXA application prevents the formation of fibrosis by reducing the GAG amount during the remodeling phase.

The fact that galectin-3 staining was similar in all three groups on Day 15 shows that the fibroblastic activity during the proliferation phase was similar in these groups. However, on Day 30, its level significantly decreased in the local and systemic TXA groups. This may be related to the

fact that local and systemic application of TXA decreases the amount of fibroblasts and prevents fibrosis during the remodeling stage of recovery. Consistent with this result, Emes et al.[17] reported that TXA adversely affected the proliferation and, thus, the number of fibroblasts in the fibroblast cell culture.

In the current study, the Bonar and Movin scores and immunohistochemical findings were consistent with each other. Considering the fact that total Bonar and Movin scores were higher in the systemic group on Day 15, but were similar among all groups on Day 30, while the fiber structure and fiber arrangement according to the Movin score was higher in the systemic group on Day 15, but were similar among all groups on Day 30, we can suggest that, although systemic application of TXA delays recovery in the proliferative phase (Day 15), it catches up with the control and local groups in the remodeling phase (Day 30). In addition, we observed that both local and systemic TXA applications disrupted the tenocyte structure and tended to delay tendon healing on Day 30. Moreover, the significantly lower GAG values in both Bonar and Movin scorings of the systemic group on Day 30, and the significantly lower amount of galectin-3 in both TXA groups, with its level being higher in the systemic group, suggest that TXA application reduces the development of fibrosis. Despite the need for advanced studies on this subject, our study suggests that galectin-3 has a fibrosis-enhancing effect on the tendon tissue.

Nonetheless, this study has some limitations. Since our study has an experimental design, human studies can be more decisive in terms of functional implications. In addition, although we did not perform a biomechanical analysis in this study, we examined tendon healing with both histological and immunohistochemical findings. Later effects on tendon healing, particularly in terms of fibrosis, could be better evaluated with groups of rats being sacrificed in the following months.

In conclusion, our study results show that the systemic use of TXA is associated with a delay in the early period of recovery; however, both local and systemic use of TXA have no adverse effect on the recovery in the long-term. Additionally, TXA seems to be associated with tendon healing with less fibrosis, being more pronounced in systemic use. Based on these findings, we suggest that local and systemic use of TXA do not impair tendon healing process during surgeries performed in the adjacency of the tendon, such as total knee arthroplasty.

Declaration of conflicting interests

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