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ORIGINAL ARTICLE

The histological effect of tranexamic acid on tendon-to-bone healing histologically in rats

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ABSTRACT

Objectives: In this study, we aimed to investigate the effect of tranexamic acid (TXA) on osteotendinous junction healing in a rat model, both biomechanically and histologically.

Materials and methods: Sixty-four male Wistar-Albino rats weighing 450 to 600 g were used in this study. The rats were divided into two groups as the experimental (n=16) and control (n=16) groups. Achillotomy and subsequent repair site was exposed to 1 mL of TXA in the experimental group, while 1 mL of saline was given to the control group. For biomechanical and histopathological investigation, each group was further divided into two subgroups. At the end of four weeks, all rats were sacrificed. Biomechanical tests were performed using the M500-50CT device. The Bonar, Movin, and Nourissat bone-tendon junction scoring systems were used for histopathological evaluation.

Results: There was no statistically significant difference in the elongation at a maximum point, maximum loading, and maximum stress variables in the biomechanical study (p=0.558 p=0.775, and p=0.558, respectively). In the histopathological evaluation, the collagen content and layout were close to the native tissue in the experimental group (p=0.047 and p=0.008, respectively). Vascularity, hyalinization, and glycosaminoglycan content were significantly lower in the experimental group (p=0.004, p=0.014, and p=0.026, respectively). The total Bonar and Movin scores were more favorable in the experimental group (p<0.001).

Conclusion: This experimental study showed that local administration of TXA accelerated bone-tendon junction healing in rats.

Keywords: Achilles tendon, bone, tendons, tranexamic acid.

Tendon-to-bone enthesis is a unique structure which plays an important role in balanced transmission of forces through tendon to bone.[1] However, this feature makes it somewhat prone to injuries. Enthesis injury includes Achilles tendon rupture, anterior cruciate ligament (ACL) injury, and rotator cuff tears.[2,3] Surgical treatment is the mainstay of treatment.[2,3] Tendon integration to bone and bone ingrowth to the tendon bone interface is the main goal of treatment, and achieving a successful result is rather challenging.[4] Avascular nature of the fibrocartilage tissue and difficulties in obtaining healing between heterogenous tissues are the main handicaps for healing. Additionally, limited regeneration potential of mammals and healing with dominant inflammatory processes usually end up with a hypertrophic scar tissue which has inferior properties of mechanical strength and histological features than original enthesis tissue.[5]

Multiple animal models have shown a perfect healing of the enthesis macroscopically, but hypercellularity and failure of organization of extracellular matrix and lack of fibrocartilage

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continuity of bone and tendon microscopically.[6-8] Tendon and bone have different mechanical features. Imbalanced weight distribution may cause an injury in the osteotendinous junction.[9] For this purpose, various adjuvants have been experienced to accelerate healing and obtain an enthesis tissue that is closest to its original pair. Osteoinductive and osteoconductive agents, platelet-rich plasma, growth factors are existing adjuvants that have been used for this purpose. Animal models have demonstrated favorable results of these products in terms of tendon-to-bone healing. Effects of non-steroidal anti-inflammatory drugs, bisphosphonates are the pharmacological agents that have been studied under this topic and controversial results have been reported.[8]

Tranexamic acid (TXA) is a synthetic analog of lysine, which has been used widespread recently and shown to reduce bleeding about 34%.[10] Clinical studies have shown that its usage may decrease bleeding and transfusion requirement in traumatic hemorrhages, cesarean delivery, endoscopic sinus, cardiac, and orthopedic surgeries.[11-15] Irrelevant from its mechanism of action, it has been also shown to relieve postoperative pain and provide an early rehabilitation following rotator cuff surgery and ACL reconstruction.[16,17] Recently, anti-inflammatory effect of TXA has been revealed.[18] Despite the unfavorable effects on soft tissue healing, its effect on osteotendinous junction has not been investigated yet.[19,20] In the present study, we aimed to investigate the effect of TXA on osteotendinous junction healing in a rat model, both biomechanically and histologically.

MATERIALS AND METHODS

Study subjects

This study was conducted at Cukurova University, Faculty of Medicine and Cukurova University Health Sciences Experimental Application and Research Center between November 2019 and December 2019. The study protocol was approved by the Çukurova University Animal Experiments Local Ethics Committee (Date: 04.11.2019, No: 6/4).

A total of 64 male Wistar Albino rats weighing between 450 and 600 g were used in this study. The subjects were divided into two groups as the experimental (n=16) and control (n=16) groups. Achillotomy and subsequent repair site was exposed to 1 mL of TXA in the experimental group, while 1 mL of saline was given to the control group. For biomechanical and histopathological investigation, each group was further divided into two subgroups. Resemblance to human anatomical and physiological features and cost-effectiveness were in favor of the choice of rats as an experiment. As described in the literature, enthesis pathology models, such as tendinosis and tendon-to-bone healing on rats are feasible to obtain.[21]

Surgical technique

General anesthesia was maintained by intraperitoneal ketamine hydrochloride (50 mg/kg, Ketasol® %10, Richter Pharma AG, Wels-Austria) and xylazine hydrochloride (5 mg/kg, Basilazin® 2%, Bavet İlaç Sanayi ve Ticaret A.Ş., Istanbul, Turkey). The posterior calves of the subjects were shaved and cleaned with povidone-iodine (Batticon®, Adeka İlaç Sanayi ve Ticaret A.Ş., Samsun, Turkey) solution to disinfect the surgical site. Once the foot was dorsiflexed, Achilles tendon was palpated and a 2-cm longitudinal incision from the calcaneus distally to the gastrocsoleus complex proximally was made (Figure 1a). Following hemostasis, the tendon was dissected and its insertion site to calcaneus was revealed. Plantaris tendon was secured and calcaneus tendon was tenotomized with a sharp incision (Figure 1b). Two intraosseous tunnels were created with the help of Kirschner wires from the original insertion site of the Achilles tendon to the plantar surface of calcaneus. No. 3/0 Polypropylene suture (Prolene®, Ethicon Inc., NJ, USA) was implemented to tendon with the modified Kessler technique and passed through the tunnels (Figure 1c). Following the adjustment of appropriate tension, the sutures were tied. The layers were closed with No. 3/0 polypropylene suture and 1 mL of TXA (Tranexel®, 250 mg/5 mL, Haver Pharma İlaç A.Ş., Istanbul, Turkey) was applied through the incision to the repair site for experimental group (Figure 1d). In the control group, 1 mL of saline solution was used. Prophylactic antibiotic was not administered before or after surgery.

Follow-up

Mobilization was allowed early after surgery. Wound dressings were removed on the first day of surgery. During the four-week follow-up period, there were no complications such as wound problem, exitus, or re-rupture of the tendon. Conditions of the room and cages of the subjects were standardized in terms of feeding, room temperature, and humidity. Nursing of the cages was performed daily.

Euthanasia and preparation of materials

The rats were sacrificed with cervical dislocation technique on Day 28 after surgery. No suture

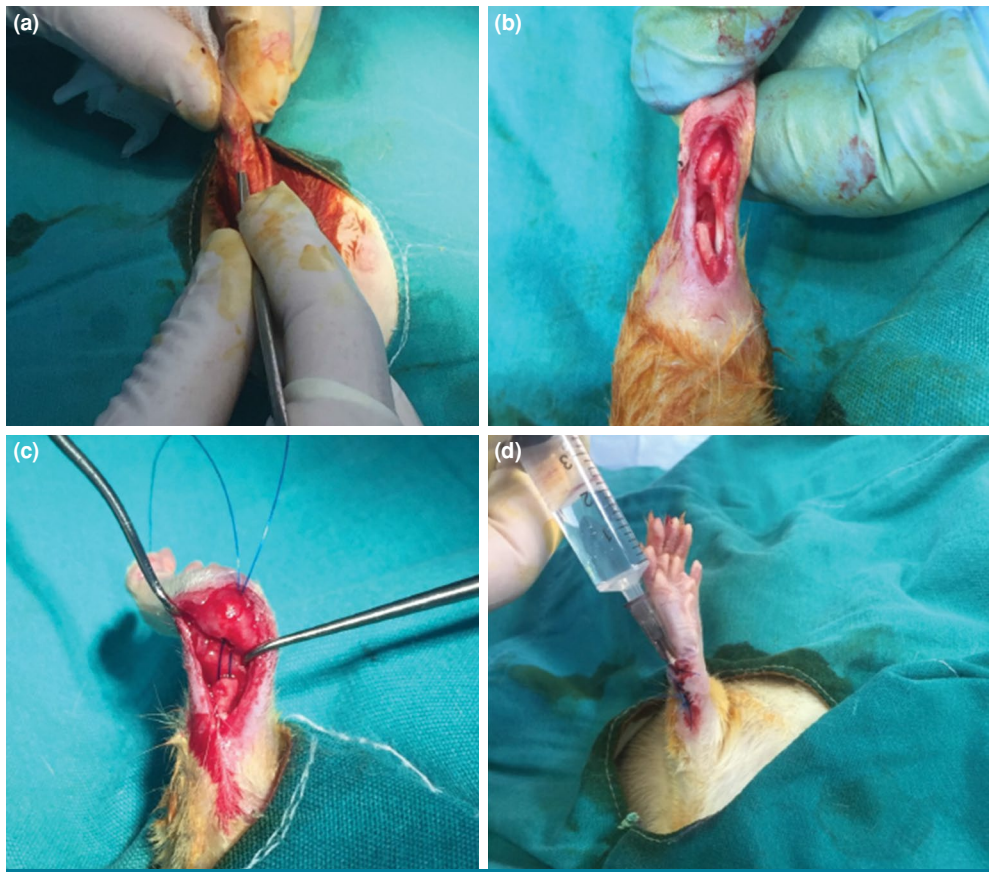

FIGURE 1. (a) Dorsiflexion of the foot and skin incision over the Achilles. **(b)** Tenotomized Achilles tendon and preserved plantaris tendon. **(c)** Suturing the Achilles tendon with the modified Kessler technique and passing the sutures through the tunnel. **(d)** 1 mL of tranexamic acid injection through the incision site.

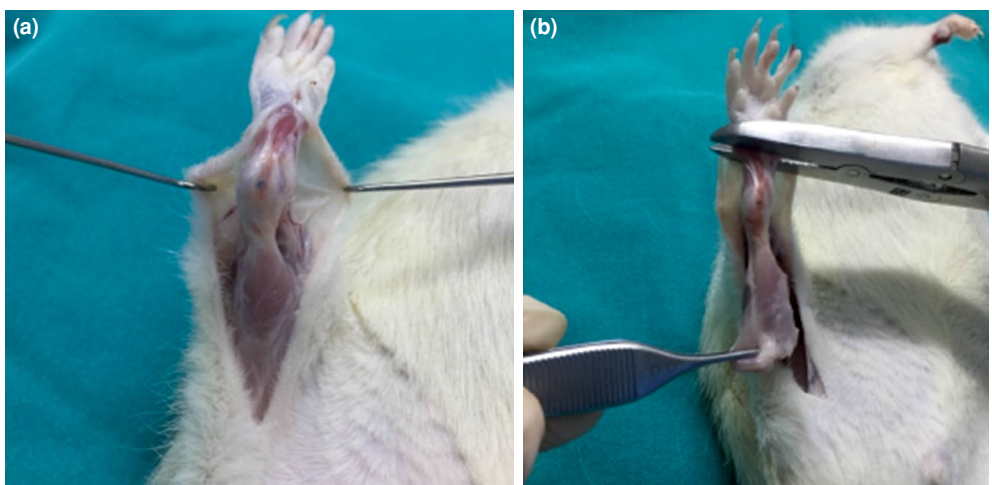

FIGURE 2. (a) Healed tendon-bone junction. **(b)** Calcaneus was disarticulated from midfoot and ankle, while the repair site was preserved. Gastrocsoleus complex was dissected and cut proximally.

material reactions and additional complications were observed. Incisions were performed through the previous incision site. Tendon-bone junctions seemed to heal in all animals (Figure 2a). No re-rupture was encountered. Calcaneus was disarticulated from the midfoot and ankle, while the repair site was preserved. The gastrocsoleus complex was dissected and cut proximally (Figure 2b). All the specimens were put into the formaldehyde impregnated sponges. Biomechanical and histopathological groups including an equal number of specimens were formed.

Biomechanical evaluation

Following the sacrifice, Group A (n=16) and Group C (n=16) were prepared for biomechanical evaluation. The gastrocsoleus muscle complexes were sutured to a 1.5-cm width of non-elastic fabric wrapped around the complex to prevent the slip from device (Figure 3a). Tests were performed using the M500-50CT device (Testometric Co. Ltd., Greater Manchester, U.K). Calcaneus was inserted into the distal site and gastrocsoleus muscle complex was inserted into the proximal site. The process was continued until avulsion was observed from the healing site (Figure 3b). Maximum loading, maximum stress, and elongation at a maximum point were recorded.

Histopathological evaluation

Specimens obtained from Group B (n=16) and Group D (n=16) were put into the 10% formaldehyde impregnated sponges. All specimens were evaluated by a blinded pathologist. After the fixation with paraffin blocks, histological samples were obtained and stained with hematoxylin-eosin, Alcian blue, and Masson's trichrome. The specimens were classified according to Bonar, Movin and Nourissat tendon-bone junction scoring systems.

The Bonar scoring system was first defined by Cook et al.[19] There are four items in this system including tenocytes, ground substance, collagen, and vascularity. A four-point scoring system is used, where 0 indicates a normal tissue structure and 3 an abnormal appearance. The total score ranges from 0 (normal tendon, very good healing) to 12 (most severe detectable pathology, very poor healing).

Similarly, Movin et al.[20] described a grading scale consisting of eight items including fiber structure, fiber arrangement, rounding of the nuclei, regional variations in cellularity, increased vascularity, decreased collagen stainability, hyalinization, and glycosaminoglycan (GAG) content. Each item is scored between 0 and 3, where 0 indicates normal and 3 markedly abnormal results. The total score ranges from 0 (normal tendon, very good healing) to 24 (most severe detectable pathology, very poor healing).

Nourissat et al.[21] developed another scale to evaluate the quality of the enthesis tissue according to the tissue contents including the percentage contact between bone and tendon with type II collagen production, type II collagen organization, chondrocyte organization, and GAG production.

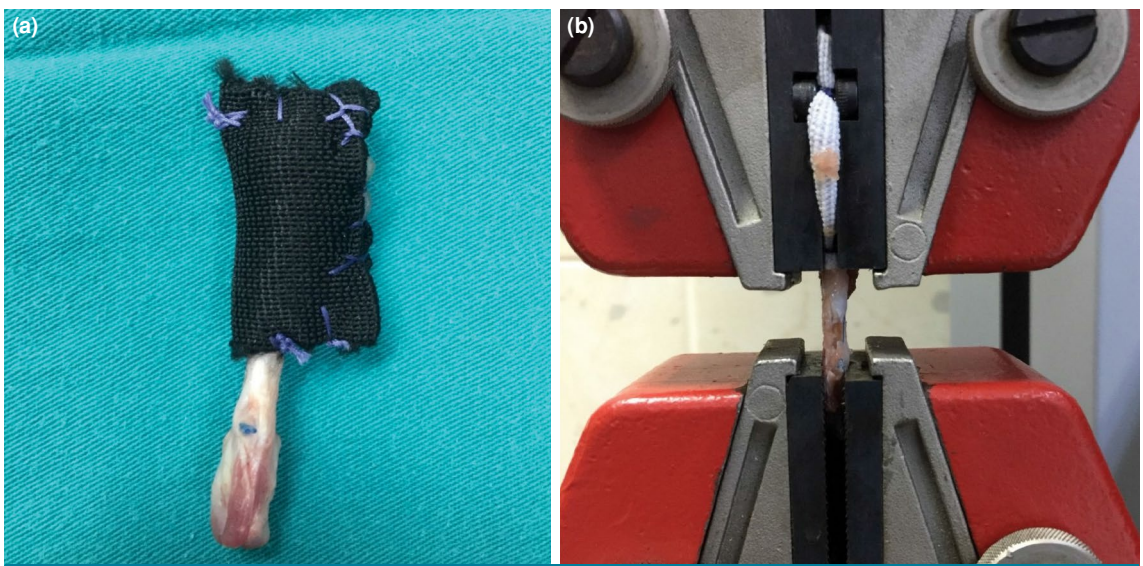

FIGURE 3. (a) Gastrocsoleus muscle complexes were sutured to a 1.5-cm width of non-elastic fabric wrapped around the complex to prevent the slip from device. **(b)** Tendon-bone junction rupture moment.

This scoring system uses a four-point scale and the total score ranges from 0 to 15. The native enthesis always scored 16 points in double-blind studies.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 25.0 software (IBM Corp., Armonk, NY, USA). Continuous variables were expressed in mean ± standard deviation (SD) or median (min-max), while categorical variables were expressed in number and frequency. Since the parametric test assumptions were not met, continuous variables were compared using the Mann-Whitney U test. Correlation between the variables was analyzed using the Spearman correlation analysis. A p value of <0.05 was considered statistically significant.

TABLE I
Biomechanical test results of specimens

Test no	Elongation at break (mm)	Elongation at peak (mm)	Energy at break (Nm)	Force at break (N)	Force at peak (N)	Strain at break (mm)	Strain at peak (Nm)
1	6.640	4.079	0.1855	2.300	57.00	9.486	5.827
2	14.651	10.330	0.6538	50.200	67.60	20.930	14.757
3	14.671	5.527	0.9019	42.500	91.30	20.959	7.896
4	8.366	6.619	0.3334	22.400	75.20	11.951	9.456
5	5.556	4.601	0.1926	24.900	69.20	7.937	6.573
6	11.808	10.056	0.5572	44.700	72.90	16.869	14.366
7	6.514	4.909	0.3048	60.100	77.10	9.306	7.013
8	10.465	6.532	0.5871	58.300	85.50	14.950	9.331
9	11.935	5.525	0.5181	42.200	63.60	17.050	7.893
10	10.263	5.878	0.5450	46.300	81.90	14.661	8.397
11	11.250	5.695	0.5122	44.600	64.20	16.071	8.136
12	9.859	6.550	0.5121	26.400	92.40	14.084	9.357
13	15.802	11.807	0.8353	65.100	72.70	22.574	16.867
14	5.508	4.235	0.3529	39.500	115.80	7.869	6.050
15	8.197	6.381	0.3786	59.700	74.00	11.710	9.116
16	6.265	5.085	0.2955	53.400	86.80	8.950	7.264
17	7.285	4.675	0.3888	58.000	85.30	10.407	6.679
18	7.199	3.584	0.2922	45.300	55.40	10.284	5.120
19	8.646	6.891	0.6430	48.500	98.90	12.351	9.844
20	8.422	6.801	0.3323	42.800	75.70	12.031	9.716
21	4.831	2.925	0.2004	21.900	64.00	6.901	4.179
22	8.954	6.521	0.4392	17.200	83.90	12.791	9.316
23	10.852	9.175	0.5182	50.300	62.30	15.503	13.107
24	11.794	4.610	0.3001	-2.700	77.50	16.849	6.586
25	11.734	4.541	0.6151	47.600	79.80	16.763	6.487
26	7.035	5.385	0.2854	34.900	67.80	10.050	7.693
27	7.146	3.333	0.3285	47.900	69.10	10.209	4.761
28	9.361	3.552	0.3171	6.000	67.30	13.373	5.074
29	8.533	5.268	0.3221	30.300	68.60	12.190	7.526
30	7.787	5.239	0.3230	42.900	65.30	11.124	7.484
31	6.176	3.938	0.2917	2.500	91.60	8.823	5.626
32	21.585	5.134	0.5261	1.500	76.50	30.836	7.334

RESULTS

Biomechanical results

Biomechanical tests of Groups A and C were performed immediately after the sacrifice. Median maximum elongation value was 5,326 mm, ultimate load-to-failure was 7,700 N, and maximum stress was 7,609.5 N in Group A. Median maximum elongation value was 5,101 mm, ultimate load-to-failure was 8,460 N, and maximum stress was 7,287.5 N in

TABLE II
Statistical analysis of biomechanical results

	Saline (n=16)		Tranexamic acid (n=16)		
	Median	Min-Max	Median	Min-Max	*p*
Elongation at maximum point (mm)	5,101	3,333-10,056	5,326	2,925-11,807	0.558
Maximum load (n)	8,460	5,540-91,300	7,700	6,360-85,500	0.775
Maximum strain (%)	7,287.5	4,761-14,366	7,609.5	4,179-16,867	0.558

TABLE III
Analysis of the groups according to Bonar scoring system

	Saline			Tranexamic acid			
	Mean	Median	Min-Max	Mean	Median	Min-Max	*p*
Tenocytes	2.2	2	1-3	1.5	1.00	-	0.051
Ground substance	2.0	2	1-3	1.7	2	1-3	0.305
Collagen	2.1	2	0-3	1.1	1	0-3	**0.008**
Vascularity	2.9	3	2-3	2.0	2	1-3	**0.004**
Bonar scoring	9.2	10	5-12	6.3	6	3-12	**0.003**

TABLE IV
Analysis of the groups according to Movin scoring system

	Saline			Tranexamic acid			
	Mean	Median	Min-Max	Mean	Median	Min-Max	*p*
Fiber structure	1.9	2	1-3	1.4	1	0-3	0.210
Fiber arrangement	1.9	2	1-3	1.4	1	0-3	0.210
Rounding of the nuclei	1.7	2	1-3	1.1	1	0-2	0.073
Regional variations in cellularity	1.7	2	1-3	1.4	1	0-2	0.341
Increased vascularity	2.9	3	2-3	2.0	2	1-3	**0.004**
Decreased collagen stainability	1.7	2	1-2	1.2	1	0-2	**0.047**
Hyalinization	1.2	1	0-2	0.6	0	0-2	**0.014**
GAG content	2.0	2	1-3	1.7	2	1-3	0.305
Movin scoring	14.9	15	8-22	10.8	10	3-19	**0.023**

TABLE V
Analysis of the groups according to histologic healing score defined by Nourissat at al.[21]

	Saline			Tranexamic acid			
	Mean	Median	Min-Max	Mean	Median	Min-Max	*p*
Cell at bone-tendon junction	2.6	3	2-3	1.9	2	1-4	**0.032**
Glycosaminoglycan content	2.7	3	2-3	2.2	2	1-3	**0.026**
Collagen organization	2.4	2	2-3	3.0	3	2-4	**0.043**
Chondrocyte organization	2.8	3	2-4	3.2	3	1-4	0.086

Group C. Avulsion of healing site was observed in 10 and 11 specimens in the experimental group and saline group, respectively. There was no statistically significant difference in the rates of load-to-failure between the groups (Tables I and II).

Histopathological results

Groups B and D were compared in terms of fibrillary structure, chondrocyte and collagen layout, cellularity, vascularity, hyalinization, and GAG content. These parameters were classified according to the Bonar,

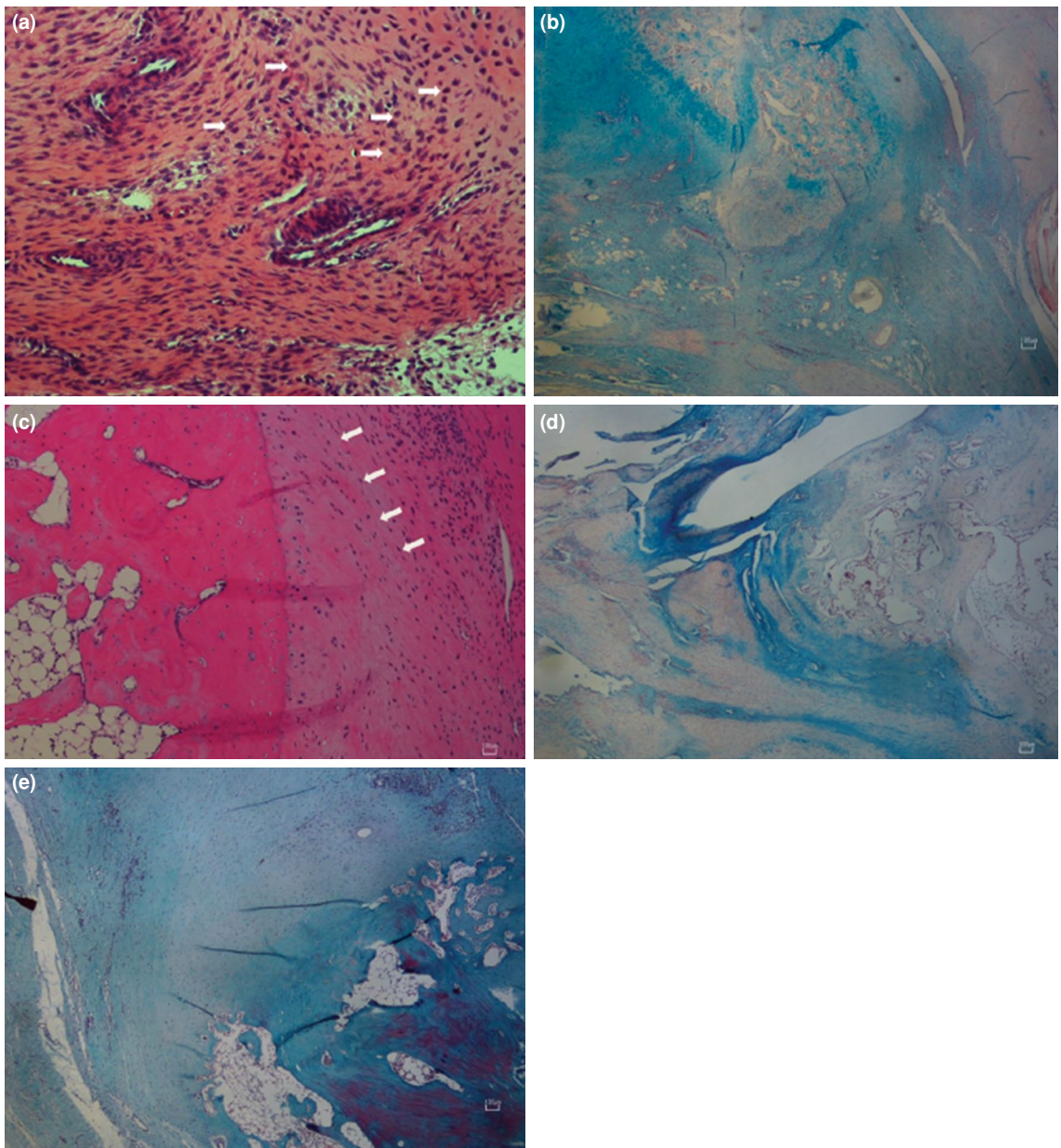

FIGURE 4. (a) Histological preparation of the control group (H-E, ×200). Rounding of tenocyte nuclei (arrow) and increased vascularity are seen. Disorganized chondrocytes are observed in the area of enchondral ossification. Columnar structure is not visible. **(b)** Histological preparation of the control group (Alcian blue, ×40). Extensive accumulation of glycosaminoglycan is seen at the tendon-bone junction. **(c)** Histological preparation of the experimental group (H-E, ×200). Columnar alignment (arrow) in chondrocytes and rare vascularity are seen. Tenocyte nuclei are observed as spindle-shaped. **(d)** Histological preparation of the experimental group (Alcian blue, ×40). There is mild GAG accumulation at the tendon-bone junction. **(e)** Increased collagen at tendon-bone junction in the experimental group (Masson's trichrome, ×40).

Movin scoring systems and histologic healing score defined by Nourissat at al.,[21] (Figure 4a-e). Group B had a significantly lower Bonar score indicating better healing than Group D (p=0.003) (Table III). The Movin score of Group B was also significantly lower than Group D, indicating better healing (p=0.023) (Table IV). Correlation between the Movin and Bonar scoring systems was identified to ensure the reliability of the results. A strong, positive correlation was found between the two scoring systems (p<0.001). In addition, the Nourissat tendon-bone junction scoring system showed significantly better results in cellularity, GAG content, and collagen organization in the experimental group (p=0.032, p=0.026, and p=0.043, respectively) (Table V).

DISCUSSION

In the present study, TXA was found to accelerate tendon-to-bone healing histologically in rats. Although there was no significant difference between the groups in terms of mechanical strength, histological evaluation of the healing site demonstrated better healing in the experimental group. This can be attributed to the modulatory effects of TXA on inflammatory cascade of the healing process.

In the literature, TXA is not classified as pure anti-inflammatory or proinflammatory molecule. Animal models and clinical studies have shown that systemic administration of high-dose TXA has both anti-inflammatory effects with a subsequent decline in the mononuclear cell recruitment and pro-inflammatory effects with the early increase in the monocyte chemotactic proteins and tumor necrosis factor-alpha (TNF-α) levels. Local administration of the TXA has already been proven to prevent blood loss during arthroplasty procedure, as it is in systemic use. Therefore, the molecule appears to be also active in the local route. Based on this rationale, two inferences can be made. First, since TXA is an effective molecule in inflammatory processes, it may also play a role in tendon-to-bone healing. Second, TXA is also a biologically active molecule through a direct application on the tissues. In our study, we hypothesized that TXA could promote enthesis tissue after surgical repair.

Investigations of human surgical healing of enthesis have mostly focused on ACL reconstruction surgeries. Several studies have shown that Sharpey-like fibers were formed at the healing site instead of the original enthesis tissue.[22,23] Thus, delayed interface healing between tendon and bone or lack of fibrocartilage or fibroosseous connection is thought to be causative factors that lead to the failure of repair. Although some authors have claimed that there is no relationship between the histological healing and mechanical strength, acquiring an original enthesis tissue after surgical repair has still been the center of interest.[24,25] Osteoinductive growth factors and osteoconductive materials were attempted to be used as a tendon-to-bone healing enhancer previously.[26,27] Growth factors such as transforming growth factors, bone morphogenic proteins, fibroblast growth factor, and granulocyte colony-stimulating factor were shown to have a promoter effect on healing.[8] Protein-rich plasma, fresh autologous bone marrow, and periosteal envelope wrapping also appeared to have a positive effect on enthesis healing, since they recruit many growth factors, mesenchymal stem cells, and progenitor cells.[8] Calcium and magnesium-embedded matrix or biocement are osteoconductive agents that are used for tendon-to-bone healing.[28,29] Although the exact mechanism of their contribution to healing is unknown, they can, theoretically, act as a scaffold and provide a more appropriate circumstances for bony ingrowth. A rabbit model showed that calcium-phosphate-hybridized tendon graft to a bone tunnel was similar to native ACL bone junction.[28]

Variable pharmaceutical agents were investigated in terms of their effect on enthesis tissue. Considering the inhibitory effect on osteoclasts, zoledronic acid was thought to diminish the bone loss adjacent to tendon and promote the healing. Somehow, animal studies revealed that no differences were shown between the groups.[30] The widespread use of cyclooxygenase inhibitors for pain relief made it necessary to investigate their effects on tendon to bone healing. Ferry et al.[31] showed that anti-inflammatory drugs, except for ibuprofen, had a negative effect on ultimate biomechanical and histological healing. In our study, the experimental group showed better histological healing; however, biomechanical features of the experimental and control groups were comparable. Early achievement of tendon-bone junction equivalent to original enthesis may have clinical importance in terms of application of more advanced rehabilitation program in the clinical practice. Therefore, TXA can be an advantageous molecule, while preventing bleeding during the operation and providing an early healing of enthesis.

The effect of TXA on both tendon and bone healing has been previously studied separately and controversial results have been reported. Cirakli et al.[32] investigated the effect of local usage of TXA on repair site after tenotomy. They found that, although

healing appeared to be better at three weeks, worse healing scores were obtained at six weeks compared to the saline group. The aforementioned authors observed the TNF-α and matrix metalloproteinase-3 (MMP-3) levels immunohistochemically at three weeks of local TXA application following tendon repair.[32] They found increased levels of both MMP-3 and TNF-α at the repair site and concluded that increased levels of both agents could promote the healing. Local application of TXA was also investigated in fracture treatment. Cevik et al.[33] designed a study which revealed its effects on fracture healing in both systemic and local application. Systemic administration of TXA had a negative effect on bone healing; however, local use promoted the bone healing. Negative effect of systemic usage was attributed to the diminished fracture hematoma which contains both the inflammatory mediators and osteoinductive components. Antifibrinolytic effect of the drug could prevent degradation of fibrin clot which could lead to preservation and increase of scaffold for bone healing. Since the local application of TXA was defined to have a promoter effect on bone healing, it could also have a favorable effect on enthesis healing by increasing the bony ingrowth to the tunnel. In the current study, we evaluated the specimens at four weeks of follow-up and achieved better histological scores in the experimental group, compared to the control group. Nevertheless, longer-term results may be more enlightening about the ultimate quality of healing for both groups.

Rats are invaluable models to perform Achilles tendinosis and tendon injury and, therefore, we preferred a rat model in our study. However, this model has a limited potential of reflecting the human physiology, and goat, dog or ovine models are considered more representative for human studies. Thus, performing similar studies with alternative animal models can provide more accurate findings. In this study, all surgeries were performed by a single surgeon and histological evaluation was made by a single blinded pathologist. Biomechanical tests were performed immediately after the euthanasia of the experimental group using the same Testometric M500-50CT device. These are the main strengths of the study. In addition, all samples were collected at a certain time period that could may have eliminated the variability of the results at a different period of follow-up for both groups. Therefore, we could only make interpretations about the time elapse for enthesis tissue healing in this study. Further studies including longer follow-up and multiple sample collection at different time points may provide a more detailed information about the healing quality and biomechanical features of the healing tissue.

In conclusion, our study results suggest that the topical use of TXA accelerates the healing process of tendon-to-bone injury. Further studies investigating the inflammatory and anti-inflammatory effects of the molecule would be helpful to gain a better understanding of the exact mechanism of its enhancer effect of enthesis healing.

Declaration of conflicting interests

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