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Effects of Cyanoacrylate in Rabbits with Induced Achilles Tendon Rupture

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Background: In this study, we aimed to investigate the effects of N-butyl-2-cyanoacrylate (cyanoacrylate) on the biomechanical and histopathological aspects of tendon healing in a rabbit model of Achilles tendon injury.

Material/Methods: In total, 36 rabbits were randomized to experimental (cyanoacrylate) and control groups (n=36 tendons in each group). A simple suture was used in the control group and a simple suture plus cyanoacrylate was used in the experimental group.
Nine rabbits from each group were euthanized at week 4 and week 6 after surgery for histopathological and biomechanical testing.

Results: Granulation tissue formation was significantly greater in the experimental group in week 4 and week 6 than in the control group. Foreign body giant cell formation was significantly higher in the experimental group in week 4 and week 6. The maximum rupture force was significantly higher in the experimental group in week 4 and week 6 than in the control group. Elasticity and stiffness were comparable between groups in week 4; however, stiffness, but not elasticity, was significantly higher in the experimental group in week 6.

Conclusions: In the short term, cyanoacrylate enhanced tendon endurance in both a histopathological and biomechanical manner. We conclude that the early initiation of rehabilitation in patients may be safe in cases of cyanoacrylate use for surgical repair of tendon injury.

Keywords: Cyanoacrylates • Rabbits • Tendon Injuries

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Background

The Achilles tendon is the strongest and largest tendon in the body. In addition, it is a superficial tendon that is most commonly exposed to trauma and rerupture after repair. Rupture of the Achilles tendon is seen most frequently in men and during sport activity [1].

Ideally, an alternative treatment modality for Achilles rupture should be rapid, feasible, inexpensive, easy to learn, readily available, and with minimum need for equipment. At the same time, it should not lead to additional complications with use in inappropriate positions and settings.

Tissue adhesives provide an alternative method for the repair of tendon injury [2]. Tissue adhesives can be divided into 3 main categories: biologic products such as fibrin, synthetic glues (eg, cyanoacrylate-based), and genetically engineered polymer protein glues [3]. Although the adhesion performance of genetically modified polymer protein adhesives is high, the mechanical properties of biological structural materials still do not match those of natural systems [4]. Fibrin glue has a medium strength effect and does not have natural bactericidal properties. N-butyl-2-cyanoacrylate (cyanoacrylate) is a biosoluble, biocompatible, biological tissue adhesive, which has a longer half-life than fibrin glue. It is also bacteriostatic and hemostatic and has strong adhesive features, which is why we chose to investigate cyanoacrylate in this research. However, cyanoacrylate can cause arterial ocular lesions [5,6]. Cyanoacrylate sutures can be used for diverse surgical treatments, such as closure of gingival flaps, closure of mucous, cutaneous lacerations, and endodontic surgeries, because they have greater biocompatibility and fewer secondary tissue reactions than conventional sutures [7].

After Achilles tendon treatment with conventional sutures, the period of inactivity required to allow for early healing ranges from 3 to 7 weeks. However, prolonged immobilization causes muscle weakness and joint contracture, and therefore the rehabilitation process becomes difficult. There is a need for new suturing approaches that can provide higher strength for patients to achieve early mobilization [8]. We hypothesized that the combination of cyanoacrylate glue and sutures would provide more strength to the tendon than do traditional non-adhesive sutures alone. Thus, patients could experience earlier mobilization.

In this study, we aimed to investigate in vivo results of cyanoacrylate use in Achilles tendon rupture during a 6-week period. For this purpose, we assessed biomechanical and histopathological features of muscle tissue in week 4 and week 6.

Material and Methods

Animals

This study was conducted on 72 Achilles tendons from 36 adult male New Zealand albino rabbits (2-4 months old, weight of 2000-2500 g) at the Experiment Animal Application and Research Center of Bolu Abant İzzet Baysal University. The study was conducted in accordance with the principles of the Declaration of Helsinki. This animal experiment was approved by the Institutional Ethics Committee (approval no. 2017/30; approval date 10.05.2017). Animals were kept in cages under a 12-h light/12-h dark cycle. Room temperature was maintained at 23°C to 25°C, and relative humidity was maintained at 45% to 55%. All rabbits in the control and experimental groups were fed with standard laboratory chow during the study period.

Experimental Design

In total, 36 rabbits were randomly assigned to 2 groups (n=36 tendons in each group). In the experimental group, the tendon injury was induced by a partial Achilles tenotomy at 1.5 cm above the calcaneal insertion in both hind legs and a primary repair was performed in all tendons. Simple sutures were used in control rabbits and simple sutures plus cyanoacrylate were used in the rabbits in the experimental group. At 4 and 6 weeks after surgery, 9 rabbits from each group (cyanoacrylate group, n=18; control group, n=18) were euthanized prior to histopathological and biomechanical testing (**Figure 1**). The histopathological evaluation was performed using the staging method described by Curtis and Delee [9] (**Table 1**). Tensile testing was used to assess biomechanical features.

In some patients who are treated conservatively or surgically, there can be rerupture of tendons between 4 and 12 weeks after surgery, when the tissue quality is poor in the late stages of healing [10]. This is the reason that tendons in other studies and in the present study were evaluated at 4 and 6 weeks after surgery [11,12].

Surgical Procedure

The surgical intervention was performed with the animals under general anesthesia. Premedication (5 mg/kg xylazine HCL, intramuscular (i.m.); Rompun, Bayer, Istanbul, Turkey) was given to all rabbits. After 15 min, the anesthesia induction was achieved using ketamine injection (35 mg/kg, i.m.; ketamine hydrochloride, Ketalar®; EWL Eczacıbaşı Warner Lambert, İstanbul, Turkey). For prophylaxis, Sefazol® (Cephazolin sodium, 20 mg/kg, i.m., Mustafa Nevzat, Turkey) was given to rabbits 30 min before the surgical intervention. The preparation of the skin was performed using povidone-iodine (Batticon®, ADEKA, Turkey). Next, a skin incision (1.5 cm in length) was made over the Achilles

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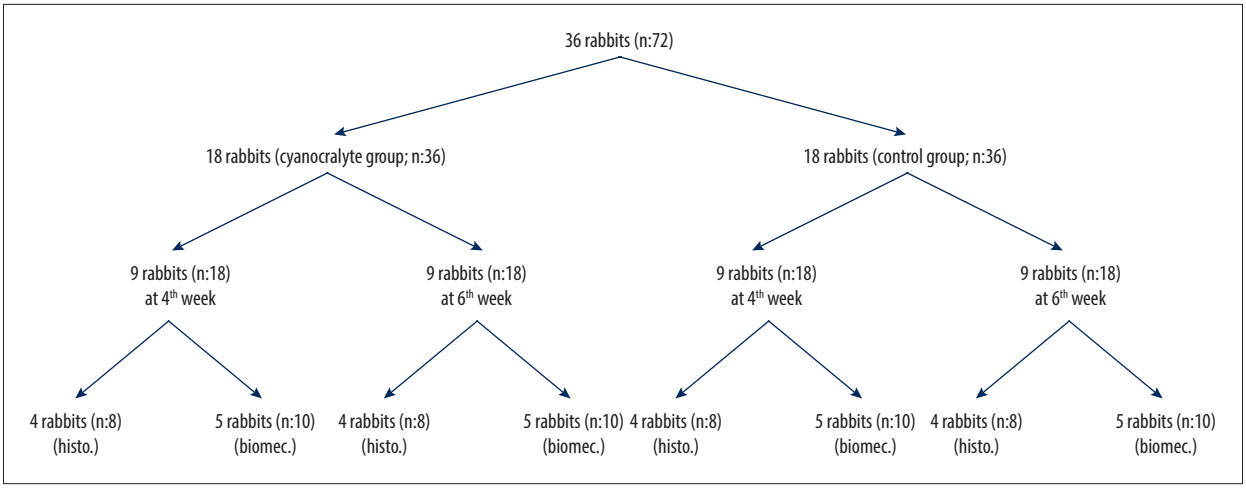

Figure 1. Experimental design of study. Histo – histopathological; biomec – biomechanical.

Table 1. Histopathological measurements were used based on a staging method [7].

1. Granulation • 0: No granulation tissue formation was observed • 1: Granulation tissue formation was observed
2. Foreing body giant cell • 0: No foreign body giant cell was observed • 1: Foreign body giant cell was observed
3. Inflammation degree • 0: No inflammatory cell at repair line on ×400 magnification • 1: Inflammatory cell at repair line on ×400
4. Neovascularization • 0: No capillary vessel in one high-power field (HPF), capillary count 0 • 1: 0-5 capillaries in one HPF • 2: 5-10 capillaries in one HPF • 3: >10 capillaries in one HPF
5. Fibroblastic activity (fibroplasias) • 0: No fibroblast in healing site at repair line • 1: Minimal fibroblast in healing site at repair line • 2: Marked fibroblast in healing site at repair line
6. Fibrillary collagen alignment • 0: Irregular fibrillary collagen alignment • 1: Regular fibrillary collagen alignment

tendon, followed by a longitudinal paratenon incision. Next, half of the tendon was tenotomized using a scalpel (no. 11) from the midline to lateral position and 1.5 cm above the calcaneal insertion. Next, a primary repair was performed on all tendons using 3/0 polypropylene suture. The rabbits remained mobile after the partial tenotomy. In the experimental group, the repair was performed by simple sutures plus 0.1 cc N-butyl-2-cyanoacrylate (Histoacryl; B. Braun Melsungen AG, Germany) (**Figure 2**). In all groups, the paratenon was closed with the skin using Vicryl 4-0 (Ethicon) after the tendon was repaired.

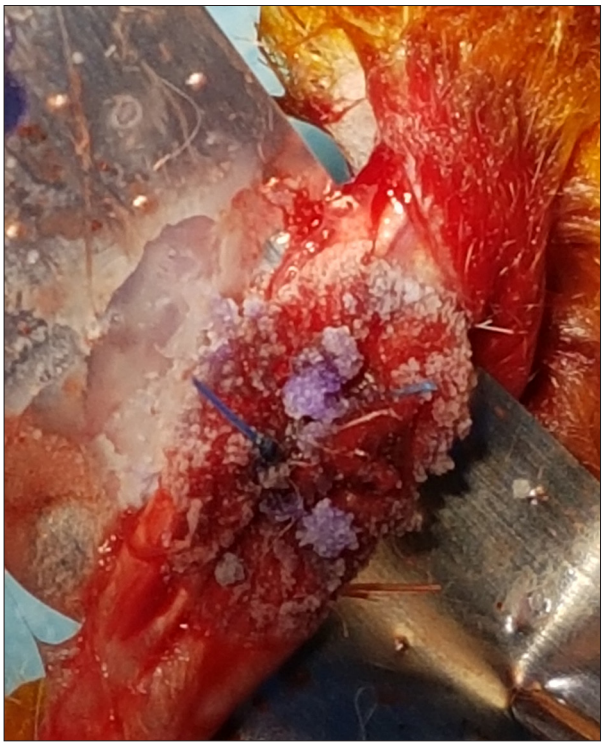

Figure 2. A close image of Histoacryl during freezing phase at wound site.

Biomechanical Evaluation

The biomechanical assessment was performed using a material testing device (Instron). In each group, 10 tendons were removed for biomechanical testing at 4 and 6 weeks after surgery. The tendon rupture forces were measured as Newton. The Achilles tendon was stored in a humidified sponge from

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Table 2. Comparisons of histopathological variables were conducted at week 4 and week 6.

Histopathological variables	Week 4 (n=16)					Week 6 (n=16)				
	Control (n=8)		Experiment (n=8)		p*	Control (n=8)		Experiment (n=8)		p*
Granulation	0	(0%)	8	(100%)	<0.001**	1	(12.5%)	7	(87.5%)	0.010**
Foreign body giant cell	0	(0%)	8	(100%)	<0.001**	0	(0%)	7	(87.5%)	0.001**
Inflammation	6	(75%)	6	(75%)	1.000	4	(50%)	7	(87.5%)	0.282
Neovascularization degree										
0	0	(0%)	0	(0%)	1.000	0	(0%)	0	(0%)	1.000
1	0	(0%)	1	(12.5%)		0	(0%)	0	(0%)	
2	2	(25%)	1	(12.5%)		1	(12.5%)	1	(12.5%)	
3	6	(75%)	6	(75%)		7	(87.5%)	7	(87.5%)	
Fibrillary collagen alignment										
Irregular	3	(37.5%)	3	(37.5%)	1.000	7	(87.5%)	6	(75.0%)	1.000
Regular	5	(67.5%)	5	(67.5%)		1	(12.5%)	2	(25.0%)	
Fibroblastic activity										
1	1	(12.5%)	0	(0%)	1.000	3	(37.5%)	0	(0%)	0.200
2	7	(87.5%)	8	(100%)		5	(67.5%)	8	(100%)	

* Fisher's exact test; ** statistically significant at α=0.05.

removal until the pull-up test. The tendon mass (g), length (cm), and thickness (mm) were equalized before biomechanical testing using a scale and caliper. The stress-strain slope was created using the obtained data, and elasticity, stiffness, and maximum tendon rupture forces were evaluated.

After fixation, samples were tested with 1 mm/s pull strength until rupture occurred. Maximum load (N), stiffness (N/mm), elasticity (Young's modulus, MPa) data were obtained, and stiffness-stress graphics were created.

Light Microscopy Evaluation

For histopathological examination, animals were euthanized by high-dose ether, and 8 tendons from each group were removed at 4 and 6 weeks after surgical intervention. The excised healing region was placed in 10% formaldehyde solution. All tendon tissue samples were embedded in paraffin blocks. Then, 5-µm sections were prepared from paraffin blocks and stained with hematoxylin and eosin and Masson's trichrome using a staging method whereby the following were evaluated with immunohistochemical staining: inflammation degree, neovascularization, fibroblastic activity, fibrillary collagen alignment, granulation tissue, foreign body giant cell formation, vascular endothelial growth factor (VEGF) positive-stained endothelial cells, and blood vessels.

VEGF Immunostaining Procedure

All skin flap tissue samples embedded in paraffin blocks and 5-µm tissue sections were used. The sections were dewaxed in xylene and rehydrated in graded ethanol. After washing with phosphate-buffered saline solution, the sections were microwaved for 20 min in 10 mM sodium citrate buffer (pH 6.0) for antigen retrieval, and sections were blocked with 3% (v/v) hydrogen peroxide solution for 10 min at room temperature. Then, the sections were blocked with Ultra V Block and incubated with primary antibody against VEGF (Cat no. MA5-13182, Thermo Fisher Scientific, USA), (1: 100) overnight at 4°C. Finally, the sections were incubated with horseradish peroxidase-conjugated secondary antibody (1: 1000), stained with 3,3'-diaminobenzidine, and counterstained with hematoxylin. After staining, tendon healing was assessed in the experimental and control groups under a light microscope (Nikon Eclipse 80i) at ×400 magnification via a staging method developed by Curtis and Delee [9]. The images were analyzed with NIS-Elements microscope imaging software (Nikon-Europe) for VEGF-positive stained endothelial cells and blood vessel counting. Ten random fields from each tissue sample were counted.

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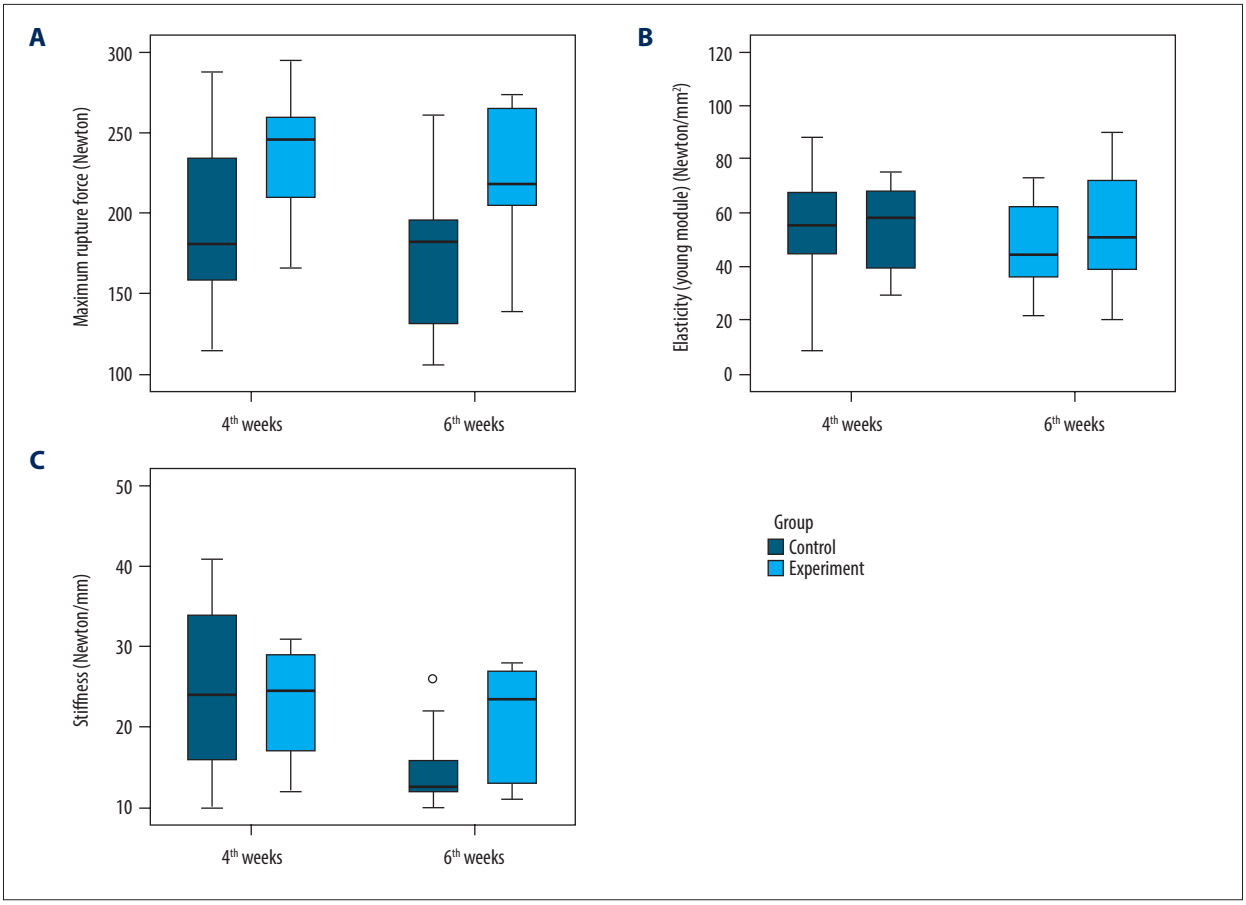

Figure 3. Summary of box-line graphics of biomechanical parameters according to groups. (**A**) maximum rupture force, (**B**) elasticity, and (**C**) stiffness. * Differences found to be significant at alpha level of 0.05 in independent sample *t* test.

Statistical Analysis

Because the biomechanical variables (maximum rupture force, elasticity, stiffness) had a continuous distribution and the sample had fewer than 50 subjects in the experimental and control groups, Shapiro-Wilk normality test was applied before further testing. The test showed a normal distribution in both groups ($P>0.05$). Because the normality assumption was proven and data were obtained from different time points and different subjects, the independent sample *t* test was used to compare variables on weeks 4 and 6. Data distributions are presented as summary statistics (**Table 2**) and box-line graphics (**Figure 3**). The differences in histopathological variables were compared between the groups using cross-tabulation and nonparametric chi-squared tests. Data were analyzed using SPSS. Statistical tests were interpreted at an alpha level of 0.05.

Results

General Observation

In weeks 4 and 6, atrophy of structures surrounding the ankle, rerupture of the healing site, tendon atrophy or hypertrophy, and adhesions to surrounding tissues were assessed in the experimental and control groups. No deaths occurred throughout the study. No complications, such as skin ulceration, necrosis, or wound site infection, were observed. There were no cases of atrophy because no limitations on movement were applied in the animals, and no rerupture was observed despite the lack of limitation of movement in weeks 4 and 6 in both groups (**Figure 4**). In week 4, mild adhesion was observed in 2 rabbits in the experimental group.

Microscopic Findings

In week 4, increased fibroblast and neovascularization was observed around the suture material, with occasional areas of inflammation in the control group identified by the histopathological assessment (**Figure 5**).

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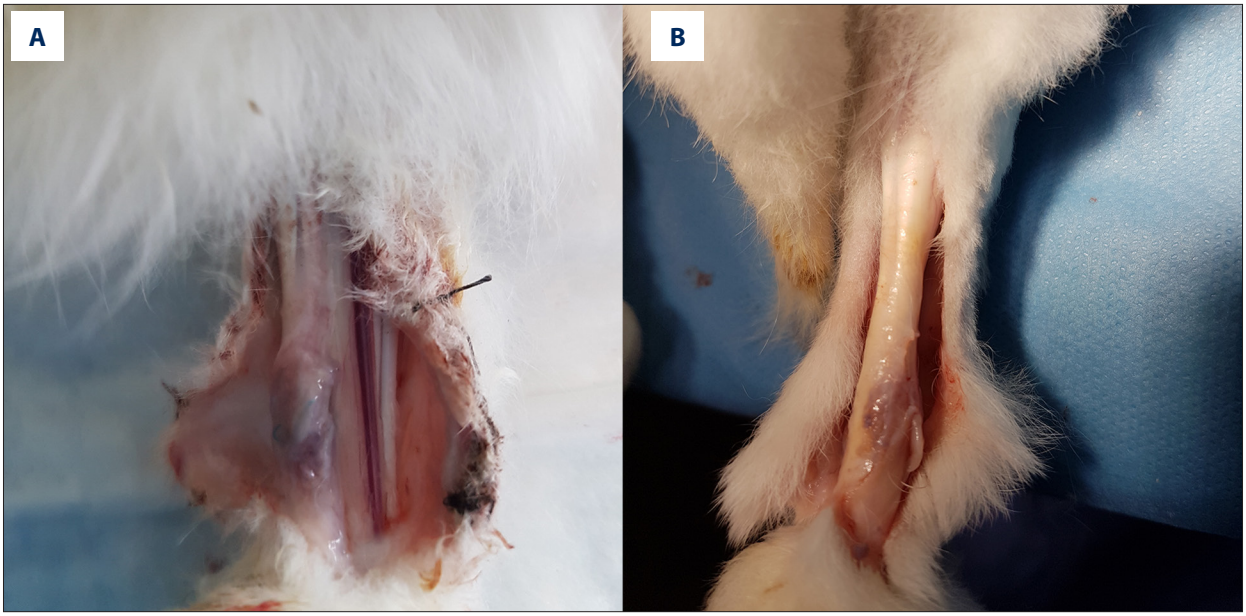

Figure 4. Gross appearance at (**A**) week 4 and at (**B**) week 6 for Achilles tendon in the experimental group.

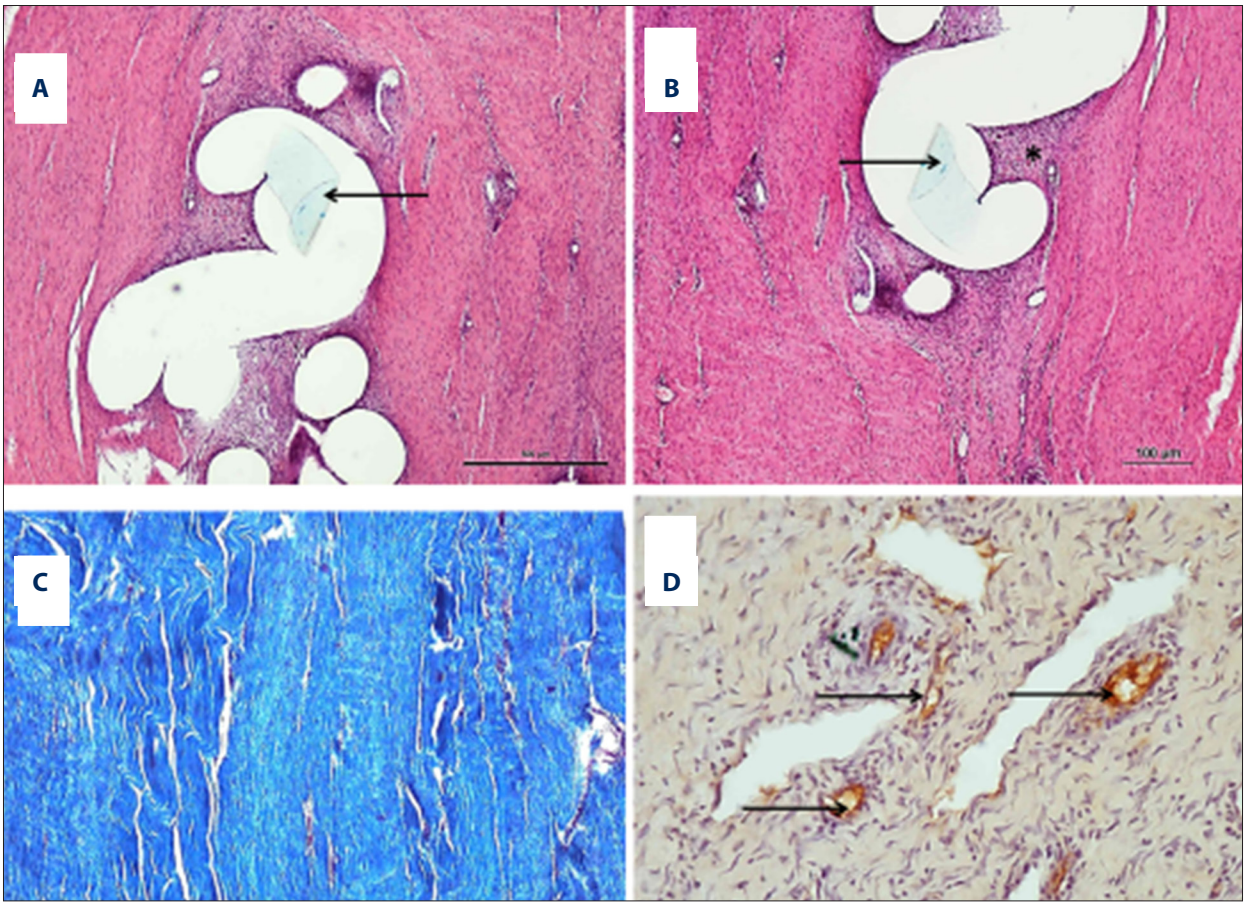

Figure 5. Image of control group at week 4. (**A**) Minimal inflammation areas around suture material (→) (hematoxylin and eosin stain [H&E] 4×). (**B**) Increased vascularization and neovascularization (*) around suture material (→) (H&E, 10×). (**C**) The parallel view of the collagen array is striking (Masson trichrome, 4×). (**D**) Vascular structures (→) marked with vascular endothelial growth factor are seen (20×).

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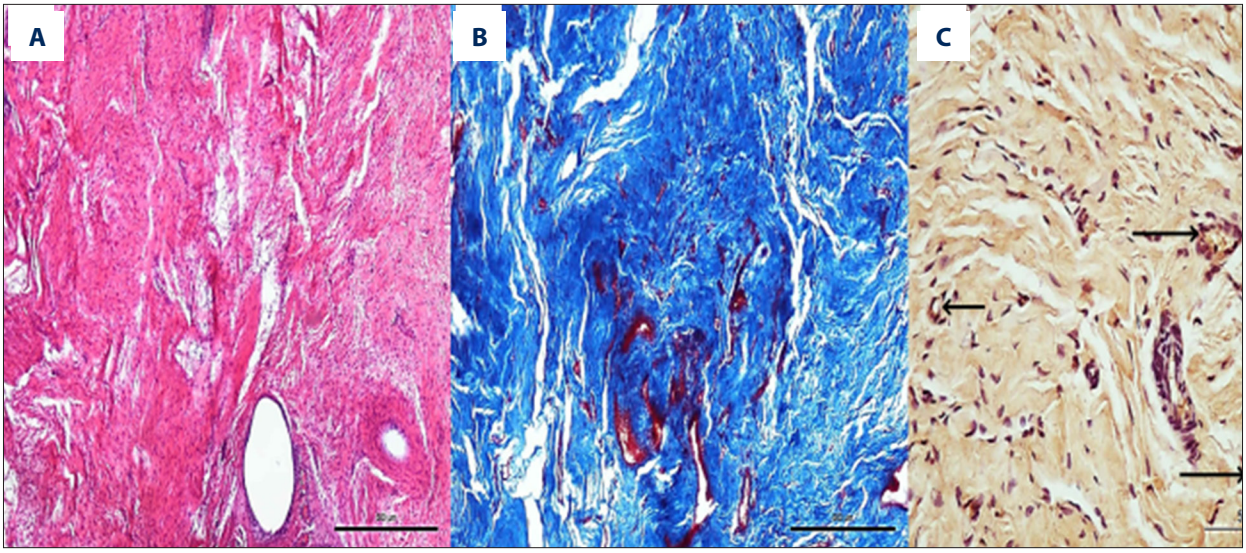

Figure 6. Image from control group at week 6. (**A**) There is irregularity in the collagen sequence (hematoxylin and eosin stain, 4×). (**B**) There appears to be a cross in the collagen sequence (Masson trichrome, 4×). (**C**) Vascular structures (→) marked with vascular endothelial growth factor are seen (20×).

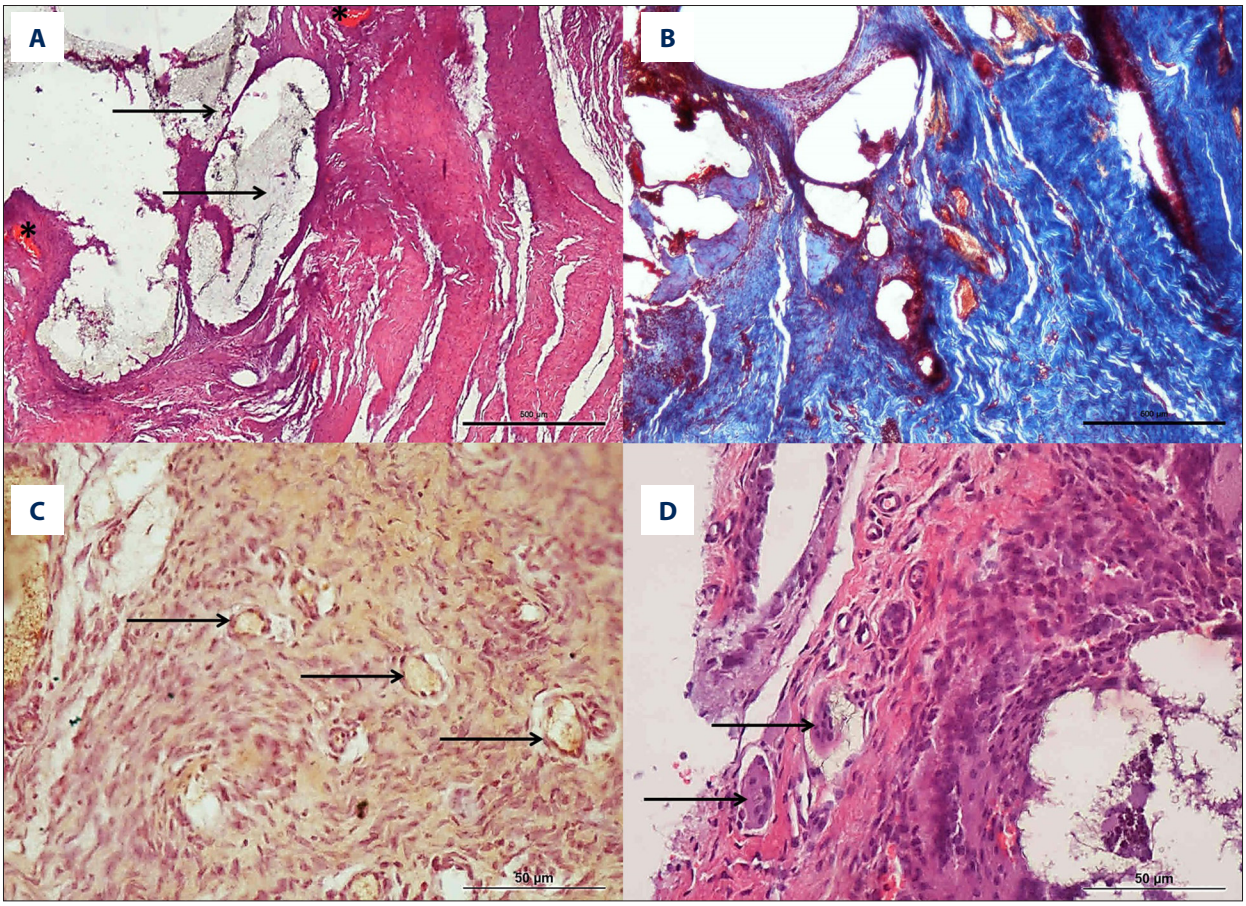

Figure 7. Image from experimental group at week 4. (**A**) Irregular collagen sequence is outstanding. Neovascularization (*) and cyanoacrylate (→) can be seen (hematoxylin and eosin stain, 4×). (**B**) There is an irregularity in the collagen sequence (Masson trichrome, 4×). (**C**) Vascular structures (→) marked with vascular endothelial growth factor are seen (20×). (**D**) Foreign body giant cells (→) are seen in the group given cyanoacrylate (hematoxylin and eosin stain, 20×).

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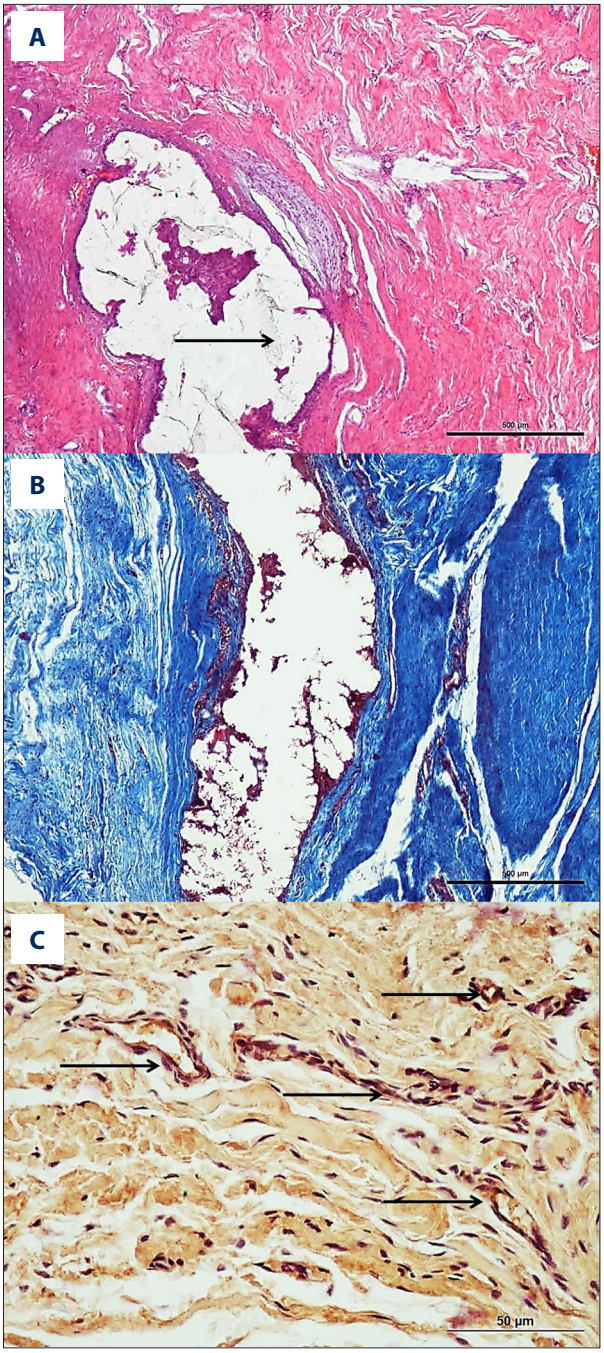

Figure 8. Image from experimental group at week 6. (**A**) Decreased amount of cyanoacrylate (→) can be seen (hematoxylin and eosin stain, 4×). (**B**) Irregular collagen sequence is outstanding (Masson trichrome, 4×). (**C**) It is seen that vascular endothelial growth factor-stained vascular structures (→) were increased at week 6 when compared to other groups (20×).

In weeks 4 and 6, the level of neovascularization was higher and the amount of cyanoacrylate was lower in the experimental group than in the control group (**Figures 6-8**).

Statistical Analysis of Histopathological Findings

Nine rabbits from each group (cyanoacrylate group n=18 tendons; control group n=18 tendons) were euthanized at weeks 4 and 6 after surgery for histopathological measurements. The following parameters were used based on the staging method shown in **Table 1**.

When granulation tissue formation was compared between the groups in week 4, no granulation tissue formation was observed in the control group, while granulation tissue was observed in all rabbits in the experimental group, and the difference was statistically significant ($P<0.001$). In week 6, granulation tissue was observed in 1 rabbit in the control group and in 7 rabbits in the experimental group, and the difference was statistically significant ($P=0.010$). The rate of granulation tissue formation was significantly higher in the experimental group than in the control group in weeks 4 and 6. We believe that the polymerization effect of cyanoacrylate was more effective in the formation of granulation tissue.

No foreign body giant cell formation was observed in the control group in weeks 4 and 6, while it was observed in all rabbits in the experiment group in week 4 ($P<0.001$) and in 7 rabbits in week 6 ($P=0.001$); therefore, the foreign body giant cell formation rate was significantly higher in the experimental group compared with control group in weeks 4 and 6.

No significant differences were found in inflammation, neovascularization, fibroblastic activity, and fibrillary collagen alignment between the groups in weeks 4 and 6 (**Table 2**).

Biomechanical Findings and Statistical Analysis

In week 4, the mean maximum rupture force was 193.5±56.9 in the control group and 239.0±36.5 in the experimental group. The mean elasticity (Young's modulus) was 55.6±23.4 in the control group and 54.9±16.5 in the experimental group. The mean stiffness was 24.3±10.3 in the control group and 23.1±7.0 in the experimental group. In week 6, the mean maximum rupture force was 177.6±49.6 in the control group and 223.6±42.0 in the experimental group. The mean elasticity (Young's modulus) was 48.9±17.0 in the control group and 53.1±22.8 in the experimental group. The mean stiffness was 14.6±5.3 in the control group and 20.6±7.0 in the experimental group.

The data distribution was normal in each group and at each time point according to the results of the Shapiro-Wilk normality test ($P>0.05$), and intragroup variances were found to

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be homogenous by the F test ($P>0.05$). Thus, the independent sample *t* test was used for binary comparisons.

In week 4, the maximum rupture force was significantly higher in the experimental group than in the control group (239.0±36.5 vs 193.5±56.9, $P<0.05$). There were no significant differences in elasticity and stiffness between the experimental and control groups.

Again, in week 6, the maximum rupture force was significantly higher in the experimental group than in the control group (223.6±42.0 vs 177.6±49.6, $P<0.05$). In addition, it was found that stiffness was significantly higher in the experimental group than in the control group (14.6±5.3 vs 20.6±7.0, $P<0.05$), but there was no significant difference in elasticity between the groups (**Figure 3**).

Discussion

The options for optimal treatment of Achilles tendon ruptures and their relative advantages and disadvantages have been discussed in the literature for many years [2,13,14]. The most important characteristics of treatment are a solid repair and lower rerupture ratio. In our study, we observed that cyanoacrylate reduced rerupture of the Achilles tendon. The histopathological results showed that the granulation tissue formation rate was higher in the experimental group than in the control group. Moreover, the mean maximum load before tendon rupture was significantly higher in the experimental group, based on the comparison of biomechanical output.

Studies have shown that suture technique has less impact on tendon durability than does suture material [15]. The increased complexity of suture techniques with a higher number of sutures will increase the amount of suture material, and tendon problems will occur in addition to potential complications due to prolonged surgery time. Impaired tendon circulation, foreign body reaction from an increased amount of material, and adhesions can result in poorer outcomes [15]. Pennington et al [15] compared the Bunnell suture with the locking loop suture in Achilles tendon repair and found that the locking loop suture did not strangulate the vessels within the tendon. In our experience, there were no residual suture material and adhesions in the tendons repaired using cyanoacrylate. Therefore, there were no vascular supply or circulation problems.

It has been suggested that end-to-end repair can be performed when the gap in an Achilles tendon rupture is <3 cm, while additional methods can be needed when the gap is 3 cm to 6 cm in size [16]. When an allograft is used as an adjunctive modality, cyanoacrylate can be used during the graft attachment, providing a wide range of options to the surgeon [3]. In our experiment, the smooth cut made by a surgical blade did not resemble a complete rupture model since a smooth cut differs from the frayed Achilles tendon rupture found in the real-world setting. Therefore, we did not perform a gap model, which can be seen as a limitation of the study.

Losi et al [3] reported a mild inflammatory reaction and glue residue in the glue and mesh group in their study. Park et al [17] found that 2-octyl cyanoacrylate and n-butyl cyanoacrylate topical skin adhesives for skin closure following repair of Achilles tendon rupture have equivalent effectiveness and safety as conventional nylon skin suture but with higher patient satisfaction. In our study, a milder inflammatory reaction was observed in the experimental group, but the difference was not statistically significant.

Ollivere et al [18] used FiberWire in Achilles tendon repair and found an excessive granulomatous reaction. Sabol et al [19] used n-butyl cyanoacrylate for skin wound closure and reported that the granulation tissue was higher on day 7 in the tissue adhesive group. In our present study using cyanoacrylate, the granulation tissue formation rate was higher in the experimental group than in the control group at weeks 4 and 6.

In a similar study, Gluckert and Pesch [20] created a partial cut in the patellar tendon of rabbits. The authors repaired the tendons using sutures in one group and fibrin glue only in the other group. In postoperative week 4, uniform scar tissue was observed in the fibrin glue group. They also found fibrotic tissue restoration by scar tissue, which showed early organization in a microscopic evaluation, while there was nodular scar tissue, irregular fibrous tissue, cellular insufficiency, tissue necrosis, and increased fibrosis in the suture group. In the present study, no scar tissue or necrosis was detected in the control or experimental groups. We concluded that cyanoacrylate had no toxic effect from the higher rate of inflammation and granulation tissue formation in the experimental group.

Lu et al [21] reported that the octyl-a-cyanoacrylate used in transverse tibia fracture in vivo had dissolved by week 2, was mostly absorbed by week 8, and had minimal residue by week 12. In addition, they reported that the glue was encased by chondrocytes and fibroblasts in week 2. In the present study, cyanoacrylate was not absent from the repair site on week 4, despite use in muscle tissue, but was largely absent from tissues in week 6.

Zhao et al [22] investigated the use of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride and cyanoacrylate to enhance the strength of the tendon-suture interface. The stiffness of the group with cyanoacrylate-augmented loops was significantly higher than that of the control group. However, in the present study, no significant difference between groups was found in stiffness in week 4, while stiffness was found to

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be significantly higher in the experimental group than in the control group in week 6.

Trail et al [23] compared Histoacryl and suture material in tendon repair biomechanically and found that the repair was more durable with Histoacryl. Bonutti et al [14] compared the breaking strength of isobutyl cyanoacrylate and the modified Kessler stitch in an in vitro study using rabbit Achilles tendon, but concluded that the study should be performed in vivo. In our in vivo study, we found that the mean maximum load weights were higher in the experimental group than in the control group at the end of week 6. We think that healing is directly proportional to fibrosis of the tissue.

Kickuth et al [24] applied superselective transcatheter arterial embolization with cyanoacrylate in patients with acute peripancreatic hemorrhage. The major complication rate was 2%, which included the death of 1 patient. No complications or deaths occurred in our study.

Tan et al [25] used cyanoacrylate to close the dermal and subcutaneous layers in spinal surgeries. Wound dehiscence and surgical site infection occurred in a small number of patients. Surgical site infection was not observed in our study.

There were several limitations of this study that should be mentioned. First, the results obtained from small animal models are not always relevant in human applications. Our data are best extrapolated to young, healthy, and not physically active rabbits. Humans, including older people, women, and patients in rehabilitation, may not respond in the same way as our animal groups. Finally, although paratenon is a parameter affecting the healing in acute Achilles tendon rupture, it is a limitation of the study that this effect level was not examined [26].

Also, rather than examining the effects of dynamic exercise on tendon properties, we conducted an experimental study. Further studies are needed to better understand the limitation of natural movements that occur in sports and physical activities. Our comparison of clinical functional results is the most important limitation of our study.

Conclusions

In conclusion, support with cyanoacrylate significantly improves strength of fixation. Surgery can be achieved with the application of simple sutures and tissue adhesion. This technique may reduce rerupture in tendon healing and soft tissues and help prevent potential adhesions. Cyanoacrylate is a tissue adhesive preferred for its high biocompatibility. Repair using cyanoacrylate may be a successful treatment modality in Achilles tendon ruptures.

Declaration of Originality

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

Ethics Statement

The study protocol was approved by our local Ethics Committee (approval date 10.05.2017; approval no. 2017/30).

Conflict of Interest

None.

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