EXPERIMENTAL STUDY

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Effect of hyperbaric oxygen treatment on tendon healing after Achilles tendon repair: an experimental study on rats

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Objective: The aim of this study was to investigate the effects of hyperbaric oxygen treatment on early tendon healing in the treatment of Achilles tendon ruptures.

Methods: Fifty-six male Wistar albino rats were randomized and divided into two groups. Intratendinous betamethasone was administered preoperatively for degeneration in 28 rats and isotonic saline injection was administered to the remaining 28 rats. The Achilles tendons of all rats were sutured following tenotomy. Fourteen rats from each group were then selected and received hyperbaric oxygen therapy. The Achilles tendons were removed, biomechanically evaluated and histopathologically studied on the 11th postoperative day. The biomechanical properties and amount of fibrosis, inflammation and vascularization were compared between the groups receiving hyperbaric oxygen therapy and those not.

Results: Histopathological study showed the amount of fibrosis was significantly higher in the hyperbaric oxygen therapy group than in the control group without the hyperbaric oxygen therapy. The amount of inflammation and vascularization were significantly higher in the steroid administration group than in the no-steroid group. There was a significant difference in the biomechanical properties of the groups in terms of maximum force, stiffness, elastic modulus and maximum allowable stress.

Conclusion: Hyperbaric oxygen therapy creates a positive histological and biomechanical effect on tendon healing after Achilles tendon repair.

Key words: Achilles tendon; biomechanics; hyperbaric oxygen.

The Achilles tendon is the strongest and thickest tendon of the human body; however, it is also most frequently traumatized and torn as it is subject to higher stresses than other tendons.[1,2] Most cases occur during sporting activities and Achilles injuries are more frequently seen among men than women.[3,4] Conservative (non-operative) or surgical treatment options are possible with the aim of enabling the patient to return to daily life in a short period of time. Additionally, for many patients, a second objective is the return to pre-injury sporting activity levels. For this reason, a variety of new treatment methods and supplementary applica-

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tions have been developed. One such subsidiary treatment method is hyperbaric oxygen therapy (HBO). HBO therapy is the inhalation of oxygen of a pressure higher than 1 atmosphere via a mask, headpiece, environment or endotracheal tube.[5]

The aim of our study was to biomechanically and histologically investigate the effects of HBO treatment on early tendon healing in Achilles tendon ruptures in rat models.

Materials and methods

Approval was obtained from the Local Animal Ethics Board of Ege University, with the number: 2009-142, prior to the study.

The study was performed on 56 male Wistar albino rats of an average age of 5 to 7 months and a weight range of 200-260 grams. Rats were fed standard laboratory food and tap water in an environment with 12 hours of light and 12 hours of dark in line with their biological rhythm.

Rats were first randomized and divided into two groups of twenty-eight. An injection of 0.1 cc betamethasone was applied to 28 rats in the right Achilles tendons, starting from the tendon-muscle conjugations and ending at the calcaneus using 22G injector needles 9 times at three-day intervals to produce degeneration in the tendons.[6] The other 28 rats received an injection of 0.1 cc isotonic saline.

A prophylactic 30 mg/kg cefazolin sodium (Iespor®; I.E. Ulagay, Istanbul, Turkey) was administered to all rats following a five-day waiting period. Anesthesia was secured using the intraperitoneal administration of 35 mg/kg ketamine HCI (Alfamine®; Ege Vet, Izmir, Turkey) and 5 mg/kg xylazine HCI (Alfazyne®; Ege Vet, Izmir, Turkey). The posterior of the right Achilles tendon was planed and cleaned and the surgical site was prepared with polyvidone iodine (Batticon®; Adeka, Istanbul, Turkey). A middle-line incision of 2.5 cm was made longitudinally to expose the Achilles tendon. The Achilles tendon was then transected horizontally with a no. 22 scalpel from 0.5 cm proximal of the point of adherence to calcaneus. The tendon was repaired using 5-0 polyglactin 910 suture (Vicryl™; Ethicon Inc, Somerville, NJ, USA) via the modified Kessler method. Skin was closed with non-absorbable suture material. No external fixation was applied and the rats were allowed to move freely inside their cages postoperatively. Dissolved paracetamol tablets were added to their water and food for analgesia.

At this stage, 14 rats were separated from each of the two groups with and without the previous intratendinous corticosteroid injection. Group 1 consisted of rats receiving no treatment, Group 2 rats which underwent HBO, Group 3 rats who received steroid injection and Group 4 rats which received steroid injection and HBO therapy. From the first postoperative day, rats in Groups 2 and 4 were given HBO for 70 minutes per day for seven days in a total of 14 fractions under 2.4 ATA pressure.

The study was carried out in the cylindrical pressure chamber specifically designed for experimental animals at the Neoks Hyperbaric Oxygen Therapy Center. Technical properties of the Barotech Ltd. BD1 model pressure chamber is given in Table 1.

Treatment was performed in sessions totaling 70 minutes each at 2.4 ATA. Before treatment, the cabin was ventilated with 100% oxygen for a period of 5 minutes. Each treatment session included 5 minutes for diving to 50 feet (at 2.4 ATA pressure), 60 minutes of breathing 100% oxygen at 2.4 ATA and 5 minutes to exit.

On the 11th day, all rats were sacrificed with the administration of a high-dose anesthetic agent (100 mg/kg sodium thiopental). The lower-right extremities of the rats were disarticulated from the hip joint in order to explore the Achilles tendons. Healing was observed in the Achilles tendons of all rats and no infection was observed during the study period.

For the optical microscope assessment, the extracted tissues were fixed with 10% formaldehyde. Divided into paraffinic blocks, the samples were made into 4-5 mm cross-sections, dyed with hematoxylin-eosin and assessed by the same pathologist.

In their histopathological assessment counting the number of cells in one field, Curtis et al.[7] checked the following entities:

- Distribution and density of inflammatory cells,
- Density of the blood capillaries in the tendinous tissue (neovascularization),
- Presence and density of fusiform fibroblasts (fibroblastic proliferation),
- Presence and density of flattened fibrocytes (fibrosis)

Table 1. Technical properties of Barotech Ltd., BD1 model pressure chamber.

Working pressure	3.6 ATA
Test pressure	4 ATA
Inner diameter	40 cm.
Total length	55 cm.
Door diameter	46 cm.
Material	Acrylic

Table 2. Study groups and assessment methods.

Groups		n	Biomechanical testing	Histopathological evaluation
1	(Tendon repair)	14	7	7
2	(HBO after tendon repair)	14	7	7
3	(Tendon repair after steroid injection)	14	7	7
4	(HBO therapy and tendon repair after steroid injection)	14	7	7

In our histopathological evaluation, we used a modified Curtis et al.[7] technique, calculating the average number of cells within more than one field to reduce subjectivity as evaluation can vary according to the evaluator. A 4-times magnified field was selected and a circular area with a diameter of 6 mm was marked. This area was divided into 25 smaller fields horizontally and vertically with widths of 1.2 mm. The inflammatory cells, veins and fusiform fibroblastic cells were counted and the average was taken in each of the 15 randomly selected regions. The inflammatory cells were graded depending on fibroblastic proliferation and fibrosis; (0) no fibroblastic proliferation and fibrosis, (1) mild, (2) moderate, and (3) significant. Neovascularization was graded as; (1) mild: when the number of capillaries was between 0 and 5, (2) moderate: if the number of capillaries was between 5 and 10, and (3) significant: if the number of capillaries was greater than 10 at a magnified field with a diameter of 0.45 micron.

For the biomechanical assessment, seven rats from each group were selected. Tests were performed by the application of a tensile load at a speed of 1 mm/min on the tensile test machine (Autograph AG-IS 100kN; Shimadzu Co., Kyoto, Japan).[8] The tensile behaviors (rigidity, elastic modulus and energy absorption density, rupture loads, maximum loads) of the tendons were studied.

Statistical analysis was performed with chi-square, one-way variance analysis (one-way ANOVA) tests. All analyses were performed with a 95% confidence interval using SPSS 15.0 Windows (SPSS Inc., Chicago, IL, USA) statistical software. P values of less than 0.05 were regarded as statistically significant.

Results

Groups and assessment methods are summarized in Table 2.

No statistically significant difference was found between Groups 1 and 2 in terms of inflammation and fibroblastic proliferation ($p>0.05$) Neo-vascularization and fibrosis were found significantly higher in Group 2 ($p<0.05$) (Table 3).

No statistically significant difference was found between Groups 3 and 4 in terms of inflammation, neo-vascularization and fibroblastic proliferation ($p>0.05$). The amount of fibrosis was found to be significantly higher in Group 4, suggesting the positive effect of hyperbaric oxygen on healing ($p=0.016$) (Table 4). In the assessment of the effect of the corticosteroid, there was a significant difference in Group 3 in terms of inflammation (Table 5). In the postoperative assessment of the groups with and without HBO treatment no significant difference was observed in terms of inflammation and fibroblastic proliferation while a significant difference was found in terms of neovascularization (Table 6).

Biomechanical comparisons between all groups were analyzed via the one-way variance analysis (one-way ANOVA). There was a significant difference between the groups in terms of biomechanical parameters with exception of strain energy ($p<0.05$) (Table 7).

Discussion

Several theories on the etiology of Achilles tendon injuries have been proposed.[9-11] The chronic degeneration theory states that degeneration affecting the tendon may lead to rupture without tendon overload.[12] Recurrent microtraumas, aging and specifically located hypovascularity are suspected susceptibility factors. The degeneration theory has been supported with angiographic and histological findings.[10,11] In these studies, scattered areas of healing and mucoid and edematous alterations were observed in the tissue samples, suggesting its chronic course.[11]

The importance of tissue oxygenation in healing is well known.[13] HBO therapy is considered to have positive effects on wound healing by increasing the amount of dissolved oxygen in the blood and tissues. Additionally, HBO is known to contribute to neovascularization in tissue with decreased vascularization.[14,15] Zhao et al. established a direct correlation between oxygen and the growth factor.[16]

Table 3. Analysis of histopathological differences between Group 1 and 2.

			Low	Medium	High	Total	Chi-square	p
Inflammation	Group 1	n	4	3	0	7	0.29	0.593
		%	57.1	42.9	0.0	100		
	Group 2	n	3	4	0	7		
		%	42.9	57.1	0.0	100		
	Total	n	7	7	0	14		
		%	50.0	50.0	0.0	100		
Neovascularization	Group 1	n	4	3	0	7	5.60	0.018
		%	57.1	42.9	0.0	100		
	Group 2	n	0	7	0	7		
		%	0.0	100.0	0.0	100		
	Total	n	4	10	0	14		
		%	28.6	71.4	0.0	100		
Fibroblastic proliferation	Group 1	n	5	2	0	7	0.31	0.577
		%	71.4	28.6	0.0	100		
	Group 2	n	4	3	0	7		
		%	57.1	42.9	0.0	100		
	Total	n	9	5	0	14		
		%	64.3	35.7	0.0	100		
Fibrosis	Group 1	n	7	0	0	7	10.50	0.001
		%	100.0	0.0	0.0	100		
	Group 2	n	1	6	0	7		
		%	14.3	85.7	0.0	100		
	Total	n	8	6	0	14		
		%	57.1	42.9	0.0	100		

Table 4. Analysis of histopathological differences between Group 3 and 4.

			Low	Medium	High	Total	Chi-square	p
Inflammation	Group 3	n	0	5	2	7	1.33	0.513
		%	0.0	71.4	28.6	100		
	Group 4	n	1	5	1	7		
		%	14.3	71.4	14.3	100		
	Total	n	1	10	3	14		
		%	7.1	71.4	21.4	100		
Neovascularization	Group 3	n	1	4	2	7	1.20	0.549
		%	14.3	57.1	28.6	100		
	Group 4	n	0	4	3	7		
		%	0.0	57.1	42.9	100		
	Total	n	1	8	5	14		
		%	7.1	57.1	35.7	100		
Fibroblastic proliferation	Group 3	n	0	4	3	7	4.4	0.111
		%	0.0	57.1	42.9	100		
	Group 4	n	1	6	0	7		
		%	14.3	85.7	0.0	100		
	Total	n	1	10	3	14		
		%	7.1	71.4	21.4	100		
Fibrosis	Group 3	n	2	5	0	7	8.286	0.016
		%	28.6	71.4	0.0	100		
	Group 4	n	0	2	5	7		
		%	0.0	28.6	71.4	100		
	Total	n	2	7	5	14		
		%	14.3	50	35.7	100		

Table 5. Inflammation and neovascularization depending on the application of intratendinous corticosteroid (IC) preoperatively.

Corticosteroid application status		Inflammation level				Chi-square	p
		Low	Medium	High	Total		
No IC (Group 1-2)	n	7	7	0	14	8.029	0.018
	%	50	50	0	100		
IC injected (Group 3-4)	n	1	10	3	14		
	%	7.1	71.4	21.4	100		
Total	n	8	17	3	28		
	%	28.6	60.7	10.7	100		
		Neovascularization level					
No IC (Group 1-2)	n	4	10	0	14	7.022	0.030
	%	28.6	71.4	0	100		
IC injected (Group 3-4)	n	1	8	5	14		
	%	7.1	57.1	35.7	100		
Total	n	5	18	5	28		
	%	17.9	64.3	17.9	100		

Various models have been used for HBO treatment in the literature. Ishii et al. showed that the highest pressure value of 2 ATA for 60 minutes is more effective for the formation of fiber and ligaments than other models.[17] The experiment carried out by Aydin et al. on rats was performed for 70 minutes at 2.4 ATA.[18] HBO treatment was applied for a period of 2 hours at 2.5 ATA in Mashitori et. al.'s experimental study on ligament healing.[19] In addition, Yeh et al. applied HBO treatment in an experimental study on rabbits for 2 hours at 2.5 ATA.[20] It is known that oxygen can only be dissolved in plasmas under hyperbaric conditions and the amount of dissolved oxygen increases proportionally with pressure (Table 8).[21] In our study, HBO treatment at 2.4 ATA for 70 minutes was applied in order to benefit from the optimum effects of oxygen on wound healing.

When the groups with (3 and 4) and without (1 and 2) intratendinous corticosteroid injection were histopathologically compared, statistically significant differences were established between both groups in terms of inflammation and neovascularization (p=0.018 and p=0.030) (Table 5). Degeneration was present in the

Table 6. Histopathological parameters of rats depending on HBO therapy postoperatively.

			Low	Medium	High	Total	Chi-square	p
Inflammation	No HBO therapy	n	4	8	2	14	0.932	0.822
		%	28.6	57.1	14.30	100		
	HBO therapy	n	4	9	1	14		
		%	28.6	64.3	7.1	100		
	Total	n	8	17	3	28		
		%	28.6	60.70	10.7	100		
Neovascularization	No HBO therapy	n	5	7	2	14	6.089	0.048
		%	35.7	50.0	14.3	100		
	HBO therapy	n	0	11	3	14		
		%	0.0	78.6	21.4	100		
	Total	n	5	18	5	28		
		%	17.9	64.3	17.9	100		
Fibroblastic proliferation	No HBO therapy	n	5	6	3	14	3.600	0.165
		%	35.7	42.9	21.4	100		
	HBO therapy	n	5	9	0	14		
		%	35.7	64.3	0	100		
	Total	n	10	15	3	28		
		%	35.7	53.6	10.7	100		

Table 7. Summary of biomechanical results in all groups.

	Group 1 (n=7)	Group 2 (n=7)	Group 3 (n=7)	Group 4 (n=7)	p
Structural properties					
Maximum force (N)	10.62±0.83	18.50±2.66	10.08±1.32	12.06±1.58	0.00
Stiffness (N/mm)	2.55±0.80	4.05±0.96	1.35±0.63	2.73±0.77	0.0002
Strain energy (J)	0.14±0.12	0.18±0.05	0.09±0.06	0.13±0.06	0.241
Material properties					
Maximum stress (MPa)	4.57±0.36	7.95±1.14	4.33±0.56	5.18±0.68	0.00
Elastic modulus (MPa)	12.69±1.41	16.87±3.77	11.83±1.01	15.34±1.39	0.001

Table 8. Amounts of dissolved oxygen for different hyperbaric conditions.

Total pressure	mmHg	%100 air breathing	%100 O_2 breathing
1	760	0.32	2.09
2	1,520	0.81	4.44
2.5	1,900	1.06	5.62
3	2,280	1.31	6.80

intratendinous corticosteroid injection groups. These findings are in line with the results of Tatari et al.[6] In the present study, the injection applied to these groups indicated the source of inflammation to be not the tendon damage, but the corticosteroid itself. This may constitute evidence that the nature of the Achilles tendon ruptures in the literature occur following the corticosteroid injection as a secondary event to degeneration.

In the assessment on the effectiveness of HBO therapy, Groups 2 and 4 with and Groups 1 and 3 without HBO therapy were compared. Statistically significant differences were found in terms of neovascularization between groups ($p<0.05$) (Table 6). The positive contribution to neovascularization and increased fibrosis following HBO therapy shows the acceleration effect of HBO on histological healing. While it was reported in the literature that HBO increases fibroblast proliferation, our study did not identify a significant increase in fibroblast proliferation ($p>0.05$).[13] A statistically significant difference was established between rats who received HBO therapy and those that did not in terms of neovascularization and fibrosis ($p<0.05$), while no statis-

Table 9. Multiple comparisons of test results for the variable of elastic modulus with Tukey's test.

					95% confidence interval	
Group (i)	Group (j)	Mean difference (i-j)	Standard error	p	Upper bound	Lower bound
1	2	-4.17993	1.173	0.008	-7.4161	-0.9438
	3	0.86000	1.173	0.883	-2.3761	4.0961
	4	-2.64912	1.173	0.136	-5.8853	0.5870
2	1	4.17993	1.173	0.008	0.9438	7.4161
	3	5.03993	1.173	0.001	1.8038	8.2761
	4	1.53081	1.173	0.569	-1.7053	4.7669
3	1	-0.86000	1.173	0.883	-4.0961	2.3761
	2	-5.03993	1.173	0.001	-8.2761	-1.8038
	4	-3.50912	1.173	0.030	-6.7453	-0.2730
4	1	2.64912	1.173	0.136	-0.5870	5.8853
	2	-1.53081	1.173	0.569	-4.7669	1.7053
	3	3.50912	1.173	0.030	0.2730	6.7453

tically significant difference could be found between other histopathological parameters (p>0.05) (Table 3).

Comparing the effectiveness of HBO in rats that received the corticosteroid injection (Groups 3 and 4), the increase in fibrosis was found to be statistically significant in the HBO therapy group (Group 4). These findings indicate the positive contribution of HBO therapy to histological healing.

On the 11th postoperative day there were significant differences among the four groups in terms of failure load. The maximum force that Group 1, 2, 3, and 4 could withstand was 10.62±0.83 N, 18.5±2.66 N, 10.08±1.32 N and 12.06±1.58 N (p<0.05), respectively. The average of maximum force in Group 2 was significantly greater than that of the other groups. Similarly, Group 2 showed a significant difference in terms of stiffness. The stiffness of Group 1, 2, 3, and 4 averaged 2.55±0.80 N/mm, 4.05± 0.96 N/mm, 1.35±0.63 N/mm and 2.73±0.77 (p<0.05), respectively (Table 7).

Hyperbaric oxygen therapy also significantly improved the biomechanical properties of the Achilles tendon, such as maximum allowable stress and elasticity modules, on the 11th postoperative day. Significant differences were observed in parameters including maximum stress for Group 1, 2, 3, and 4 which averaged 4.57±0.36, 7.95±1.14, 4.33±0.56 and 5.18±0.68 (p<0.05), respectively (Table 7).

An assessment was performed to determine the effectiveness of HBO therapy in terms of elastic modulus using the Tukey's test. The elastic moduli for Group 1, 2, 3 and 4 averaged 12.69±1.41, 16.87±3.77, 11.83±1.01 and 15.34±1.39, respectively (Fig. 1). Significant differences between the groups in terms of elasticity modulus were found during biomechanical evaluation (Table 9). Group 2 had higher elastic modulus values than Group 1 (p<0.05) and Group 3 (p<0.05). Group 4 had higher values than Group 3 (p<0.05). Mean stress energy value in all groups is shown in Figure 2. No significant differences were found in strain energy between the groups (p>0.05) (Table 7).

Differences established between groups in terms of biomechanical parameters (p<0.05) were consistent with the findings obtained by Mashitori et al.[19] Horn et al. reported that HBO application creates significant difference in the biomechanical healing of the medial collateral tendon in the 4th week.[22] In this study, the 11th postoperative day provided sufficient time for the rat model Achilles tendons to heal to biomechanical competence.

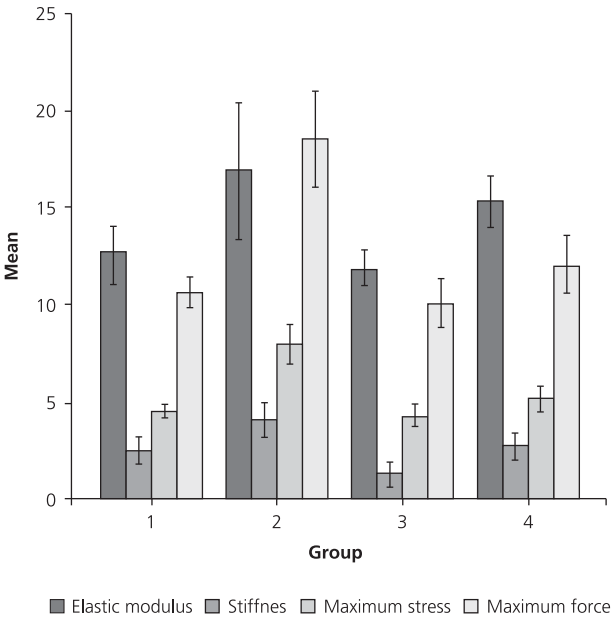

Fig. 1. Biomechanical test results in all groups.

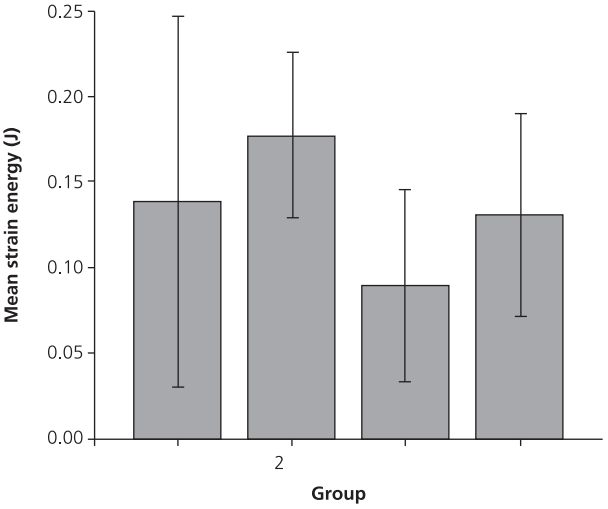

Fig. 2. Mean strain energy results in all groups.

In conclusion, it can be stated that HBO therapy has a positive effect on histological and biomechanical healing and speeds up the healing process in the treatment of Achilles tendon rupture.

Conflicts of Interest: No conflicts declared.

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