DELETERIOUS EFFECTS OF LOCAL CORTICOSTEROID INJECTIONS ON THE ACHILLES TENDON

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ÖZET

LOKAL KORTİKOSTEROİD İNJEKSİYONLARININ AŞİL TENDONU ÜZERİNDEKİ ZARARLI ETKİLERİ

Giriş: Çalışmanın amacı, rat Aşil tendonuna değişik intervallerde uygulanan intratendinöz kortikosteroid injeksiyonlarından sonra, tendon ve paratenonda oluşan patolojik değişiklikleri incelemek, bu ilaçların sağlıklı tendon üzerindeki etkisini ortaya koymak ve ayrıca bu enjeksiyonların oluşturduğu patolojik değişikliklerle tendonun bir klemple sıkılmasıyla oluşan değişiklikleri kıyaslamaktır.

Materyal ve Metod: Bu amaçla 26 Vistar erkek ratın 52 Aşil tendonu kullanıldı. Sol Aşil tendonlarına değişik intervallerde Betamethasone enjeksiyonu yapılırken sol tendonları, cerrahi insizyon yapıldıktan sonra, değişik zaman sürelerinde klemple komprese edildi. 30 gün sonunda, tüm tendon ve paratenonlar eksize edilerek yarı kantitatif skorlama sistemine göre histopatolojik olarak değerlendirildi.

Bulgular: Histopatolojik değerlendirme, her iki grupta da, dejenerasyon bulguları gösterdi. İstatistiksel değerlendirmede, iki grup arasında anlamlı bir fark saptanmadı; fakat Betamethasone uygulanan tendonlarda makroskopik olarak genişleme ve subkutan dokuya kuvvetli yapışıklık görüldü.

Tartışma: Bulgulara göre, tendona lokal Betamethasone uygulanması, klemple kompresyonu kadar zararlı sonuç verebilir ve ayrıca, ileri çalışmalarda dejenerasyon oluşturma modeli olarak kullanılabilir. Tendon kitlesinin genişlemesi ve subkutan dokuya yapışıklığın nedeni, uygulanan Betamethasone enjeksiyonlarının kısmen tendon dışına çıkması olabilir.

Anahtar Kelimeler: *Aşil Tendonu, Kortikosteroidler, Tendinit.*

SUMMARY

Purpose: The purpose of this study is to examine the pathologic changes in the Achilles tendon and its paratenon after intratendinous corticosteroid injections at different intervals and to reveal the effects of this drug on healthy tendon, and also to search the effects of these injections comparing to that of compression with a clamp on the Achilles tendons of the rats.

Material and Method: Fifty-two Achilles tendons of twenty-six male Vistar rats were included in the study to search the effects of intratendinous Betamethasone injections comparing that of compression with a clamp. Betamethasone injections were applied to the left tendons in different intervals, while the right tendons served for compression with Mosquito clamps in varied durations. At the end of 30 days, all tendons were excised and examined histopathologically according to a semiquantitative scoring system.

Results: Histopathologic evaluation showed some degree of degeneration in both groups. Statistical analysis showed no significant difference among two groups, but in macroscopic evaluation, the tendons in Betamethasone group demonstrated enlargement and strong adhesiveness to the subcutaneous tissue.

Discussion: It is concluded that intratendinous Betamethasone injections are as harmful as compression of it with a clamp and it can be used as a degeneration performing model in further studies. Enlargement of the tendon mass and strong adhesiveness to the subcutaneous tissue can be due to injection of the Betamethasone partly outside of tendon.

Key Words: *Achilles Tendon, Corticosteroids, Tendinitis.*

INTRODUCTION

Surgical and non-surgical treatment modalities have been described for Achilles tendinopathies, both on clinical[1-3] and experimental studies[4-7]. Local or systemic corticosteroid injections are widely used by orthopaedic surgeons in the

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treatment of such chronic overuse injuries with hesitancy because of isolated case reports of spontaneous rupture of the Achilles tendon[8-10]. Wiggins et al.[5] have suggested that treatment of an injured ligament with local corticosteroids is detrimental to the healing process while Shrier et al.[6] have reached the conclusion that the decreased tendon strength with intratendinous injections in animal studies suggested that rupture might be a potential complication for several weeks following injection. Despite abundance of the experiments on the injured tendons, the reply of the healthy tendon and paratenon to local corticosteroid injections is unclear. An answer to this entity will probably explain more vigorous effects of local corticosteroids on the tendon tissue.

The purpose of this study is to examine the pathologic changes in the Achilles tendon and its paratenon after intratendinous corticosteroid injections at different intervals and to reveal the effects of this drug on healthy tendon, and also to search the effects of these injections comparing to that of compression with a clamp on the Achilles tendons of the rats.

MATERIALS AND METHODS

The experiment was carried on twenty-six male Vistar white rats. Their weights ranged between 322-429 grams. The left hind limb Achilles tendon of the rats served as the corticosteroid injection group and the right hind limbs as the control group compressed with Mosquito clamps.

The left Achilles tendons were injected with 0,1 ml. of Betamethasone Sodium Phosphate (Diprospan®-Eczacıbaşı, Turkey) intratendinously by the same author (C.K.) with a 22-gauge needle, beginning from the insertion of the tendon to the calcaneus in different intervals for each rat, with randomized selection as seen on Table I.

For the study on the right hind limb, the rats were kept under general anesthesia, induced by intraperitoneal injection of ketamine (10 mg/kg). After induction of anesthesia, the hairy skin at the back of the right leg was shaved with the animal clipper. All right tendons were exposed by the same author (H.T.) with a longitudinal midline incision, approximately $^1/_2$ inch, taking care not to damage the paratenon. Then, the tendons were compressed with Mosquito clamps during different time periods, with a randomized selection as seen on Table II. At the end of the selected period, the incision was sutured with a 4-0 silk suture.

Table I

Histopathological Changes in Each Rat Infected with Betamethazone

		Tendon			Paratenon				
Rat No.	Days of Injection	Staining Affinity	Nuclear Appearance	Fibrillar Appearance	Thickness	Fibrosis	Edema	Capillaries	Inflammation
1L	A	1	2	1	1	0	1	1	1
2L	A	0	0	2	1	1	2	1	2
3L	B	1	0	2	1	2	1	1	2
4L	B	2	2	2	2	2	1	2	2
5L	A	0	0	2	0	0	0	0	0
6L	A	1	1	2	0	1	1	1	1
7L	B	0	0	1	0	2	1	1	2
9R	B	0	1	0	0	0	1	1	1
10L	B	2	2	1	1	2	2	1	2
11L	B	2	3	2	2	2	1	1	2
12L	A	2	1	1	1	1	1	0	1
13L	A	0	0	0	0	0	0	0	0
14L	B	1	1	1	1	1	2	2	2
15L	B	2	3	2	2	1	1	1	2
16L	A	2	3	2	2	2	1	1	2
17L	B	1	2	1	2	3	1	1	3
18L	B	2	0	1	1	1	0	1	1
19L	B	0	0	0	1	0	0	0	0
20L	B	0	3	3	2	2	1	1	2
21L	A	2	1	2	2	1	0	0	1
22L	A	0	1	1	0	2	1	2	1
23L	A	1	0	2	0	0	0	0	0
24L	A	2	0	2	1	2	0	1	2
25L	B	1	2	1	1	3	0	1	3
26L	A	1	1	1	1	1	0	0	1

0 = no change, 1 = slight change, 2 = moderate change, 3 = marked change.
L: Left, R: Right.
A: 1-8-15-22. days.
B: 1-4-7-10-13-16-19-22-25-28. days.
Left Achilles tendons ofthe rats no. 8 and 9 have been used to demonstrate the normal histology of the tendon.

Table II
Histopathological Changes in Each Rat Compressed with Clamp

		Tendon			Paratenon				
Rat No.	Period	Staining	Nuclear Affinity	Fibrillar Appearance	Thickness	Fibrosis	Edema	Capillaries	Inflammation
1R	30	1	1	1	1	1	2	1	1
2R	30	0	1	1	1	0	0	0	1
3R	30	1	0	2	1	2	1	1	2
4R	30	1	3	2	2	2	1	1	2
5R	60	1	2	1	1	0	0	1	1
6R	60	1	1	1	1	0	1	1	1
7R	30	1	1	1	1	1	1	1	1
8R	60	0	0	1	0	0	0	0	0
10R	30	1	1	2	1	1	1	1	1
11R	60	1	1	0	0	0	0	1	1
12R	60	2	1	2	2	2	1	1	2
13R	60	1	2	2	2	2	1	1	2
14R	60	1	1	1	1	1	1	1	1
15R	60	2	3	2	2	2	1	1	1
16R	30	2	3	2	1	1	1	1	1
17R	60	3	2	1	2	2	1	1	2
18R	60	2	0	3	1	0	0	0	0
19R	30	1	0	0	1	0	0	0	0
20R	60	0	0	3	2	0	0	0	0
21R	60	0	2	2	1	1	0	0	1
22R	30	1	3	2	1	1	1	1	1
23R	30	1	1	2	2	3	1	2	2
24R	60	3	3	3	2	0	0	0	0
25R	30	1	2	2	1	0	0	0	0
26R	30	2	1	1	0	1	0	0	1

0 = no change, 1 = slight change, 2 = moderate change, 3 = marked change.
R: Right. Right achilles tendon of the rat no. 9 has served as the corticosteroid injection.

Two Achilles tendons were excluded from the experimental process to demonstrate the normal histology of the tendon.

At the end of the experiment, the rats were kept in their individual cages allowing freedom of movement and free access to food and water.

At the end of 30 days, under general anesthesia inducted by the same dosage of Ketamine, both Achilles tendons were exposed and the tendons and paratenons were excised beginning from the distal insertion site up to the musculotendinous junction, fixed in a buffered 10% formalin solution for two days. After embedded in paraffin, the tendons were cut transversely (section thickness of 5-6 μm) and stained with hematoxylin-eosin.

Light microscopic examination was performed under x 100 power. Histopathological changes including staining affinity, nuclear appearance, fibrillar appearance and thickness, occurrence of fibrosis and edema, capillary changes and inflammation were assessed according to a semiquantitative scoring system[11] such as 0 = no change, 1 = slight change, 2 = moderate change, and 3 = marked change.

Statistical analysis of the histopathologic scores was performed using the Kruskal-Wallis nonparametric one way analysis method.

RESULTS

During the waiting period, the rats were in good condition in convenient room temperature. While excising the tendons at the end of 30 days, it was observed that all left tendons (Betamethazone group) were thickened and demonstrated a visible adhesiveness to the subcutaneous tissue. Therefore, their exposure and separation from the subcutaneous tissue was very hard when compared with the right side.

Light microscopic examination revealed a normal appearance of tendons and paratenons in two Achilles tendons which were examined to demonstrate the normal histology of the tendon (Figure 1). The staining affinity varied in different portions of the tendons in both groups. The nuclei of the tendons exhibited slight difference in size, contour and staining affinity between two groups (Figure 2). Fibrillar appearance was encountered

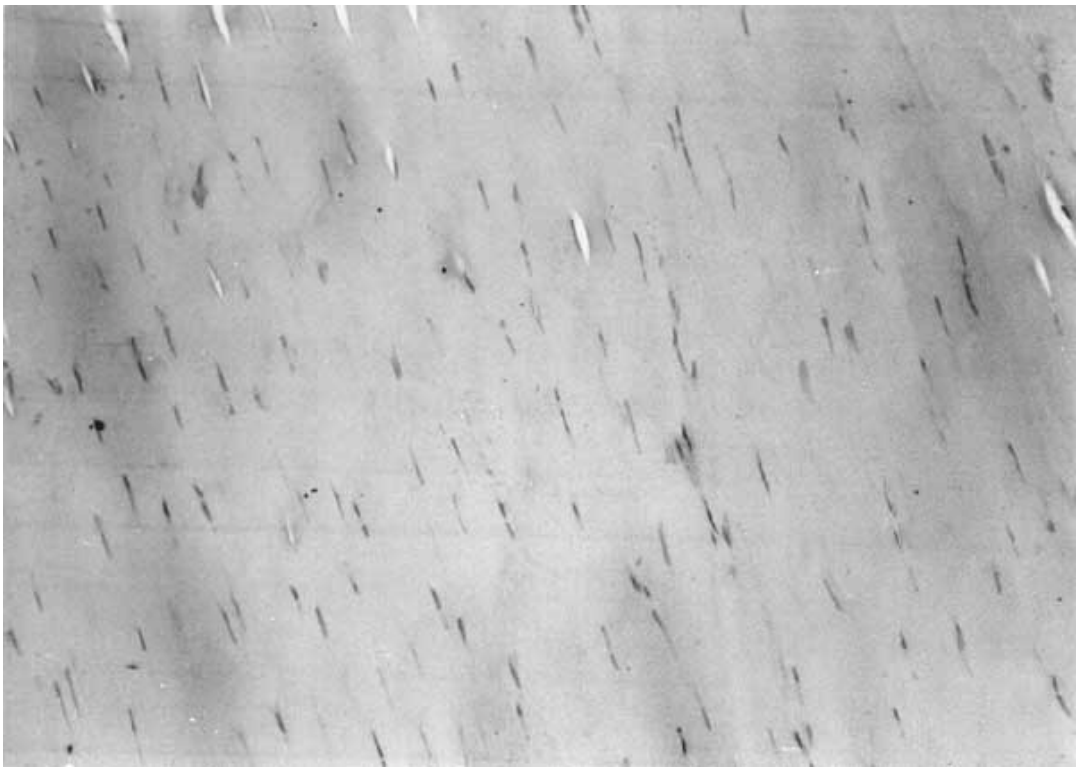

Fig. 1: Normal histologic appearance of Achilles tendon (HE x 100).

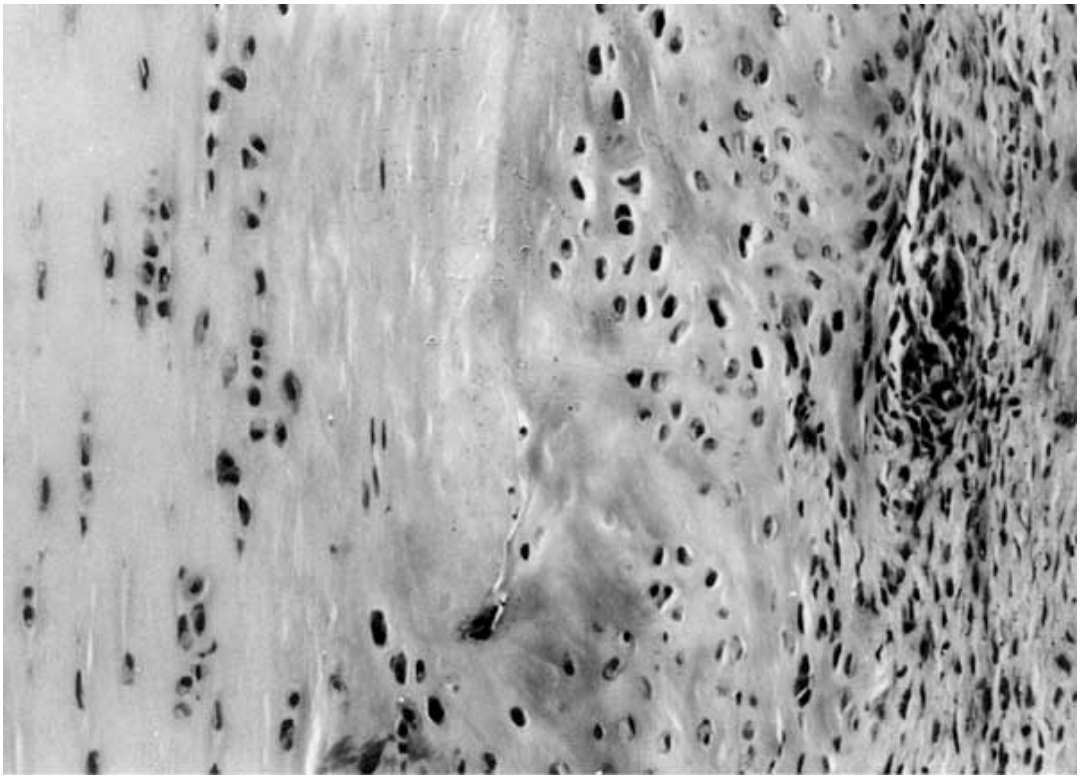

Fig. 2: Nuclear polimorphism, staining heterogenity in the tendon (HE x 100).

in tendons in varying densities. The paratenon was thickened with the infiltration of fibroblasts. Additional changes in the paratenon were edema and infiltration of mononuclear cells. The number of capillaries was increased and these vessels were filled with red blood cells (Figure 3).

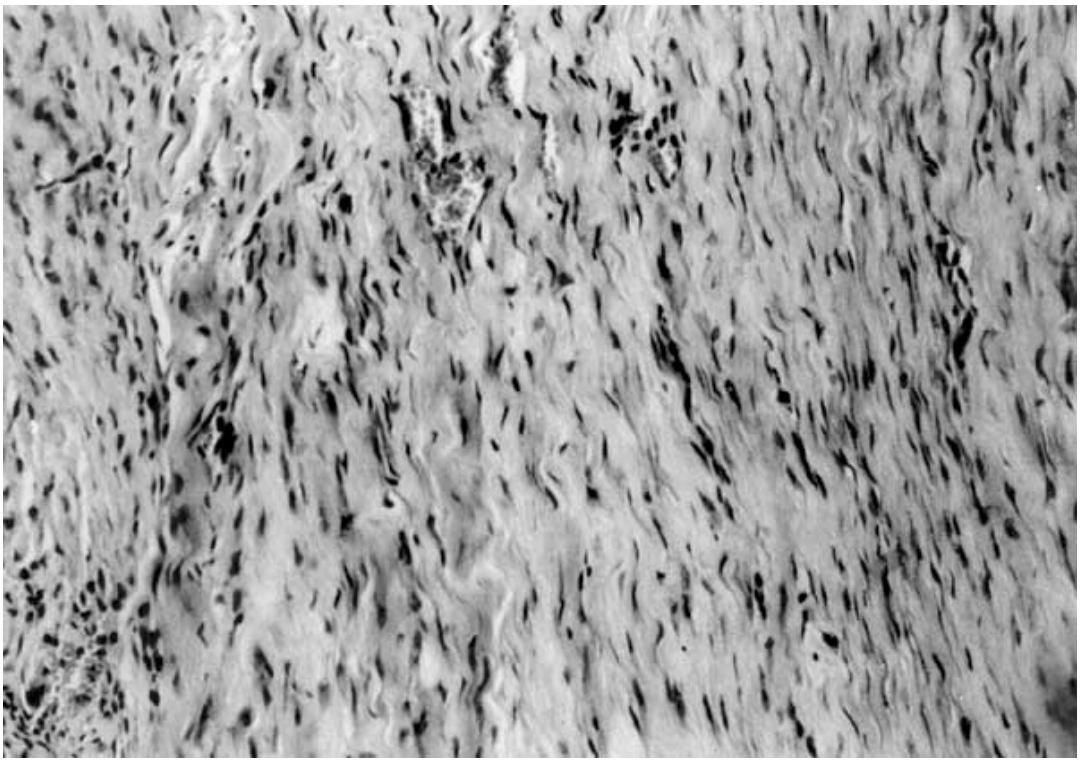

Fig. 3: Fibrillary apearance, mononuclear cell and fibroblast appearance, capillary congestion (HE x 100).

According to the semiquantitative scoring system, the minimum and maximum values can be 0-9 for tendon, whereas for paratenon, the values are 0.15 (Tables I-II). Maximum values show degeneration with full features. The average value for the rats compressed with mosquito clamp was 4.2 for tendon, and 4.6 for paratenon, and the values for the ones injected with corticosteroids was 3.6 for tendon, and 5.1 for paratenon (Table I-II).

According to statistical analysis, there was no significant difference between two models, corticosteroid injection and compression (p-0.44). Even between the compression periods of the clamping group and injection intervals of the Betamethasone group, the statistical difference was insignificant (p-0.68).

DISCUSSION

Achilles tendon degeneration has attracted the attention of many authors since Palla[12]. The most popular drugs used in Achilles tendinopathies are still corticosteroids because of their anti-inflammatory properties. However, they are also known to inhibit collagen synthesis[5]. Evidences of tendon degeneration, like tendon sheath thickening, fibrinoid and myxomatous degeneration and metaplastic calcification[9], marked degenerative, obliterative and/or inflammatory vascular changes[13] were observed in some cases of tendon ruptures due to corticosteroids. Shrier et al.[6] have revealed that in animal studies, corticosteroid injections have decreased the adhesion formation and temporarily weakened the tendon.

In 1956, Davidsson ligated the Achilles tendons of rabbits and observed that even after $5^1/_2$ months, the tendon tissue was extremely irregular and cellular. Dahmen reached almost same results with the same method[12]. Because of this knowledge and expecting that compression will lead to an absolute degeneration in the tendon, this model was used to compare the effects of corticosteroids against compression in the present study. Mosquito clamps were used in different durations (30-60 minutes) for better understanding the reply of tendon tissue to compression.

In 1990, Backman et al.[11] has built an experimental model in rabbits for chronic Achilles paratenonitis with tendinosis. They formed a kicking machine producing passive flexion and extension of the ankle joint of the rabbits. Light microscopic examination revealed varying degrees of degenerative changes of the tendon, increased number of capillaries, infiltration of inflammatory cells, edema and fibrosis in paratenon. This was really a natural, successful, but difficult method. In the present study, the table for semiquantitative assessment of histopathological changes in the experimented animal was taken from the study of Backman et al.

The injection dosage of 0.1 ml. is the one that equals to the normal human dosage for once. But repetition of this dosage even at weekly intervals exceeds the normal human dosage as suggested by McWhorter et al.[4] and should be enough to perform a degeneration. Therefore, in some rats, Betamethasone was injected in seven daily intervals; and even at this frequency, same degree of degeneration was demonstrated in the present study.

As evaluated according to the semiquantitative assessment of histopathological changes in the tendons and paratenons of each animal[11], no significant statistical difference between two models was found. The statistical analysis showed that there was no statistical difference even when the groups were subdivided to subgroups (Table I-II), according to the compression time or injection interval. But, there was a visible fact; and that was the thickness, enlargement and adhesiveness of all achilles tendons to the subcutaneous tissue in the injection group. This macroscopic surgical change revealed that corticosteroid injection is very harmful for the healthy tendon. But when discussed, this conclusion could be due to injection of the Betamethasone partly outside of tendon. In two rats of Betamethasone injected group, no findings of degeneration in tendon was found, whereas the number of the rats with no degeneration for paratenon was three, and there was only one rat with no degeneration in clamp group for paratenon. In all other rats, various levels of degeneration were created successfully.

As a result, it can be said that corticosteroid injections even at seven daily intervals can cause some degree of degeneration in the Achilles tendon and paratenon as much as obtained with that of clamping models. Furthermore, it is obvious that corticosteroids can be used to perform a degeneration model in healthy tendons.

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