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Effects of a Single Application of Adcon Gel on Peritendinous Adhesion: An Experimental Study in Rabbits

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(Accepted for publication, January 20, 2014)

Abstract: Peritendinous adhesions are serious complications after surgical repair of tendons and can lead to poor functional outcome. In the present study, the tensile strength of repaired tendons was measured biomechanically in two groups using a rabbit Achilles tendon model, and the effects of Adcon gel on peritendinous adhesions and tendon healing were examined by means of histological and mechanical analyses. In the treatment group, the Achilles tendon was transected, followed by a primary repair using a modified Kessler technique, and Adcon gel was injected between the tendon and skin of the right leg. The same operation was done for the control group, and 1 mL of normal saline solution was applied locally in a similar fashion. The experimental protocols were approved by the local animal ethics committee. Microscopic evidence of the formation of adhesions and of inflammation was less in the treatment group than in the control group. There was no significant difference in the tensile load necessary to rupture the repaired tendons between the two groups. Adcon gel reduced the peritendinous adhesions histologically without impairing tendon healing, as determined with mechanical analyses. The use of Adcon gel may provide a simple means of preventing of postoperative peritendinous adhesions, thereby offering a beneficial effect on tendon repair.

Key words: Adcon gel, Tendon injury, Peritendinous adhesion

Introduction

Tendons and ligaments have poor regenerative capability. The techniques for the repair of tendon injury include surgical treatment, physical therapy, biomaterials of adjuvant therapy, biological treatment and so on¹⁾. The most frequent complication after tendon repair is the loss of motion as a result of restrictive adhesions between the tendon and the surrounding tissues despite improvements in surgical techniques and postoperative rehabilitation programs²⁻⁴⁾. It is well known that tendon healing ideally should occur in the absence of peritendinous adhesions and through the intrinsic process by the activity of tenocytes in the tendon sheath with adequate supplies of cytokines and growth factors from the outside^{5,6)}. Numerous materials and agents have been used as a mechanical barrier to envelop sutured tendons in attempts to minimize the adhesion formation after primary tendon repair. Currently, the modalities used for preventing adhesions without affecting the healing process include; human amniotic fluid, hyaluronic acid, alginate solution, mannose-6-phosphate, 5-fluorouracil, injection of growth factors or platelet concentrate,

local application of extracorporeal shock wave therapy or ultrasound therapy, local injection of bone-marrow-derived mesenchymal stem cells, systemic administration of anti-inflammatory drugs⁷⁻¹⁶⁾. The use of a barrier during surgery to protect raw tissue surfaces has been shown to be one of the most effective methods of preventing tendon adhesions. The barrier should not impede with tendon healing. Maintaining the tendon's mechanical properties and movement are essential. Adcon gel provides a physical barrier and inhibits fibroblast migration thus protects tendon from postoperative adhesions and is fully absorbed within 4–6 weeks¹⁷⁾. It has been shown to be effective and safe in inhibiting adhesions in clinical and experimental studies^{18,19)}. It is composed of gelatin and polyglycan ester in phosphate buffered saline and it is applied before wound closure.

In this study, we explored the application of Adcon gel in the rabbit Achilles tendon injury model for the prevention or alleviation of peritendinous adhesion.

Materials and Methods

Animals

Experiment were accomplished on New Zealand white male rabbits weighing 2-3 kg were selected. The rabbits were randomly

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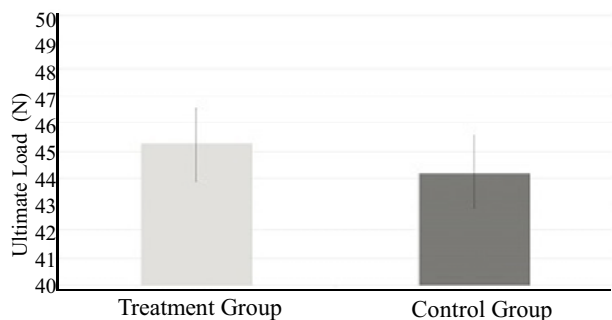


Figure 1. Ultimate load (N) of tendons after four weeks. There is no significant difference between the control and treatment group.

assigned to control and treatment groups of fifteen animals each. Right Achilles tendon of rabbits were used in each group. The experimental protocols were approved by the local animal ethical committee. The rabbits were housed in a room at $24 \pm 1^\circ\text{C}$.

Surgical Procedure

All surgical procedures were performed under aseptic conditions. Animals were anesthetized intramuscularly with 5 mg/kg xylazine hydrochloride (Rompun, Bayer, Turkey), 1 mg/kg atropine sulfate (Atropan, Vetast, Turkey), and 50 mg/kg ketamine hydrochloride (Alfamine, Egevet, Turkey). The hind leg were shaved, scrubbed and disinfected with povidone-iodine solution. Single longitudinal midline skin incisions were made on the Achilles tendon and carefully dissected to uncover the synovial sheath. To access the Achilles tendon, the sheath was incised longitudinally. A standard division of the Achilles tendon was accomplished. In the treatment group Adcon gel was applied locally around the injured tendon between the tendon and skin. In the control group, 1 mL of normal saline was administered to the sheath and tendon. The tendon was repaired with 4-0 polypropylene using modified Kessler stitch and sheath incision were not repaired. Skin closure was done with 5-0 nylon interrupted sutures. The operated hind limbs were immobilized above the knee with a plaster cast with the ankle in 30 degree flexion position. After 4 weeks the rabbits were sacrificed with high doses of Ketamin hydrochloride 200 mg/kg (Alfamine, Egevet, Turkey) given intravenously. All tendons were removed through previous surgical incisions. After the skin incision, the tissue plane around the synovial sheath was dissected and the tendon/sheath complex was divided distal to the ankle joint and proximally at the level of the 3 cm above the tendon insertion respectively. The tendons used for biomechanical testing were wrapped in saline-soaked gauze and biomechanical testing was done on the same day.

Biomechanical Tests

Five of the tendons were selected to test the ultimate load of the injured tendon. Tendons were vertically held in the nonslipping jaws of soft tissue clamps, which were mounted onto a material

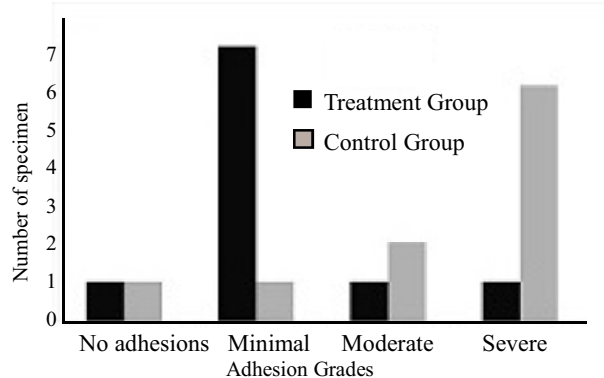


Figure 2 . Schematic presentation of the adhesion grades in the control and treated tendons.

testing machine (Zwick Roell AG, Ulm, Germany). All specimens were consequently loaded to failure point at a static rate of 20 mm/min and force versus displacement data was recorded. Biomechanical data were studied using the Mann-Whitney- U test.

Histologic Evaluation

Ten of the tendons for each group were used for histopathologic evaluations. The tendon/sheath complexes went through a standard method of fixation using 10 % neutral formalin and decalcification solution for a period of 48 hours, which permitted the excision of the specimens. The tendons were cut longitudinally and embedded in paraffin after usual processing. Serial sections were prepared and stained with hematoxylin and eosin. The grading scale of Tang et al.²⁰ was used to assess severity of the formation of adhesions in the peritendinous area. In this grading system the adhesions were evaluated both quantitatively and qualitatively. The extents of the adhesions were classified into 4 grades: no adhesions, minimal adhesions, moderate adhesions, and severe adhesions. An experienced histopathologist performed histologic evaluation the review as a blind observer without having any information about the tendons. The chi-square test was used to evaluate the histologic results. A P value of less than 0.05 was considered statistically significant for histologic and mechanical results.

Results

Biomechanical Results

Ultimate load of the tendons was (45.23 ± 1.23 N) for the treatment group, and (44.17 ± 1.34 N) for the control group. No significant difference was found in ultimate load between two groups ($P > 0.05$). From these biomechanical results it was seen that a single application of Adcon gel did not change the ultimate load of the tendons, and therefore the tensile strength of the tendons were not affected adversely (Fig. 1).

Histopathologic Results

Four weeks after operation, the Adcon gel was degraded.

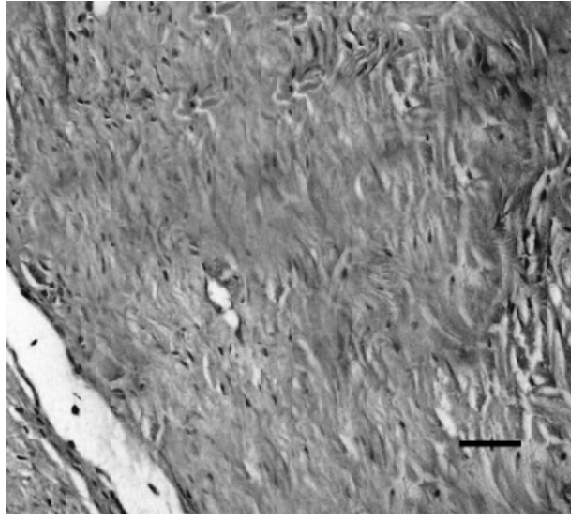


Figure 3. Minimal adhesions. A longitudinal section from the adcon gel treated tendon, showing almost no adhesion and a less cellular synovial sheath. The synovial space is well-preserved (hematoxylin-eosin staining, 200-fold magnification, cross sections, scale bar: 30µm).



Figure 4. Moderate adhesions. Longitudinal section from the control group, more irregular, mixed, shortened, filamentous structures and increased cellularity (hematoxylin-eosin staining, 200-fold magnification, cross sections, scale bar: 30µm).

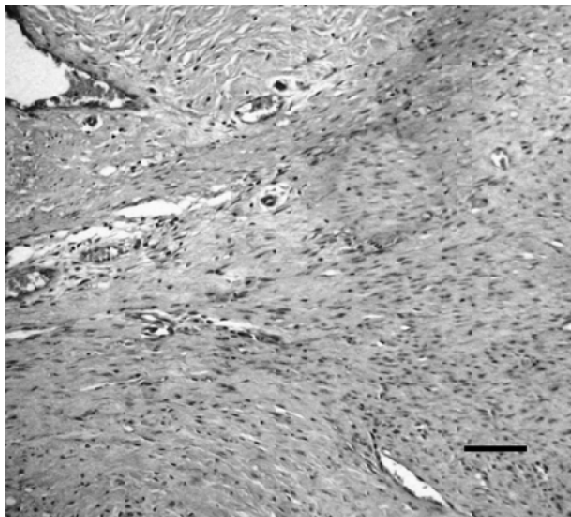


Figure 5. Severe adhesions. Longitudinal section from the control group, showing increased cellularity of the sheath, obliteration of the synovial space and dense ingrowth of adhesion from the synovial sheath into the tendon substance. Severe vascular hyperemia (200-fold magnification, cross sections, scale bar: 30µm).

Histopathologically, less inflammation, and no granuloma was found between the tendon and the surrounding tissue in the Adcon gel treated group. Adcon gel treated group displayed significantly less adhesion compared with the control group (Fig 2). The tendon, incision site, and the skin healed completely in both groups and no infection was seen in either group. There was no adhesions in 1 (10 %), minimal adhesions in 7 (70 %) (Fig 3), moderate in 1 (10 %), and severe in 1 tendon (10 %) in group I (treated tendons); while in group II (untreated tendons), it was absent in 1 tendon (10 %), minimal in 1 tendon (10 %), moderate in 2 (20 %) (Fig 4), and severe in 6 (60 %) (Fig 5). There was significantly less

adhesions in the treatment group compared with control group ($P < 0.05$).

Discussion

In order to prevent peritendinous adhesions while allowing tendon regeneration, we used Adcon gel to investigate if it could prevent adhesions between the injured tendon and the surrounding tissues and provide mechanical strength to the incised Achilles tendon in rabbits.

Surgery is the main treatment for injured tendons.²¹⁾ Peritendinous adhesion, the most frequent complication following tendon surgery, is still a challenging subject for orthopaedic surgeons⁴⁾. Tendon healing is a complicated process through extrinsic and intrinsic mechanisms.²²⁾ Biomaterials function as the sheath that block passage of the fibroblasts but allow the passage of cytokines and growth factors²³⁾. However, some failures were encountered in such usage because of induced serious inflammatory reaction, or prevention of diffusion of nutrients into the healing tendon that at last leads to tendon necrosis.²⁴⁾ Also many synthetic materials for adhesion resistance have failed because of excessive calcification, reject reaction, inadequate biocompatibility and ingrowth of adhesions around the materials.^{8,25-29)} Ding et al. used a commercially available anti-adhesion polylactide film to prevent adhesion of the cecum and peritoneal wall in rabbits. They noticed that a number of animals still suffered from tissue adhesion 30 days post-surgery.³⁰⁾ Therefore, it is critical to alleviate inflammation during the process of material degradation and tissue repair^{31,32)}. Thus, ideal mechanical barriers should be biocompatible, easy to use, properly flexible and absorbable such as hydrogel and autogenous vein graft.³³⁾ Injectable hydrogels are good candidates of barrier

materials, because they exhibit better coverage on the surface of a complex geometry and are appropriate to handle. Numerous pharmacologic agents have been tested to reduce the restrictive adhesion and improve the functional result after flexor tendon injuries. The decrease in synovial reaction and adhesion formation by using of antiproliferative and antimetabolite agents has been proved in previous experimental studies. The effects of treating the synovial sheath with 5-fluorouracil for a period of 5 minutes had been examined in a rabbit model of flexor tendon injury. Restrictive adhesion and local inflammation can be modulated by using this simple technique.^{11,12,34} In a rabbit flexor tendon injury model, Bates et al.⁹ observed that a single intraoperative dose of mannose-6-phosphate, a natural inhibitor of transforming growth factor-beta, enhanced the postoperative range of motion. Adcon gel provides a physical barrier to inter-tissue adhesions and inhibits fibroblast migration on and around neural and tendinous structures and prevents adhesion formation.^{19,35} In a study tendon rupture rates were comparable between the control and Adcon gel treated patients. At six months follow-up, the Adcon gel treated group had better proximal interphalangeal motion.³⁶ It has also been used in treatment and prevention of adhesions at strabismus surgery in rabbits.³⁷ It is a cost effective treatment³⁸. In an experimental study using a murine model intraabdominal administration of Adcon gel reduced postoperative adhesions.³⁹ It seems to be both safe and effective in reducing extraneural scar formation after peripheral nerve surgery.¹⁸ The results of the present study demonstrate that Adcon gel does not affect the healing of flexor tendons. The purpose of the ultimate load assessment was to evaluate the effects of the applied Adcon gel on the biomechanical properties of the healing tendons. Data suggested that the Adcon gel we used had good biocompatibility and could attenuate tendon adhesion after tendon injury.

In conclusion, methods of primary tendon repair keep evolving, tendon adhesions compromising the surgical repair, unfortunately, can not be totally prevented. This study suggests that Adcon gel, may be used to inhibit the formation of peritendinous adhesions.

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