The Effect of Local Corticosteroid or Ketorolac Exposure on Histologic and Biomechanical Properties of Rabbit Tendon and Cartilage

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Abstract Tendonitis, tenosynovitis, and the arthritides are clinical problems commonly encountered in daily orthopaedic practice. Systemic anti-inflammatories, physical therapy, and local corticosteroid injections all are used as nonoperative treatments of these conditions. Systemic anti-inflammatory agents and local corticosteroid agents, however, can be associated with adverse effects that render them intolerable to some patients. As a preliminary study assessing the feasibility of local injection of nonsteroidal anti-inflammatory medication, the histological and biomechanical effects of local exposure of rabbit cartilage and tendon to injectable steroidal (corticosteroid) and injectable nonsteroidal anti-inflammatory agents (ketorolac tromethamine, KT) were determined. Thirty rabbits underwent bilateral knee joint, patellar tendon, and Achilles tendon injections with either normal saline, corticosteroid, or KT. Mechanical and histo-

logic evaluation of the tissues was performed at 6 and 15 weeks after injection. Gross tendon adhesions were observed in more corticosteroid-treated specimens than those exposed to normal saline or KT. Microscopic evaluation of tendons revealed no significant differences among the three groups. Mild cartilage degenerative changes were noted across all groups. Evidence of cartilage necrosis was noted for the corticosteroid-treated group only. Tendons exposed to corticosteroid or KT demonstrated increased load and energy to failure, but exhibited no difference in material stiffness or strain. The use of an injectable nonsteroidal anti-inflammatory agent may be safe and even pose less threat to local tissues after intra-articular and peri-tendinous administration.

Keywords Cartilage · Corticosteroid · Injection · Ketorolac · Tendon

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Introduction

Tendonitis, tenosynovitis, and the arthritides are clinical problems commonly encountered in daily orthopaedic practice. These inflammatory processes often cause considerable discomfort and impair function. Treatment is directed at reducing inflammation through the use of physiotherapeutic modalities, systemic nonsteroidal anti-inflammatory agents (NSAIDs), local corticosteroid injections, and when recalcitrant, surgical intervention.

Each of these current treatment modalities has limitations. The least invasive, physiotherapy, can be used with some success. However, physiotherapy alone often is a painful and slow process without the adjunct of pharmaceutical agents.

Systemic anti-inflammatory agents, while often effective, can be accompanied by annoying and sometimes

dangerous side effects. In general, most NSAIDs inhibit the production of prostaglandins in the tissues [1]. This depression of the protective effect of prostaglandins in the gastrointestinal mucosa has been shown to lead to an increased incidence of gastric ulceration and intestinal bleeding [2, 3]. Prostaglandin inhibition also can lead to impaired renal function, which may result in hypertension and congestive heart failure [4]. Addressing a localized inflammatory reaction using a systemic medication, therefore, despite being the mainstay of treatment, can be fraught with adverse effects more problematic than the initial condition.

Local injection of corticosteroids theoretically avoids the systemic toxicity of medication but can be accompanied by other adverse effects. These include postinjection flare [5], facial flushing [6], rupture of tendons [7–10] and ligaments [11], subcutaneous fat atrophy [12], skin pigmentation changes [13–15], and cartilage damage [16]. Local injection of steroid also has been associated with infection incidences of 1 in 3,000 to 1 in 50,000 [17]. Finally, systemic effects of injected corticosteroid have been demonstrated, including hypothalamic–pituitary–adrenal axis suppression [18–20] and increased glucose synthesis leading to hyperglycemia [21]; although these generally are transient, prolonged endocrine effects—even association with Cushing’s syndrome [19]—have been reported.

The advent of soluble and injectable nonsteroidal anti-inflammatory drugs offers the potential advantage of delivering these anti-inflammatory agents to the local site of the inflammatory process. Such local delivery theoretically would avoid the systemic side effects of these medications. If favorable results could be seen with regard to tendon and cartilage tissue both biomechanically and structurally after injection of NSAIDs peri-tendinously and intra-articularly, this treatment modality might be preferable to local injection of corticosteroids. Therefore, as a preliminary step to determining the safety and efficacy of local injection of NSAIDs in humans, a study of the biomechanical and structural effects on tendon and cartilage tissue is warranted. The purpose of this study was to examine the effects of local injection of corticosteroid and of ketorolac tromethamine (Toradol, Roche Laboratories), a nonsteroidal anti-inflammatory drug, on mechanical and structural properties of intact tendon and cartilage. Although this drug has been approved by the Food and Drug Administration for intramuscular injection, its safety in peri-tendinous and intra-synovial use has not been established.

Materials and Methods

Permission for use of animal subjects was granted by and animal care complied with guidelines of the authors’ institution, the National Institutes of Health, and any

national law on the care and use of laboratory animals. Thirty New Zealand white rabbits were obtained (weight range 2.6–3.5 kg). All rabbits were fed standard ration and quartered in standard cages in accordance with the above-mentioned animal care guidelines.

All rabbits were anesthetized using intramuscular injections of ketamine, xylazine, and acepromazine mixture. Each injection site was prepared sterily using a 10% povidone–iodine solution. Sterile syringes and 25-gauge needles were used for each injection.

Each rabbit was assigned randomly to one of three groups. Isovolumetric injections of normal saline (Group 1, 0.5 cc), methylprednisolone (Solu-medrol, Upjohn, Group 2, 33.3 mg/0.5 cc), or ketorolac tromethamine (Toradol, Roche Laboratories, Group 3, 15 mg/0.5 cc) were performed on three occasions at 10-day intervals. Because a therapeutic dose of peri-tendinous or intra-articular ketorolac is not known, the dose of ketorolac chosen was the highest concentration available in a volume which allowed isovolumetric injection with respect to the methylprednisolone. Each rabbit received injections into the tenosynovial sheaths of bilateral Achilles tendons, into the tenosynovial sheaths of bilateral patellar tendons, and intra-articularly into bilateral knee joints.

There were no complications after injections, and no animal was excluded from the study, leaving ten rabbits in each group. Six weeks after the first injection period, five rabbits from each group were euthanized in a CO₂ chamber. The remaining five rabbits in each group were euthanized in a similar fashion 15 weeks after the first injection. Tissue for analysis was harvested within 5 hours of animal sacrifice.

Evaluation of Gross Characteristics Bilateral Achilles tendons and femoral condyles were harvested from each specimen and examined for gross characteristics including presence of peri-tendinous adhesions and gross cartilaginous damage, respectively.

Evaluation of Histological Characteristics Achilles tendons and femoral condyles were fixed in 10% formalin solution, decalcified, and embedded in paraffin. Specimens were prepared using hematoxylin and eosin staining. Systematic microscopic analysis by a pathologist (RL) blinded to each specimen’s treatment group was performed. Tendon specimens were analyzed for evidence of necrosis, lymphocytic/plasmacytic inflammatory infiltration, focal histiocytic inflammation, and vascularity. Cartilage specimens were analyzed for evidence of degenerative changes including fragmentation and cellular proliferation. The presence of cartilage necrosis also was noted.

Biomechanical Analysis Bilateral patellar tendons including attachments to patellae and tibial tubercles were harvested and

immediately frozen in liquid nitrogen. Biomechanical testing of bone–patellar tendon–bone samples was performed by an examiner blinded to each specimen's treatment group. Each patella was transfixed with a 0.035-in. Kirschner wire and each proximal tibia with a 0.045-in. Kirschner wire; these then were embedded in methylmethacrylate blocks (Fig. 1a–d). After equilibration, the specimens were loaded on an Instron Testing Machine at a deformation rate of 10 in./min (Fig. 2). Ultimate load to failure (pounds, or lbs), absorbed energy to failure (joules), material stiffness (inch-lbs, or in-lbs), and material strain (percentage change in length) were calculated from the recorded load/elongation curve.

Statistical Analysis Fisher's exact test for general two-way contingency tables was used to assess the statistical significance of the association between type of injection and binary outcomes such as presence versus absence of gross peri-tendinous adhesions. Because outcomes on the left and right sides of the same animal might not be independent, outcomes were coded for each animal as present if seen on either side and absent only if absent on both sides. The unit of analysis for statistical tests was, thus, animals ($N=30$) rather than sides ($N=60$). For numeric outcomes such as load to failure, the average of the left and right side values was used for each animal. If one was missing, the single value was used. Because these outcomes showed evidence of non-normal distributions, the nonparametric Kruskal–Wallis test was used to assess the statistical significance of differences between types of injections, with exact p values calculated for comparisons involving fewer than all 30 subjects. Analyses were performed both with all

Figure 2 Specimens were loaded on an Instron testing machine at a deformation rate of 10 in./min.

animals and separately for animals studied 6 and 15 weeks. Fisher's exact test and the Mann–Whitney U test were used to assess the impact of weeks on outcomes.

Results

Evaluation of Gross Characteristics Eighteen of 20 corticosteroid-treated Achilles tendons showed evidence of peri-tendinous adhesions (90%), compared to 6/20 (30%) exposed to normal saline and 8/20 (40%) treated with ketorolac (Table 1). Analysis of the corresponding 3×2 contingency table by Fisher's exact test produced a p value of 0.019. Examination of the femoral condyles did not reveal evidence of gross cartilage damage in any of the groups (Table 1).

Evaluation of Histological Characteristics Microscopic examination of the tendons revealed no evidence of necrosis (Table 2). Four normal saline-treated specimens (20%) and four corticosteroid-treated specimens (20%) showed evidence of increased vascularity (Fig. 3a, $p=0.15$); this was not observed in any specimens exposed to ketorolac. Two specimens exposed to corticosteroid (10%) and two exposed to ketorolac (10%) contained a mild and focal infiltrate of chronic inflammatory cells, whereas those exposed to normal saline did not (Fig. 3b, Table 2, $p=0.51$). Two normal saline-treated specimens (10%) and two corticosteroid-treated specimens (10%) contained focal histiocytic infiltrates; those treated with ketorolac did not (Fig. 3c, Table 2, $p=0.51$).

Histologic evidence of degenerative changes of the femoral condyle cartilaginous surfaces as manifested by fragmentation, cleft formation, and cystic degeneration was present in 8/20 (40%) normal saline-treated specimens, 12/20

Figure 1 Specimens were harvested (a), transfixed with Kirschner wires (b), and embedded into methylmethacrylate blocks (c and d).

Table 1 Gross evaluation of peri-tendinous adhesions and cartilage damage.

	Gross Peri-tendinous Adhesions			Gross Cartilage Damage		
	Group 1 (%)	Group 2 (%)	Group 3 (%)	Group 1 (%)	Group 2 (%)	Group 3 (%)
% at 6 Weeks	40	80	40	0	0	0
% at 15 Weeks	20	100	40	0	0	0

(60%) corticosteroid-treated specimens, and 10/20 (50%) ketorolac-treated specimens (Fig. 4c, Table 3, $p=0.43$). Infarcted cartilage was present in 14/20 (70%) of specimens exposed to corticosteroids, but not at all in specimens exposed to either normal saline or ketorolac (Fig. 4a and b, Table 3, $p<0.0001$).

Biomechanical Analysis Two modes of failure were observed. The first (93%) was a transverse substance tear at the proximal one fourth level of the patellar tendon. The second (7%) was a transverse fracture-separation of the patella at the level of the transfixing Kirschner wire.

The ketorolac-treated tendons required a greater load to failure ($p<0.05$) and energy to failure at both 6 and 15 weeks postinjection than specimens exposed to normal saline (Table 4). Corticosteroid-treated tendons also required a greater load to failure and energy to failure at 15 weeks that was not present at 6 weeks postinjection. Differences between outcomes at 6 and 15 weeks were not statistically significant, although suggestive p values were found for load to failure ($p=0.12$) and energy to failure ($p=0.085$). The possible differences appear to be because of strengthening in the corticosteroid-treated group, with median load increasing from 16 at 6 weeks to 35 at 15 weeks ($p=0.17$) and median energy increasing from 471.5 to 1,168.5 ($p=0.17$). Pooling 6 and 15 weeks of data and comparing outcomes by type of injection produced statistically significant or suggestive p values for load ($p=0.057$) and energy ($p=0.015$), but not for strain ($p=0.62$) or stiffness ($p=0.68$). No differences in material stiffness or material strain were seen between groups at either 6 weeks ($p>0.25$) or 15 weeks ($p=0.83$, 0.092, respectively) postinjection (Table 4).

Differences at time points For all binary outcomes (Tables 1–3), rates at 6 and 15 weeks were very similar ($p=1.0$ in each case).

Discussion

Corticosteroid injections have been used for many years to treat a variety of orthopaedic inflammatory conditions. Adverse systemic effects such as hyperglycemia in diabetic patients [22] and adverse local effects such as tendon rupture [7] and skin depigmentation [14, 15] have been reported.

The present study demonstrated evidence of peri-tendinous adhesions in all three treatment groups with increased frequency seen in the corticosteroid-treated group (Table 1); it is notable that we examined *non-traumatized* tissue. Our results differ from those of Wrenn et al. [23] and Kapetanios [24], who observed less adhesion formation in tendons injected with corticosteroid compared with control; however, these investigators examined effects of intra-tendinous injections on *healing* tendons, not normal tendons. Our observation of increased adhesion formation may be the result of a paradoxical inflammatory reaction to peri-tendinous injection of these substances. A recent study of the effects of corticosteroid injection on the acute collagen expression response to rotator cuff injury demonstrated that corticosteroids did not seem to inhibit the response of traumatized tendon to the injury but created a similar injury–response environment in a *non-traumatized* tendon [25]. If one were to extrapolate these results, our observations are corroborated by this recent study.

Table 2 Histologic examination of tendons.

	Increased Vascularity			Chronic Inflammatory Cell Infiltrate			Histiocytic Infiltrate		
	Group 1 (%)	Group 2 (%)	Group 3 (%)	Group 1 (%)	Group 2 (%)	Group 3 (%)	Group 1 (%)	Group 2 (%)	Group 3 (%)
% at 6 Weeks	40	40	0	0	20	20	40	0	0
% at 15 Weeks	40	20	0	0	20	20	0	40	0

Figure 3 Achilles tendon specimens harvested 6 weeks after injection. **a** Corticosteroid-treated specimen showed evidence of increased vascularity. **b** Ketorolac-treated specimen exhibited a focal lymphocytic infiltrate. **c**. Normal saline-treated specimen showed a focal histiocytic and giant cell infiltrate.

Despite the increased adhesion formation noted grossly, minimal differences in lymphocytic/plasmacytic infiltration, focal histiocytic infiltration, and vascularity were noted between the three treatment groups. In contrast to the study of Balasubramaniam and Prathap [26], which showed evidence of collagen necrosis as early as 45 min after hydrocortisone injection, none of the treatment groups in the present study revealed evidence of tendon necrosis. It is possible that the tendon sustains an initial pathophysiologic insult from which it ultimately recovers.

Whether tendon rupture after local steroid injection is because of an inherent tendon defect [27], steroid inhibition of healing in degenerating tendon [28], or the avascular nature of tendon [29] is unclear; just as the biological response of musculoskeletal tissues to local anti-inflammatory agents is disputed, the literature is divided with respect to the biomechanical effects of corticosteroids on tendons and ligaments. Several studies have reported deleterious effects including decreased tendon strength as exhibited by decreased maximum failure load, energy absorption before failure, and linear stiffness [24, 30]. Recent studies by Haraldsson et al. [31] show decreased tensile strength of collagen fascicles of

rat tendons exposed to methylprednisolone acetate for 3 to 7 days; this collagen weakening after incubation in clinically relevant doses of a commonly used corticosteroid might be associated with tendon rupture. In a study similar to the current investigation, Hugate et al. [32] noted a detrimental effect of retro-calcaneal and intra-tendinous injection on the rabbit Achilles biomechanical properties. Other investigators did not observe such deleterious effects [33, 34]; critics proposed that these studies allowed an inadequate time interval to observe effects after corticosteroid administration. For example, Noyes et al. [30] suggested that reduction in biomechanical parameters would not occur for at least 15 weeks after injection. For this reason, the present study was continued for 15 weeks after the first injection. In contrast to Noyes' results, corticosteroid-treated tendons were found to have larger loads and energies to failure at 15 weeks postinjection. It is possible that this is related to the increased peri-tendinous adhesions in the corticosteroid-treated group. An alternate explanation for the lack of tendon ruptures in our corticosteroid-treated tendons is that tendon rupture in situ may be a result of repetitive loading; tendons were loaded only once all the way to failure in the present study.

Figure 4 Cartilage specimens harvested 15 weeks after injection. **a** Normal saline-exposed specimen with normal appearing cartilage. **b** Corticosteroid-exposed specimen showed evidence of infarcted cartilage including ghost-like shadows of chondrocyte nuclei in all but the deepest cartilage layers. **c** Ketorolac-exposed specimen exhibiting evidence of fragmentation, cleft formation, and regenerative clustering of chondrocytes.

Table 3 Histologic examination of cartilage changes.

	Degenerative Change			Cartilage Necrosis		
	Group 1 (%)	Group 2 (%)	Group 3 (%)	Group 1 (%)	Group 2 (%)	Group 3 (%)
% at 6 Weeks	60	80	80	0	80	0
% at 15 Weeks	60	80	100	0	100	0

Like the corticosteroid-treated tendons, the ketorolac-treated tendons were found to have greater loads and energies to failure at 6 and 15 weeks postinjection. No comparison can be made in terms of biomechanical effects of ketorolac on tendon, as this has not been studied.

In the present study, no gross evidence of cartilage damage was observed in knees injected with normal saline, corticosteroid, or ketorolac when specimens were euthanized at 6 or 15 weeks postinjection. In vitro studies have been performed on the effects of both corticosteroids and nonsteroidal anti-inflammatory drugs on articular cartilage tissue. Glucocorticoids have been shown to inhibit proteoglycan, collagen, and protein synthesis in cartilage [35, 36]. Behrens reported “multiple yellowish lesions” on the weight-bearing surfaces of rabbit articular cartilage after 8 and 12 weekly intra-articular injections of corticosteroids [36]; these lesions were not seen in controls or in knees receiving two or four weekly injections. Microscopically, these defects appeared as cystic lesions filled with tissue debris and were thought to be because of direct mechanical damage to corticosteroid-induced proteoglycan deficiency of chondrocytes. Many other in vivo and in vitro studies have elucidated detrimental effects of intra-articular corticosteroids on cartilage [37–40]. Silberberg et al. [40] noted marked destructive changes in the ultrastructural morphology of hip articular cartilage in mice. Mankin and Conger [38] described a decrease in matrix protein synthesis as measured by decreased glycine- H^3 utilization by rabbit articular cartilage. Both Salter and Kopta reported gross and histologic changes in rabbit cartilage including decreased chondrocyte population, matrix fissuring, and cyst development [37, 39]. Kopta also demonstrated biomechanical and histochemical changes as noted by

decreased cartilage elasticity and decreased mucopolysaccharide content, respectively. In the present study, findings similar to those described by Kopta including matrix fissuring and cyst development were observed in similar ratios for all three groups (Fig. 4c, Table 3). It is unlikely, then, that these findings were unique to any one of the three treatment groups. The most striking finding, however, was the finding of chondrocyte necrosis at both 6 weeks (80%) and 15 weeks (60%) postinjection for *only* the corticosteroid-treated group. As proposed by Kopta, a possible mechanism for this chondrolysis might be related to increased lysosome number with subsequent rupture as described by Silberberg et al. [40]. The absence of gross cartilage damage after three injections of corticosteroid in the current study is in agreement with Behren’s results; it is known that metabolic chondrocyte changes and histologic alterations in cartilage precede gross structural changes [36, 38].

In contrast to corticosteroids, some NSAIDs have been shown not to suppress proteoglycan synthesis and actually enhance net protein synthesis in cartilage [41]. Oral administration of salicylates has been shown to inhibit both cartilage synthesis and cartilage degradation [42–44]. Simmons demonstrated oral salicylate inhibition of cartilage degeneration histologically in rabbit knees [45]. In an in vitro study, Palmoski and Brandt [41] demonstrated a reduction in net glycosaminoglycan synthesis in dog cartilage after treatment with the NSAIDs fenoprofen and ibuprofen. Lutfi and Kosel [46] reported electro-micrographic changes in rabbit cartilage after intra-articular salicylate injection. Kalbhen [47] did not find radiographic or macroscopic degenerative alterations in hen knee joint cartilage after 12 weekly injections of the NSAID fenbuten.

Table 4 Biomechanical analysis of patellar tendon.

	Load to Failure			Energy to Failure		
	Group 1	Group 2	Group 3	Group 1	Group 2	Group 3
Median at 6 Weeks	12	16	28	540.5	471/5	1,252
Median at 15 Weeks	18.5	35	28.5	541.5	1,168.5	1,309.5
Strain				Stiffness		
Median at 6 Weeks	0.26	0.21	0.23	101	120	134.5
Median at 15 Weeks	0.215	0.27	0.23	141	166	178

Few studies have examined the effect of intra-articular ketorolac on cartilage. In an effort to determine the effect of ketorolac and morphine on cartilage after intra-articular injection, Dogan et al. [48] demonstrated mild histopathologic changes to cartilage 1, 2, and 10 days after injections; changes were more evident in cartilage exposed to morphine than to ketorolac, but both differed from control (saline). An inflammatory response also was noted in rat knees after intra-articular ketorolac administration [49]. In the present study, ketorolac injection resulted in degenerative changes, which were noted microscopically in a ratio similar to the control group. In contrast to the corticosteroid-treated group, the ketorolac-treated group showed no evidence of cartilage necrosis (Fig. 3a and b). By the parameters of this study, the effects of intra-articular ketorolac injection on cartilage appear similar to those after injection of normal saline.

The above data suggests that peri-tendinous injection of either corticosteroid or ketorolac might not be harmful to these tissues. Histologic evidence of cartilage necrosis suggests that intra-articular corticosteroid injection may be harmful to articular cartilage. Differences between species in the response to corticosteroids prevent direct extrapolation of the experimental data to clinical human cases. However, the use of an injectable NSAID agent for the treatment of inflammatory and arthritic conditions potentially might avoid the systemic complications associated with oral administration and the systemic and local effects associated with corticosteroid injection. The potential uses of ketorolac as an injectable NSAID agent in humans is encouraging and warrants further study; investigations of ketorolac as a treatment for trigger finger are being conducted at this time.

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