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The Early Effect of Ibuprofen on the Mechanical Properties of Healing Medial Collateral Ligament

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ABSTRACT

We tested the hypothesis that injured ligaments in rabbits treated with ibuprofen would have decreased values of mechanical properties compared with the values of those treated with a placebo. In 24 New Zealand White rabbits, the medial collateral ligament of one hindlimb was ruptured; the contralateral ligament served as an internal control. The rabbits were treated orally, twice daily, with a 14-day course of either 35 mg of ibuprofen per kilogram of body weight or a placebo. The rabbits were sacrificed at 14 or 28 days, and the ligaments were tested in tension to failure at 0.15 mm/sec. There was no statistically significant difference in the values of mechanical properties of ligaments from rabbits treated with ibuprofen versus those treated with placebo at either 14 or 28 days after injury. Our findings suggest that there is no early deleterious effect of a short course of ibuprofen on the mechanical behavior of medial collateral ligaments.

Nonsteroidal antiinflammatory drugs (NSAIDs) are commonly used to treat patients with ligament injuries, yet the effect of such drugs on ligament healing is poorly understood.[1] Few studies have focused on the effect of NSAIDs on the mechanical properties of biologic tissue, and those that do present conflicting findings. Törnkvist et al.[16] reported diminished torsional strength in femora with bicortical defects treated with ibuprofen or indomethacin compared with those treated with placebo. In contrast, another study reported an increase in strength for connective tissue in uninjured rats treated with various NSAIDs.[17] Similar increases in strength were noted in a healing medial collateral ligament (MCL) injury model in rats treated with piroxicam.[2,8] In another study,[6] the plantaris longus tendon in rabbits was transected and then the rabbits were given indomethacin or a placebo. After 16 weeks, the tendons in the rabbits given indomethacin exhibited greater strength than those from the rabbits given a placebo; however, at 4 and 8 weeks, the tendons in the indomethacin-treated group were weaker than those in the placebo-treated group. The difference noted at 8 weeks was significant.

The current study was designed to test the hypothesis that the antiinflammatory action of ibuprofen might impede the early healing response of an injured MCL and thereby compromise the mechanical properties of the ligament, that is, that injured MCLs in rabbits given ibuprofen would be weaker than those in rabbits given a placebo.

MATERIALS AND METHODS

In 24 female New Zealand White rabbits (11 months old), the MCL of one hindlimb was ruptured and the other hindlimb served as an internal control. Using sterile technique, and with the rabbits under surgical inhalant anesthesia (Earrane, Ohmeda Caribe, Guayama, Puerto Rico), we exposed the MCL of one hindlimb of each rabbit through a 2-cm skin incision caudal to the MCL. A 3–0 braided stainless cardiac pacing wire was passed underneath the MCL. Both ends of the wire were pulled medially, creating a midsubstance rupture in the ligament.[10] The limb receiving the injury was alternated between the right and left limbs to avoid any right/left bias. No attempt was made to repair the ligaments. The ruptured ends of the ligaments were placed in apposition and a subcutaneous closure was made using 2–0 monofilament resorbable suture. The skin incision was closed using 3–0 monofilament nonabsorbable suture.

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TABLE 1
Mechanical Property Values for Each Test Group

Group[a]	Failure load (N)	Failure deformation (mm)	Stiffness (N/mm)	Work-to-failure (N·mm)
14 days				
Ruptured ligament				
Ibuprofen	34.7	2.5	40.0	49.0
Placebo	24.3	3.2	5.4	51.0
Control ligament				
Ibuprofen	353.9	4.8	814.0	813.0
Placebo	364.6	4.5	828.0	828.0
28 days				
Ruptured ligament				
Ibuprofen	115.2	2.8	35.0	164.0
Placebo	83.4	2.8	116.0	116.0
Control ligament				
Ibuprofen	358.4	4.6	763.0	764.0
Placebo	338.0	4.4	713.0	713.0
SEM	20.0	0.4	61.0	64.0

[a] Each group contained six MCLs.

Of the 24 rabbits, 12 received a 14-day course of ibuprofen (35 mg/kg) in oral suspension (children's Motrin, 100 mg per 5 ml, McNeil PPC, Inc., Fort Washington, Pennsylvania) administered orally via a syringe twice daily. Thus, each treated rabbit received a total daily dose of 70 mg of ibuprofen per kilogram of body weight.[15] The remaining 12 rabbits received a sugar-water placebo administered twice daily in the same manner as the ibuprofen so that all rabbits experienced similar stress of handling. Administration of ibuprofen or placebo commenced the morning (approximately 18 to 24 hours) after surgery. Rabbits were assigned to either the treatment or placebo group using a fully blocked design to minimize potential systematic influences. The surgeon (CTM) was unaware of the treatment group of each rabbit. The rabbits were housed one per cage and allowed to eat and exercise ad libitum. To reduce the stress of handling, each rabbit was given Honey Nut Cheerios (General Mills, Minneapolis, Minnesota) immediately before and after administration of the ibuprofen or placebo (C. DeCamp, personal communication, 1996).

At 14 and 28 days after surgery, 12 rabbits (6 from the ibuprofen group and 6 from the placebo group) were anesthetized with a mixture of 1 ml of acepromazine and 4 ml of ketamine and then given an intravenous overdose of sodium pentobarbital (20 to 45 mg/kg). This method of sacrifice was in accordance with American Veterinary Medical Association guidelines[3] and was approved by our Institutional Review Board. Each knee joint was harvested by transecting the femur and tibia 6 cm above and below the joint line, respectively. The surrounding muscles and joint capsule were excised while keeping all ligaments and menisci around the knee joint intact. All MCLs were subjected to uniaxial tensile tests to determine ligament mechanical properties.

Six-millimeter lengths of 0.062-inch diameter Kirschner wire were inserted transversely through each femur and tibia to increase the hold of the bone cement on the test specimen. The test specimens were then potted with polymethyl methacrylate cement into specially designed stainless steel bone pots so that the knee was in 70° of flexion (the neutral position for the rabbit knee).[9] This position was maintained by securing the bone pots with a stabilizing bar. While the cement hardened, the specimen was kept moist and longitudinally aligned. Subsequently, the MCL in each specimen was isolated by excising the remaining soft tissues, such as the collateral ligaments and menisci.

The potted specimen was placed into an environment chamber into which heated saline (37°C) was sprayed, thus creating a 100% humidity environment. The potted specimen was affixed to the materials testing machine (model 8521, Instron, Canton, Massachusetts) and aligned horizontally so that the long axis of the ligament passed through the axis of the actuator and load cell. The stabilizing bar was then removed and ligament zero was determined.[13] Length, thickness, and width were measured using a digital micrometer. The specimen was then stretched to failure at a grip-to-grip rate of 0.15 mm/sec.[11] The resulting force-versus-deformation data were recorded. The parameters of interest were failure load, failure deformation, stiffness, and work-to-failure. Failure load was defined as the peak load, and failure deformation was defined as the deformation corresponding to the failure load. Stiffness was calculated as the maximum slope of the force-versus-deformation curve, and work-to-failure was calculated as the area under the force-versus-deformation curve up to the point of failure load.

Experimental effects were analyzed using a multivariate analysis of variance, and post hoc comparisons between groups were checked for significance (set at $P < 0.05$) using the Student-Neuman-Keuls test. The dependent variables were the parameters of interest defined earlier (failure load, failure deformation, stiffness, and work-to-failure); the experimental factors were treatment (ibuprofen versus placebo), leg (operated versus control), and harvest time (14 versus 28 days).

RESULTS

The mean failure load values for ligaments from the ibuprofen group were higher than those for ligaments from the placebo group, but none of these differences was significant (Table 1). This finding was valid for rabbits sacrificed at 14 or 28 days. There was a significant increase in failure load from 14 to 28 days for both the ibuprofen- and placebo-group MCLs. Even so, at 28 days, the average failure loads of ibuprofen- and placebo-group MCLs were 32% and 25% of their contralateral controls, respectively. There was no significant change in failure load of control ligaments from 14 to 28 days, regardless of treatment.

Similar trends were noted for failure deformation, work-to-failure, and stiffness, that is, there were no significant differences between ruptured ligaments from the ibuprofen or the placebo group at either 14 or 28 days (Table 1). Unlike failure load, however, there was no significant increase in failure deformation, stiffness, and work-to-failure for ruptured ligaments between the two time periods, regardless of treatment group. In all cases, the ruptured ligaments had significantly diminished parameters in comparison with the control ligaments, regardless of treatment group.

DISCUSSION

Contrary to our original hypothesis, the results of the current study indicated there was no diminution in failure load of healing MCLs in rabbits given a 14-day course of ibuprofen compared with those given a placebo; nor was there a significant decrease in the other mechanical properties. Our original hypothesis was motivated by a concern that the antiinflammatory action of ibuprofen might impede the early healing response of injured MCL and thereby compromise the mechanical strength of the ligament.

The benefit of NSAID therapy for acute soft tissue injury has been documented.[14] Diminished pain and swelling in the acute phase of healing promotes earlier mobilization and allows strengthening exercises, which minimize atrophy and shorten recovery time. However, concern has been raised that reducing inflammation might impede the early healing process and thus affect ligament strength,[7,14,18] fueling controversy about the appropriateness of corticosteroid and NSAID therapy for the management of acute soft tissue injuries.

Ibuprofen and indomethacin have been shown to decrease torsional strength in healing bone.[16] Furthermore, transected plantaris longus tendons in rabbits treated with indomethacin were shown to have diminished failure load values at 4 and 8 weeks compared with those from rabbits given a placebo.[6] However, caution should be used in comparing these results and those of the current study. First, the plantaris longus tendon is anatomically distinctly different from the MCL, and it is subject to a different mechanical environment. Second, the hindlimbs of the rabbits in the plantaris longus tendon study were immobilized with casts to protect the healing tendon. Immobilization results in decreased failure load of healing MCLs compared with nonimmobilized specimens.[2,12] It is unknown how much of the decreased tendon strength was a result of immobilization and how much was a result of the action of indomethacin. Finally, although indomethacin and ibuprofen are both NSAIDs, they may have different actions and effects on the mechanical properties of soft tissues.[17]

In the current study, MCLs of rabbits given ibuprofen exhibited greater mean failure load values than those of rabbits given a placebo, but none of the differences was statistically significant. Vogel[17] showed that the strength of uninjured tissue in rats increased after treatment with various NSAIDs. He attributed this change to an increase in collagen cross-linking. Similarly, Dahners et al.[8] and Almekinders and Gilbert[2] reported an increase in MCL strength in rats treated with piroxicam compared with those treated with a placebo. They attributed the increase in strength to increased collagen production. Although Carlstedt et al.[6] reported weaker tendons at 4 and 8 weeks in rabbits treated with indomethacin compared with those treated with placebo, the indomethacin-group tendons at 16 weeks were significantly stronger than their placebo-group counterparts. Those authors suggested that the late increase in strength was a result of increased collagen cross-linking.

We estimated that more than 100 rabbits would be required to show a significant difference between MCLs in those treated with ibuprofen or placebo in the 28-day group, and we decided that such a commitment of resources was not warranted. The mechanical property values obtained in the current study were in agreement with those reported elsewhere for uninjured[19] and healing[5] rabbit MCLs. We chose not to report material properties because of the inaccuracies associated with measuring cross-sectional areas of MCLs during the early stages of healing. We focused on the early, not long-term, effects of a short course of ibuprofen on healing.

We chose to administer a high dose of ibuprofen to our rabbits under the assumption that any effect would be most notable in response to a high dose. We found no information equating ibuprofen dosage in rabbits to that in humans, and little information exists regarding the pharmacokinetics of ibuprofen in rabbits.[4] The maximum ibuprofen dose tested in human rheumatologic studies was 4800 mg/day (Upjohn Co., Kalamazoo, Michigan; personal communication, 1998). Based on a 70-kg man, this dosage equates to 68 mg/kg per day in rabbits. Therefore, the rabbit dosage used in the current study was calculated as 35 mg/kg administered twice daily, for a total daily dose of 70 mg/kg. Rabbits have been given as much as 280 mg of ibuprofen per kilogram per day without complications.[15]

A recent review of clinical studies regarding the efficacy of various NSAIDs indicated that outcomes in patients treated with NSAIDs were either no different or better than in those treated with a placebo.[1] In any case, none of the studies suggested negative outcomes in patients treated with NSAIDs relative to the patients treated with a placebo.[1]

In conclusion, the results of the current study suggest that a short course of ibuprofen does not adversely affect the mechanical properties of MCLs in the early and intermediate phases of healing.

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knee: Driving reaction time before and after anterior cruciate ligament reconstruction

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Abstract Driving reaction time was studied in 73 patients under anterior cruciate ligament (ACL) reconstruction using a computer-linked automobile simulator. Each patient was tested pre-operatively and 2, 4, 6 and 8 weeks after surgery. Stepping and standing tests were studied at each time point. Twenty-five normal subjects were also tested as controls. Pre-operative test results did not differ significantly between groups on any of the tests. Post-operatively it took 6 weeks for driving reaction time of the right ACL group to be equivalent to that of the controls, compared to 2 weeks in the left ACL group. There was a strong correlation between the stepping and standing tests and the driving reaction time; this made them good clinical tests to monitor patients' progress and to suggest the appropriate time to resume driving.

Keywords Driving reaction · ACL reconstruction

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