

Indomethacin and Celecoxib Impair Rotator Cuff Tendon-to-Bone Healing

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Background: Nonsteroidal anti-inflammatory drugs are commonly prescribed after rotator cuff repair. These agents can impair bone formation, but no studies have evaluated their impact on tendon-to-bone healing.

Hypothesis: Traditional nonselective nonsteroidal anti-inflammatory drugs and cyclooxygenase-2-specific nonsteroidal anti-inflammatory drugs interfere with tendon-to-bone healing.

Study Design: Controlled laboratory study.

Methods: One hundred eighty Sprague-Dawley rats underwent acute rotator cuff repairs. Postoperatively, 60 rats received 14 days of celecoxib, a cyclooxygenase-2-specific nonsteroidal anti-inflammatory drug; 60 received indomethacin, a traditional nonselective nonsteroidal anti-inflammatory drug; and 60 received standard rat chow. Animals were sacrificed at 2, 4, and 8 weeks and evaluated by gross inspection, biomechanical testing, histologic analysis, and polarized light microscopy to quantify collagen formation and maturation.

Results: Five tendons completely failed to heal (4 celecoxib, 1 indomethacin). There were significantly lower failure loads in the celecoxib and indomethacin groups compared with the control groups at 2, 4, and 8 weeks ($P < .001$), with no significant difference between nonsteroidal anti-inflammatory drug groups. There were significant differences in collagen organization and maturation between the controls and both nonsteroidal anti-inflammatory drug groups at 4 and 8 weeks ($P < .001$). Controls demonstrated progressively increasing collagen organization during the course of the study ($P < .001$), whereas the nonsteroidal anti-inflammatory drug groups did not.

Conclusion: Traditional and cyclooxygenase-2-specific nonsteroidal anti-inflammatory drugs significantly inhibited tendon-to-bone healing. This inhibition appears linked to cyclooxygenase-2.

Clinical Relevance: If the results of this study are verified in a larger animal model, the common practice of administering nonsteroidal anti-inflammatory drugs after rotator cuff repair should be reconsidered.

Keywords: rotator cuff; shoulder; nonsteroidal anti-inflammatory drug (NSAID); tendon-to-bone

The rotator cuff tendon-bone insertion site is a highly specialized tissue in which there is a fibrocartilage zone between the tendon and the bone.^{4,9} The insertion site provides a gradual transition from soft tissue to hard tissue, allowing diminished stress concentration at the junction of these tissues.³³ Most rotator cuff repairs require reattach-

ment of the tendon to the bone. After rotator cuff repair, a fibrovascular interface tissue forms between the tendon and the bone, followed by bone ingrowth into the interface tissue. Eventual healing occurs by reestablishment of collagen fiber continuity between the bone and the tendon. Healing between the repaired rotator cuff tendon and the bone is a gradual process,^{18,27} with the tendon-bone attachment site being the weak link during the early healing period. Previous studies have demonstrated high failure rates of rotator cuff tendon healing when evaluated objectively using ultrasound or MRI.^{8,15-17,23} Thus, it is essential to determine factors that might improve success. Numerous studies have focused on methods to improve the initial fixation strength between the tendon and the bone, with attention to the type of fixation device (suture anchors, sutures alone, or newer devices), suture pattern,

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or suture material. However, there is little information available about methods to improve the biology of tendon-to-bone healing. Because rotator cuff tendon repair appears to depend on bone ingrowth and new bone formation, factors that can affect bone metabolism may play an important role in modulating healing.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed after orthopaedic surgical procedures, including rotator cuff repair. They function by inhibiting the enzyme cyclooxygenase (COX), which catalyzes the conversion of arachidonic acid to prostaglandins and thromboxane. Two forms of COX have been identified (COX-1 and COX-2).²⁸ COX-1 is a constitutively expressed enzyme found in most tissues and organs, including the gastric mucosa and kidneys, in which production of normal prostaglandin levels is vital to tissue homeostasis.¹⁰ COX-2, on the other hand, is an inducible enzyme produced by inflammatory cells and tissues.²⁸ Although traditional (nonselective) NSAIDs inhibit both COX-1 and COX-2 enzymes, the newer generation of NSAIDs, COX-2 inhibitors, selectively inhibit COX-2, with the advantage of minimizing gastrointestinal and platelet-inhibitory side effects. Both forms of NSAIDs are commonly administered in the postoperative period because of their presumed value in the reduction of pain and inflammation, thereby minimizing narcotic requirements.²⁸

With the widespread use of NSAIDs in the perioperative period and the increasing use of COX-2 inhibitors, their influence on healing has come under investigation. Recent studies have shown NSAID-induced inhibition of healing, as well as inhibition of ligament healing, in a spine fusion model.^{12,13} To our knowledge, however, no studies have examined the impact of NSAIDs on tendon-to-bone healing. The purpose of this study was to test the hypothesis that traditional NSAIDs and COX-2 inhibitors would impair tendon-to-bone healing. We tested this hypothesis using a previously established rat rotator cuff repair model.

MATERIALS AND METHODS

Study Design

Based on previous studies that have demonstrated anatomical similarities with the human shoulder, the rat rotator cuff was chosen to study rotator cuff tendon healing.³⁰ After obtaining approval from our Institutional Animal Care and Use Committee, we obtained 180 mature, male Sprague-Dawley rats with a mean preoperative weight of 384.6 g. They were provided with fresh water and rat chow ad libitum and housed in pairs preoperatively. Each animal underwent detachment and immediate repair of the right supraspinatus tendon using bone-tunnel suture fixation. Postoperatively, they were housed individually for 14 days and then in pairs afterward. The animals were divided into 3 experimental groups: celecoxib, indomethacin, and no drug. The animals were sacrificed at 2, 4, and 8 weeks, and the tissues were analyzed using histologic and biomechanical testing.

Surgical Technique

The rats were anesthetized with intraperitoneal injection of ketamine (80 mg/kg) and xylazine (5 mg/kg). Anesthesia was maintained using 2% Isoflurane (Baxter, Deerfield, Ill). All operations were performed using a sterile technique with the rat in the lateral position. A deltoid-splitting incision was made, and the acromioclavicular joint was divided, allowing visualization of the rotator cuff tendons. The anterior margin of the supraspinatus was identified adjacent to the biceps tendon, and the posterior margin was determined by the junction with the infraspinatus tendon fibers. A modified Kessler stitch using 5-0 Prolene (Ethicon, Johnson and Johnson, Piscataway, NJ) suture was placed into the supraspinatus tendon. The tendon was then sharply dissected from the greater tuberosity. The tuberosity was gently roughened with a scalpel blade and debrided of all soft tissue and fibrocartilage. Bone tunnels were created at the anterior and posterior extents of the insertion site, 2 mm from the articular surface, in a crossed fashion. The suture ends grasping the tendon were then passed through the bone tunnels and tied over the humeral cortex, reapproximating the supraspinatus tendon to the greater tuberosity. The incision was closed in layers. Buprenorphine (0.05 mg/kg) was administered subcutaneously for analgesia during the postoperative period. Weightbearing activities were ad libitum postoperatively.

Experimental Groups

The rats were randomly assigned to 1 of 3 experimental groups postoperatively (60 rats per group). The first group received celecoxib (10 mg/kg/d), the second group received indomethacin (3 mg/kg/d), and the third group received no drug (controls). The drugs were mixed into a standard rat diet by Purina Mills Test Diets (Richmond, Ind) based on dietary requirements of 5 mg chow per 100 g rat weight. Indomethacin and celecoxib were administered for 2 weeks postoperatively, after which a standard diet was provided. The dose of indomethacin was chosen based on the dose known to inhibit fracture healing and spine fusion.²⁴ We used a lower indomethacin dose than did previous studies to limit adverse effects. We chose a celecoxib dose based on studies of rat ligament, fracture, and spinal fusion healing.^{13,24,29} Any remaining food in each cage was weighed before the next feeding to quantify drug ingestion.

The 3 groups of rats were divided into sacrifice times of 2, 4, and 8 weeks, resulting in 9 groups of 20 rats. Within each group of 20 rats, 17 specimens were used for biomechanical testing and 3 for histologic analysis. After sacrifice, the rat shoulders were harvested and either frozen at -80°C or prepared for histologic analysis.

Biomechanical Testing

On the day of testing, each shoulder was thawed at room temperature, and the humerus with attached supraspinatus was meticulously dissected from the surrounding tissues. All dissections were performed in a blinded fashion. The supraspinatus muscle was bluntly removed from the

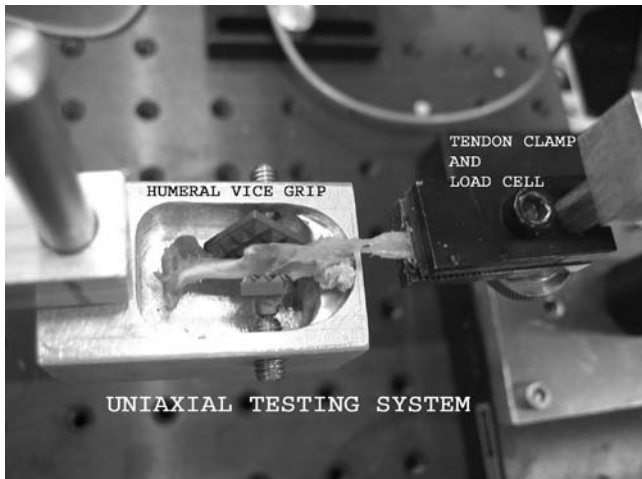


Figure 1. Custom-designed uniaxial testing system for biomechanical testing.

tendon. The cross-sectional area of the supraspinatus tendon at its insertion site was measured using a digital micrometer. The specimen was then placed into a custom-designed uniaxial testing system (Figure 1). The tendon was secured in a screw grip using sandpaper and ethyl cyanoacrylate (Krazy Glue, Elmer's Products Inc, Columbus, Ohio). The humerus was secured in a custom-designed vice grip that prevented fracture through the humeral physis. The supraspinatus tendon was secured to a 45-N load cell attached to a linear bearing that allowed alignment of the tendon in the direction of its pull. The humeral jig was secured to the linear stage. The specimen was preloaded to 0.10 N and then loaded to failure at a rate of 14 $\mu\text{mol/s}$, corresponding to approximately 0.4% strain. The maximum load at failure and the failure site were recorded. Displacement was measured using a 1- μmol resolution micrometer system attached to the linear stage. The linear region of the stress-strain curve was used to calculate the stiffness for each specimen.

Histologic Analysis

A total of 27 animals were used for histologic analysis. Nine rats (3 of each control, celecoxib, and indomethacin groups) were sacrificed at 2 weeks, 4 weeks, and 8 weeks after surgery. The tissue specimens were fixed in 10% neutral buffered formalin for 48 hours. After fixation, tissues were decalcified in Immunocal (Decal, Congers, NY) for 24 hours and washed in phosphate-buffered saline solution. The tissues were then dehydrated and embedded in paraffin. Five micrometer-thick sections including the repaired supraspinatus tendon and the greater tuberosity were cut in the coronal plane and then stained with hematoxylin and eosin and picrosirius red. Three slides were made from each specimen (9 slides per group). The appearance of the repair site and histologic findings were then evaluated in a blinded fashion.

Picrosirius red staining was used for semiquantitative analysis of collagen content. The sulphonic acid groups on the sirius red molecules bind to the amino groups in collagen in an oriented fashion, resulting in a 7-fold increase in

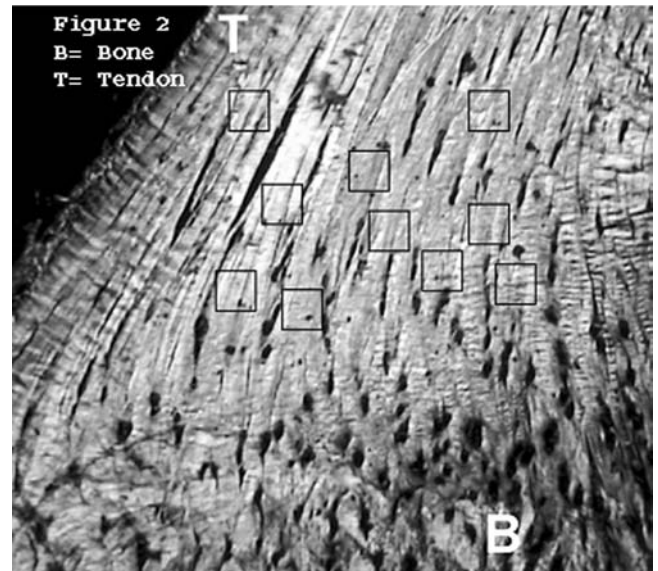


Figure 2. Digitized image of tendon insertion after staining with picrosirius red. Ten $50 \mu\text{m} \times 50 \mu\text{m}$ ($2500 \mu\text{m}^2$) randomly selected squares were selected to measure birefringence.

collagen birefringence.²² To evaluate the organization of collagenous tissue in the repaired supraspinatus tendon, sections were stained with picrosirius red and illuminated with monochromatic polarized light.^{22,26} By quantifying the birefringence of collagen under polarized light (based on brightness), time-dependent differences in collagen deposition and maturation in the healing tendon could be detected.²⁶ Measurements were obtained by rotating the polarization plane until maximum brightness was obtained to control for variations in specimen orientation on the slide. To facilitate comparisons between groups, all tissues were embedded and cut in exactly the same orientation, and sections were cut to a uniform thickness. The greater tuberosity, repaired tendon-bone insertion site, and midsubstance of the supraspinatus tendon were examined under light and polarized light microscopy using an Olympus BH-2 light microscope (Olympus Optical, Lake Success, NY). The light microscope was interfaced to a CCD video camera mounted on an eyepiece tube. The video signal underwent 8-bit digitization by Image J software (NIH, Bethesda, Md), with a resolution of 640 (horizontal) by 480 (vertical) pixels. The microscope fields were digitized using a computer-video system, yielding an image in which noncollagenous material was dark (gray level 0) and collagenous material was depicted by gray scales from 1 to 255. The measurement of gray scale was performed at the tendon end adjacent to the insertion site using the Image J Software program. Ten rectangular areas ($2500 \mu\text{m}^2$ each) were randomly selected, and gray scales were measured (mean \pm SD) (Figure 2). Three sequential coronal sections of each specimen were examined to reduce sampling error. The light intensities were measured under exactly the same conditions of illumination for all specimens.

We also assessed new bone formation at the greater tuberosity, cellularity and vascularity in the tendon-bone

interface, new matrix deposition in the tendon-bone interface, the presence of cartilage at the tendon-bone interface, and collagen fiber continuity from the bone surface into the interface tissue.³¹ Newly formed bone was evident as poorly organized, woven bone under polarized light, in contrast to the lamellar appearance of native bone. The number of osteoclasts were counted in 10 randomly selected high-power fields at the tendon attachment site, and means were calculated.

Statistical analysis was performed using SYSTAT software (SYSTAT Software, Richmond, Calif). Comparisons between groups were performed with 1-way analysis of variance with significance set at $P < .05$.

RESULTS

Two rats died intraoperatively from anesthesia-related causes and were replaced. There were no postoperative complications. Measurements of food remaining in the animal's cages during the first 14 days demonstrated no significant differences between the control, celecoxib, and indomethacin groups, with 91.4%, 92.8%, and 93.2% of total food consumed, respectively. Despite this outcome, significantly greater weight loss was noted in the indomethacin group compared with the control and the celecoxib groups during the first 2 weeks. In the 2-week group, the indomethacin group lost a mean of 17.26 ± 10.56 g, whereas the celecoxib and control groups lost a mean of 4.10 ± 13.83 g and 8.89 ± 11.27 g, respectively. Statistically significant differences were found in weight loss between the indomethacin group and both the control ($P = .035$) and the celecoxib groups ($P = .001$). This finding is consistent with clinical findings in humans, suggesting greater gastrointestinal upset in the indomethacin group. In the 4-week and 8-week groups, all rats gained weight with no significant differences between groups.

Gross Observations

There was continuity between the repaired tendon and the bone in all animals. At 2 weeks, there was poorly organized, thin tissue connecting the tendon to the bone, with no detectable differences between groups. However, clear differences were observed at the 4-week and 8-week time periods. The tendon and tendon-bone interface tissue in the celecoxib and indomethacin groups were distinctly less robust and less organized than in the control group. Furthermore, 5 tendons were noted to have completely failed to heal to bone: 4 were in the celecoxib group, and 1 was in the indomethacin group. No tendons in the control group failed to heal.

Biomechanical Testing

All specimens failed at the tendon-bone attachment site during biomechanical testing. There were significantly lower failure loads in the celecoxib and indomethacin groups compared with the control group at all time points (Table 1). There were no statistically significant differences

TABLE 1
Comparison of Load to Failure (Newtons)
Among Control, Indomethacin, and Celecoxib Groups
at 2-Week, 4-Week, and 8-Week Time Periods

	Control	Indomethacin	Celecoxib
2 weeks	8.4 ± 3.0	5.1 ± 2.6^a	5.3 ± 3.8^a
4 weeks	20.0 ± 4.7	10.5 ± 4.8^b	9.3 ± 6.1^b
8 weeks	34.8 ± 7.3	26.4 ± 9.2^c	24.8 ± 5.9^c

^aCompared with control group, $P < .006$.

^bCompared with control group, $P < .0001$.

^cCompared with control group, $P < .001$.

in the load to failure between the indomethacin and celecoxib groups at any time period. Despite discontinuation of the drugs after 2 weeks, significant differences persisted at 8 weeks (Table 1).

There were no significant differences in stiffness between the control group and the NSAID groups, nor between the NSAID groups themselves, at any time period. A significant difference in cross-sectional area measurements was found only between the control group and the indomethacin group at 8 weeks ($P < .001$).

Histologic Analysis

Controls. At 2 weeks, there was a poorly organized, highly cellular, fibrovascular granulation tissue at the tendon-to-bone interface. There was bone remodeling with osteoclastic activity and new bone formation at the bone-insertion site. The tendon proper was hypercellular, containing a mixture of fibroblastic cells and round cells (Figure 3A). The interface tissue became progressively more organized with time. At 4 weeks, the interface was less cellular and began to show matrix organization in line with the tensile pull of the tendon (Figure 3D). Early fibrocartilage formation was seen in the interface by 4 weeks. By 8 weeks, there was better collagen fiber organization in the control group (Figure 3G). The tendon itself became progressively less cellular, and the tendon fibroblasts were increasingly oriented along the tendon (Figures 4 A, D, and G).

Experimental Groups. The celecoxib and indomethacin groups displayed similar morphologic characteristics at the healing tendon-bone attachment site at all time points. At 2 weeks, there was a highly cellular granulation tissue in the tendon-bone interface comparable to the controls. This tissue gradually remodeled over time but remained poorly organized, even at 8 weeks. In contrast to the control specimens, a fibrocartilage zone did not consistently reform between the tendon and the bone. No difference in vascularity was observed between the control and experimental groups (Figure 3).

Osteoclast Numbers. The number of osteoclasts at the tendon insertion site declined faster in the control group than in the NSAID-treated groups. The control group demonstrated significant differences in osteoclast numbers between the 2-week and 4-week groups ($P = .04$) as well as between the 2-week and 8-week groups

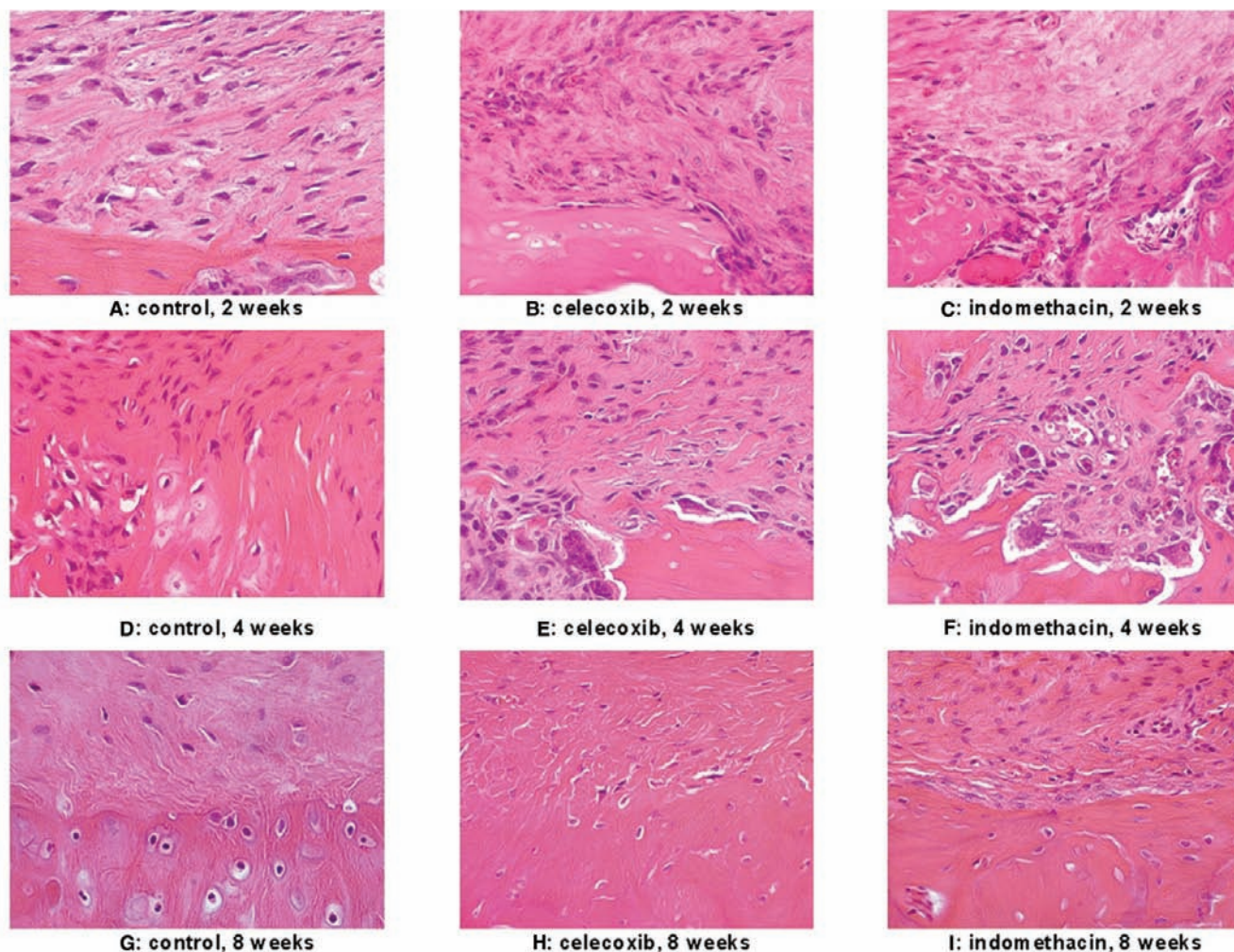


Figure 3. Photomicrograph demonstrating tendon-bone insertion site at 2 weeks (A, control group; B, celecoxib group; C, indomethacin group), 4 weeks (D, control group; E, celecoxib group; F, indomethacin group), and 8 weeks (G, control group; H, celecoxib group; I, indomethacin group) after surgery (hematoxylin and eosin, $\times 320$).

TABLE 2
Number of Osteoclasts at the Supraspinatus Insertion Site (cells/mm² \pm SD)

	Control	Indomethacin	Celecoxib
2 weeks	6.7 \pm 2.5	4.5 \pm 3.1	6.6 \pm 2.7
4 weeks	4.2 \pm 2.5 ^a	6.9 \pm 2.8	6.8 \pm 1.5
8 weeks	1.8 \pm 1.9 ^b	2.8 \pm 2.8	2.5 \pm 2.7 ^c

^aCompared with value at 2 weeks, $P = .04$.

^bCompared with value at 2 weeks, $P = .001$.

^cCompared with value at 2 weeks, $P = .003$.

($P = .001$). In contrast, there were no significant changes in osteoclast numbers between 2 and 4 weeks in either the celecoxib or the indomethacin group. A significant decrease in osteoclast numbers was found in the celecoxib group between the 2-week and 8-week time periods ($P = .03$) (Table 2).

Collagen Maturity and Organization Using Polarized Light Microscopy

Picrosirius red staining was used to examine collagen fiber organization and maturity. Collagen birefringence was measured as brightness under polarized light microscopy. The control group exhibited progressively increasing collagen birefringence in the healing tendon with time, indicating improving collagen maturity and organization. There was a significant difference in collagen birefringence between each time point in the control specimens ($P < .001$). In contrast, there were no appreciable changes in the collagen birefringence measurements in the celecoxib and indomethacin groups over time ($P = .552$ and $.938$, respectively) (Figure 5). At 2 weeks, there was a significant difference between the control and the indomethacin groups ($P = .007$) (Figure 5 and Table 3). No significant differences, however, were present between the control and the celecoxib groups ($P = .122$) and between the celecoxib and indomethacin groups ($P = .178$) at 2 weeks. At

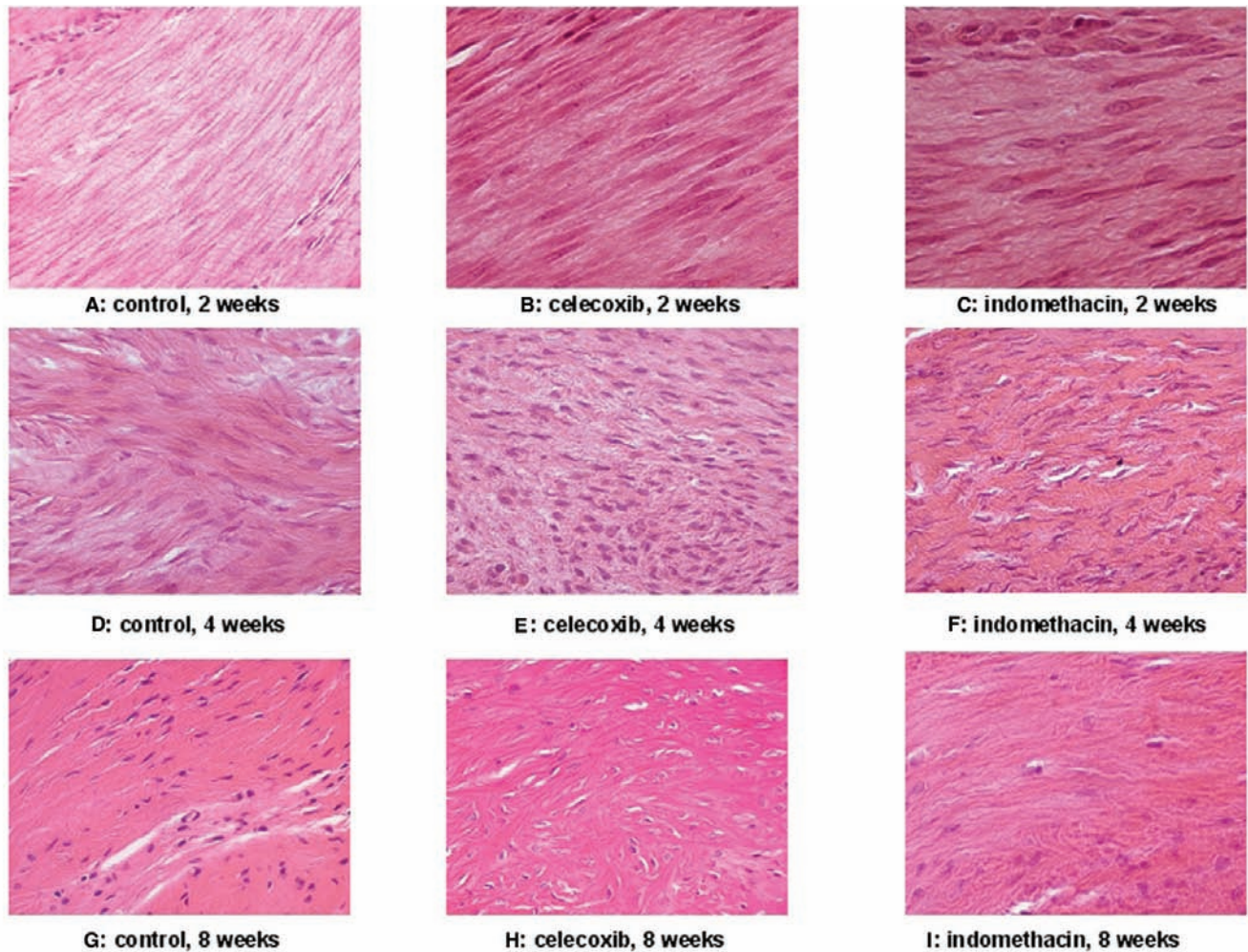


Figure 4. Photomicrograph showing the tendon proximal to the insertion site at 2 weeks (A, control group; B, celecoxib group; C, indomethacin group), 4 weeks (D, control group; E, celecoxib group; F, indomethacin group), and 8 weeks (G, control group; H, celecoxib group; I, indomethacin group) after surgery (hematoxylin and eosin, $\times 320$).

4 weeks, significant differences were found between the controls and both the NSAID groups (celecoxib, $P < .001$; indomethacin, $P < .001$). There were no significant differences between the 2 NSAID groups ($P = .09$). At 8 weeks, there were no significant differences between the celecoxib and the indomethacin groups ($P = .203$), but there were highly significant differences between the controls and both the celecoxib ($P = .001$) and the indomethacin groups ($P < .001$) (Figure 5 and Table 3).

DISCUSSION

It is well established that NSAIDs have inhibitory effects on bone healing and bone formation.¹ Because rotator cuff tendon healing requires bone ingrowth and mineralization,²⁷ we hypothesized that administration of these medications would have an adverse effect on rotator cuff tendon-to-bone healing. We found that both celecoxib, a

TABLE 3
Comparison of Collagen Birefringence (Brightness) Among Control, Indomethacin, and Celecoxib Groups at 2-Week, 4-Week, and 8-Week Time Periods (mean \pm SD)

	Control	Indomethacin	Celecoxib
2 weeks	85.7 \pm 18.7	72.0 \pm 13.0 ^a	82.7 \pm 16.4
4 weeks	111.2 \pm 29.0	74.0 \pm 16.5 ^a	84.8 \pm 12.8 ^a
8 weeks	120 \pm 36.4	74.3 \pm 17.4 ^a	82.3 \pm 29.1 ^a

^aCompared with control group, $P < .001$.

COX-2 selective NSAID, and indomethacin, a traditional, nonselective NSAID, inhibited healing based on histologic and biomechanical criteria. Although previous studies have investigated the impact of NSAIDs on fracture, ligament, and tendon healing, to our knowledge, this study is the first to examine the effect of these medications on tendon-to-bone healing. Both traditional and COX-2-selective

¹References 1-3, 6, 12, 13, 19, 21, 27, 30, 34.

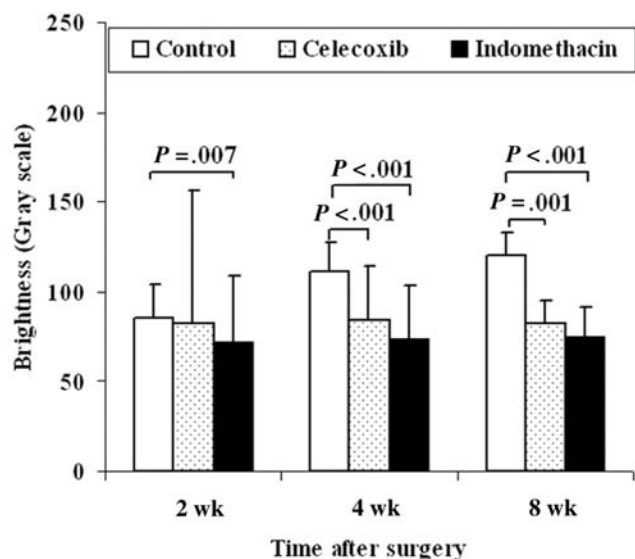


Figure 5. Brightness (collagen birefringence) expressed as gray scales for each group after surgery. The control group exhibited progressively increasing collagen birefringence in the healing tendon during all time periods, reflecting improving collagen maturity and organization. There was a significant difference in collagen birefringence between each time point in the control specimens ($P < .001$). In contrast, there were no appreciable changes in the collagen birefringence measurements in the celecoxib and indomethacin groups over time ($P = .552$ and $.938$, respectively). Lines represent standard deviations.

NSAIDs are commonly used after many orthopaedic surgical procedures, including rotator cuff repair. These medications have been shown to diminish pain and inflammation and, therefore, improve the patient's recovery and return to function. However, the results of this study indicate that these medications may have adverse effects on rotator cuff tendon healing.

Clinical studies demonstrate a high rate of incomplete healing of rotator cuff tendon repair.^{8,15,16,23} It is important that the functional results after rotator cuff repair are superior in shoulders in which the repaired tendon is intact at follow-up.¹⁷ It is therefore imperative to identify factors that might interfere with the biologic healing process. Our results have important implications for clinicians who perform rotator cuff tendon repair.

The impact of NSAIDs on soft tissue healing is still poorly understood. The majority of studies have found that NSAIDs diminish the cross-sectional area and collagen content in healing tendons^{6,7,14}; however, the reported effects on tensile strength are variable.^{13,24,29} A recent study examined the effect of indomethacin and celecoxib on rat Achilles tendon healing after transection and demonstrated reduced cross-sectional area in tendons treated with NSAIDs, although load to failure was unaffected up to 18 days after tendon transection. There were no differences between the traditional, nonselective NSAID (indomethacin) and COX-2 inhibitor (celecoxib) in the relatively short time period studied.¹⁴ Dahners et al¹¹

studied the effect of 6 days of piroxicam (a nonselective NSAID) on healing of a rat medial collateral ligament transection and found an increase in ligament strength in the treated group at 14 days but no difference from controls at 21 days. Moorman et al²⁵ performed a similar study in a rabbit medial collateral ligament healing model. They found that 14 days of ibuprofen administration after a ligament injury did not alter the mechanical properties of the healed ligament at either 14 or 28 days after injury compared to placebo. Elder et al¹³ treated rats with a COX-2 inhibitor (celecoxib) for 6 days after medial collateral ligament transection and reported 32% lower load to failure in the drug-treated group at 14 days. In a recent study, Virchenko et al³² examined the impact of the timing of NSAID administration on tendon healing in a rat model. They demonstrated that the early administration (5 days postoperatively) of parecoxib, a COX-2 inhibitor, negatively affected the biomechanical properties of a healing Achilles tendon. On the other hand, the group treated with late parecoxib (day 6 until sacrifice at day 14) showed a significant increase in maximum stress, suggesting that inflammation during the remodeling phase may have a detrimental effect. Similar to previous studies, these animals were observed for a short time postoperatively.

Several studies have demonstrated that fracture healing (bone-to-bone healing) is impaired by traditional NSAIDs.^{2,3,5,20} Simon et al²⁹ recently reported that the COX-2 inhibitors rofecoxib and celecoxib inhibited fracture healing in a rat model and also reported that normal fracture healing failed in mice with a null mutation in the COX-2 gene. In a rat spine fusion model, Dimar et al¹² found that 12 weeks of indomethacin (3 mg/kg) inhibited fusion compared with controls. Using a rabbit model, Long et al²⁴ reported that 8 weeks of indomethacin (10 mg/kg) also interfered with spinal fusion; however, administration of celecoxib (10 mg/kg) did not interfere with spinal fusion.

The mechanism by which nonselective NSAIDs and COX-2 inhibitors inhibit the healing of tendon to bone appears to be linked to the enzyme COX-2. Both nonselective NSAIDs and COX-2 inhibitors interfere with the production of COX-2. This finding is consistent with our findings of no significant difference between these drugs in their negative effect on rotator cuff tendon healing to bone. Studies have demonstrated impaired fracture healing with both traditional NSAIDs and COX-2-selective inhibitors. Histologic examination of fracture healing models in mice treated with COX-2 inhibitors indicates that COX-2 is required for normal endochondral ossification during fracture healing. COX-2 is induced at sites of inflammation and leads to the production of proinflammatory prostaglandins that are required for normal endochondral ossification.²⁹ Furthermore, the absence of COX-2 has been shown to interfere with the differentiation of mesenchymal cells into the osteoblast lineage.³⁴ Because successful tendon-to-bone healing relies on bone ingrowth, mineralization, and maturation of the healing tissue, osteoblasts play a vital function in this process.²⁷ The impaired rotator cuff tendon-to-bone healing observed in our study may be because of impaired osteoblast differentiation caused by inhibition of prostaglandin production by

COX-2 inhibition. This observation may also be related to our findings that higher numbers of osteoclasts were present for longer periods of time in the NSAID-treated groups compared with controls.

In our model, NSAIDs appeared to inhibit the formation and maturation of collagen at the tendon attachment point. We did not measure bone formation, but we believe that the osteoblasts mediate development of anchoring collagen fibers between tendon and bone, which is likely the mechanism of inhibited healing in our model. It is possible that the excessive osteoclastic activity seen in the drug-treated groups may have contributed to this impaired healing. Furthermore, this study demonstrated that a 2-week course of either NSAID was sufficient to significantly inhibit tendon-to-bone healing at 2-week, 4-week, and 8-week time periods. Despite discontinuation of the drugs after 14 days, load to failure was negatively affected up to 8 weeks after the repair. This finding suggests that interfering with early events in the inflammatory cascade via COX-2 inhibition can significantly alter healing at later time points. If these findings are verified in a larger animal model, the common practice of NSAID use after rotator cuff repair and other procedures requiring tendon-to-bone healing (such as anterior cruciate ligament reconstruction) must be reconsidered.

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