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ORIGINAL ARTICLE

Ibuprofen impairs capsulolabral healing in a rat model of anterior glenohumeral instability

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Background: Failure of glenoid labrum and capsular healing after glenohumeral dislocation can lead to persistent shoulder instability. The purpose of this study was to determine the effect of nonsteroidal anti-inflammatory drugs (NSAIDs) on the healing glenoid labrum and capsule after glenohumeral dislocation in a rat model.

Methods: Sixty-six rats had surgically induced anterior-inferior labral tears and anterior glenohumeral dislocation. Postoperatively, the animals were assigned to either normal (n = 32) or ibuprofen drinking water (n = 31). Animals were euthanized at 2 and 4 weeks postoperatively for biomechanical testing and histologic analysis.

Results: The maximum load increased from 2 to 4 weeks after injury in the NSAID groups but not in the control groups. At 2 weeks, the maximum load was lower in the NSAID group compared with the control group. In a matched comparison between injured and uninjured limbs, the maximum load was significantly decreased in the injured limb of the 2-week NSAID group. At 4 weeks, the NSAID group had decreased stiffness compared with the 4-week control group.

Conclusions: In a new rat model of glenohumeral instability, the postinjury administration of ibuprofen resulted in decreased capsulolabral healing. A matched pair analysis of injured to uninjured limbs supported the findings of impaired healing in the NSAID-treated animals. These findings demonstrate that the use of NSAIDs after glenohumeral dislocation may impair capsulolabral healing and should be limited or avoided to optimize glenohumeral stability.

Level of evidence: Basic Science Study; Biomechanics/Histology

Keywords: Shoulder; glenohumeral; instability; NSAIDs; labrum; healing; animal; rat

Anterior glenohumeral dislocation is a common injury that often results in damage to the native soft tissue static restraints, such as the glenoid labrum, anterior inferior glenohumeral ligament, and joint capsule.[7,9,24,34,38,45,46] If these soft tissue injuries do not sufficiently heal, the patient may have persistent shoulder instability.[25,45,46] Multiple studies have

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reported a >90% recurrent dislocation rate in younger individuals after a first-time anterior glenohumeral dislocation.[38,45,46]

We developed a new rat model of shoulder instability to study capsulolabral healing. Large-animal and primate models have the disadvantages of cost, need for larger animal facilities, and ethical concerns. Scougall was the first to describe labral healing in a primate model, demonstrating healing after 8 weeks of a posterior labral avulsion (n = 1).[40] Abe et al[1] reported on a rabbit model of inferior glenohumeral dislocation and the healing of the inferior glenoid labrum. However, rabbit glenoids are clover shaped and have anatomy distinctly different from that of humans.[1] The rat shoulder is a particularly good model for the study of shoulder disease because the bone, ligament, and muscle anatomy resembles that of a human.[11,39,44] To our knowledge, there are no small-animal studies in the literature evaluating the healing of the capsulolabral complex to the glenoid.

Despite the prevalence of acute glenohumeral dislocations, little is known about the biologic and biochemical factors that are important for the healing of the glenoid labrum and capsule. By identifying the factors important in healing after shoulder dislocation, healing could potentially be improved by the modulation of the biologic environment. In previous work from our laboratory using a new rat model of shoulder instability,[31] we found that immunohistochemical expression of the proinflammatory cytokines interleukin 1β and transforming growth factor β1 was increased in the tissues of injured animals compared with controls. There was also increased expression of matrix metalloproteinase (MMP) 3 and MMP-13 in tissues of injured animals. Whereas the exact mechanism is not known, these findings suggest that an acute inflammatory process had a role in the healing process.

The proinflammatory properties of prostaglandins during acute inflammatory responses are well established.[37] Prostaglandins are derived from arachidonic acid by the action of cyclooxygenase isoenzymes, and their biosynthesis is blocked by nonsteroidal anti-inflammatory drugs (NSAIDs).[16,26,37] Numerous animal studies have investigated the effect of NSAIDs on the healing of bone, tendon, enthesis, and ligaments.[2,3,12,13,15,18,20,21,28,29,43] NSAIDs are a commonly prescribed medication for analgesia in the perioperative period and after musculoskeletal injuries, including shoulder dislocations. Although the deleterious effects of NSAIDs on tendon and rotator cuff healing have been described,[12,13,18,20] the effect on capsulolabral healing has not been studied.

We hypothesized that the downregulation of this initial inflammatory response may inhibit the healing of the labrum and capsule to the glenoid. The purpose of this study was to determine the effect of ibuprofen, a commonly used NSAID, on the healing glenoid labrum and capsule after glenohumeral dislocation in a rat model. Our hypothesis was that the administration of ibuprofen would lead to decreased biomechanical properties and impaired healing on histologic evaluation compared with controls.

Materials and methods

This is an animal study using a rat model of glenohumeral instability to evaluate the effect of postoperative ibuprofen on the biomechanical properties of capsulolabral-glenoid healing. Sixty-six male Lewis rats (weight, 250-300 g; age, 9-10 weeks) underwent a surgical anterior glenohumeral dislocation with injury to the anteroinferior glenoid labrum. There were 3 animal deaths in the perioperative period. The remaining animals were assigned to either a control group (n = 32) or an experimental group (n = 31). At either 2 or 4 weeks postoperatively, the animals were sacrificed and the forelimb was harvested. Three specimens from each group (n = 12) were assigned to histologic analysis, and the remaining 51 specimens were assigned to biomechanical testing.

Surgical technique (Fig. 1)

The animals were anesthetized with intraperitoneal injections of ketamine (90 mg/kg) and xylazine (4 mg/kg). Inhaled isoflurane and oxygen were administered as needed through a coaxial nose cone. Cefazolin (20 mg/kg, intramuscular) was given for perioperative antibiotic prophylaxis. Buprenorphine extended release (72 hours) was administered subcutaneously for perioperative pain control. The posterior right shoulder was shaved and prepared, and the surgical field was sterilely draped. A 3- to 4-cm longitudinal incision was made along the posterior aspect of the shoulder. The posterior deltoid was incised to expose the posterior rotator cuff. The rotator cuff and posterior capsule were then incised longitudinally to expose the glenohumeral joint. Traction was applied to the forelimb for additional exposure of the glenoid and the attached labrum. A No. 11 blade scalpel was used to create a laceration in the anteroinferior labrum at the level of the glenoid rim. The shoulder was then traumatically dislocated anteriorly and inferiorly until the humeral head was completely dislocated on the glenoid. The humeral head was relocated and the deltoid was repaired with absorbable sutures. No repair was performed anteriorly. The wounds were irrigated with sterile normal saline. The skin was reapproximated with surgical clips. Animals were allowed to move freely in the cage, and no immobilization was used.

Postoperative animal care

The animals were housed in our institution's animal facility with full-service housing and fed a standard diet and water without restriction. The animals in the control group were given standard drinking water. The animals in the experimental group were given water mixed with ibuprofen (Walgreens Children's Ibuprofen 100 Oral Suspension Berry; Walgreens Co., Deerfield, IL, USA). The ibuprofen suspension and water were mixed to create a solution of 0.3 mg/mL. The average 300-g rat will consume approximately 30 mL of water daily. Therefore, a 0.3 mg/mL ibuprofen concentration would result in the consumption of 9 mg daily (30 mg/kg/d). The amount of 30 mg/kg/d was used because it is the equivalent to 800 mg 3 times daily in an 80-kg individual. The animals were monitored daily until the clips were removed on postoperative day 14 and then were monitored twice per week. On either postoperative day 14 or 28, the animals were euthanized with carbon dioxide inhalation. The histology group was immediately harvested, and the forelimb was