Healing rates after rotator cuff repair for patients taking either celecoxib or placebo: a double-blind randomized controlled trial

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Background: Use of anti-inflammatory medications (NSAIDs) is an important component of multimodal pain control after orthopedic procedures to avoid opioid overutilization and abuse. However, the deleterious effects of NSAIDs on tendon healing are of particular concern in rotator cuff repair (RCR). The purpose of this study was to evaluate the effect of celecoxib or placebo on healing rates after RCR when administered in the perioperative and immediate postoperative period using MRI evaluation at one year postoperatively. A secondary aim was to determine whether clinical differences existed between patients with intact or non-intact repairs.

Methods: Patients aged ≥65 years with partial- or full-thickness rotator cuff tear (<25x25 mm) were randomized to receive celecoxib 400 mg or placebo 1 hour before the procedure and 200mg bid for 3 weeks postoperatively. All patients were treated as clinically indicated at the time of surgery and followed standard postoperative protocol. Repair integrity was evaluated with MRI using the Sugaya classification for repair integrity. Data were analyzed using multivariable logistic regression by intent to treat.

Results: Seventy-nine patients were enrolled; 21 were lost to follow-up, 6 did not have cuff repair, 5 were revised, and 2 declined follow-up, leaving 45 patients with one-year follow-up. Five of these patients did not complete MRI, leaving 40 patients for review. Eighteen of 20 patients (90%) who received celecoxib completed all doses of study medication as did 15 of 20 patients (75%) who received placebo.

The patient groups were similar for demographics, clinical results, and healing rate. After adjusting for tear size, no statistically significant difference in healing rate was found between groups, with 10 of 20 celecoxib patients (50%) having intact repair at 1 year compared with 14 of 20 placebo patients (70%) (OR = 0.53, 95% CI: 0.14, 2.08, P = 0.35).

Conclusion: Half of the patients who received celecoxib had an intact repair compared with 70% intact repair for patients receiving placebo. Although not statistically significant in this small study, larger studies are needed to clarify this important clinical concern. The authors do not recommend use of celecoxib for postoperative pain control after RCR.

Opioid analgesics are the mainstay for postoperative pain control after orthopedic surgery. Opioid medications, although effective, have a significant risk profile including nausea and vomiting, constipation, psychiatric changes, as well as potential for overutilization and abuse. This risk profile has fostered interest in managing postoperative pain with a multimodal approach, combining medications with different mechanisms of action to provide superior pain relief and fewer side effects than a single class of medication.22.

Nonsteroidal anti-inflammatory (NSAID) medications are the most common nonopioid analgesic prescribed to mitigate postoperative pain. NSAID medications exert their effect by inhibiting cyclooxygenase 1 and 2 enzymes, decreasing the synthesis of prostaglandins. Prostaglandins sensitize nerve terminals, leading to
a hyperalgesic response. A pain management approach incorporating NSAIDs has an opioid-sparing effect with the downstream advantage of a reduced opioid side effect profile and reductions in postoperative nausea and vomiting by 30%. However, NSAID medications carry risk for renal injury, gastric ulcer, and hemorrhage.

Selective COX-2 inhibitors, including celecoxib, were developed to minimize drug-specific side effects and demonstrate platelet function sparing and decreased risk for GI bleeding compared with nonselective COX inhibitors. Several studies have examined the effectiveness of celecoxib for improving pain control and reducing opioid utilization after orthopedic surgery. Administration of celecoxib after arthroscopic rotator cuff repair (RCR) lowers postoperative pain scores and antinausea medication requirements. A recent systematic review of randomized controlled trials in orthopedics concluded that preoperative oral celecoxib was safe, efficacious, and cost effective when given 1 hour before incision.

While perioperative COX-2 inhibitors are beneficial for pain management, they have been reported to cause a deleterious effect on tendon-to-bone healing in animal models. In a recent systematic review, Ghosh et al found that COX-2 inhibitors can negatively impact healing of musculoskeletal soft tissue after surgery. For that reason, concern remains regarding use of anti-inflammatory medications and COX-2 inhibitors in shoulder surgery. RCR in particular involves prolonged postoperative rehabilitation and requires adequate tendon-to-bone healing for long-term success. A recent study comparing celecoxib, ibuprofen, and tramadol after arthroscopic RCR revealed no differences in pain control but a significantly higher re-tear rate in the celecoxib group.

The purpose of this study was to determine the effect of early administration of celecoxib on healing rates after RCR using MRI evaluation at a minimum of 1 year after surgery, and to evaluate clinical results between these groups at a minimum of 1 year after surgery. A secondary aim was to determine whether clinical differences existed between patients with intact vs. nonintact repairs at a minimum of 1 year postoperatively.

Patients and methods

The surgeon author conducted a double-blind, placebo-controlled randomized clinical trial. Patients who had agreed to participate in a previous IRB-approved study evaluating effectiveness of celecoxib for pain control after shoulder surgery were potential candidates for the study. IRB approval for this study was obtained independently and patients consented separately to participate in this study. All patients participated on a voluntary basis after undergoing the informed consent process.

Patients eligible for inclusion included those with substantial partial- (greater than 50%) or full-thickness rotator cuff tears less than 25 x 25 mm in size as estimated by preoperative MRI and were under age 65 years at the time of surgery. Patients undergoing revision repair were not eligible for inclusion, nor were patients with substantial partial- or full-thickness subscapularis tears, associated glenohumeral arthritis (Samuelson Prieto grade 2 or higher), or preoperative shoulder stiffness (defined as less than 100 degrees of elevation or 45 degrees of external rotation). These criteria were utilized based on a previously published study by Keener et al.

Exclusion criteria included the following medical exclusions: allergy, sensitivity, or inability to take celecoxib; renal insufficiency as defined by serum creatinine >1.5; history of bleeding gastric ulcers or severe inflammatory bowel disease; known coagulation abnormality or hepatic disease; use of anticoagulants including warfarin, clopidogrel, rivaroxaban, and dabigatran; current congestive heart failure; previous MI or CVA; refusal by PCP or cardiologist to allow participation; baseline opioid use of long acting opioids including fentanyl patches, oxycodone controlled release, or morphine sulfate controlled release tablets, and age older than 65 years at the time of surgery.

Eligible patients who agreed to participate had been randomized using block randomization to receive celecoxib 400 mg or placebo 1 hour before surgery, and then continued to receive the same medication (either celecoxib 200 mg or placebo) twice daily for 3 weeks. The placebo medication was provided by the manufacturer and was identical in appearance, containing all inert ingredients present in the active medication. Pharmacy staff who were not involved in patient care delivered the study medication to the patient preoperatively to ensure identical appearance of the medication and to ensure all who were involved in clinical care were blinded with regard to allocation. Opioids used in conjunction with the study medication included oxycodone/acetaminophen, hydrocodone/acetaminophen, codeine, or tramadol. Patients were instructed not to take any additional NSAID medications (either prescription or over the counter) for the first 3 weeks after surgery while taking the study medication.

All patients received an interscalene block, and all patients were given standard opioid medication postoperatively, which patients took as needed. Compliance with study medication and documentation of amount of opioid use was assessed on a weekly basis via phone follow-up and in the office at 3 weeks follow-up. Pill counts, which were standardized to morphine equivalents, were recorded. Data were analyzed as intent to treat, with patients who did not complete all doses of the medication noted but included in the analysis.

Data collection

After meeting all inclusion criteria and agreeing to participation, patients underwent routine preoperative laboratory studies and evaluation, including review of preoperative medications and documentation of preoperative opioid use. Baseline shoulder ROM, clinical and demographic data, visual analog scale for pain (VAS), and shoulder scores including the simple shoulder test (SST), American Shoulder and Elbow Surgeons (ASES) score, and the UCLA shoulder score were collected preoperatively and at a minimum of 1 year postoperatively. Complications and adverse events including death, reinfection, reoperation, medical complications, rash, or allergic reactions were tracked and recorded.

At one year postoperatively, the patients who participated in the study were re-evaluated for clinical results and patient satisfaction after RCR. Patients who underwent RCR were offered a repeat MRI without contrast at 1 year postoperatively; patients who did not have RCR were excluded from participation. Patients who did not complete the study medication were eligible for inclusion as intent to treat. Informed consent for participation in the study and to undergo follow-up MRI was obtained at the time of the postoperative follow-up appointment; those patients who agreed and obtained a repeat MRI at a minimum of 1 year postoperatively were included in this study.

Surgical methods

The surgeon author performed all surgeries. All RCR procedures were performed with the patient in the lateral position. All patients received general endotracheal anesthesia in conjunction with an interscalene block. The tear was repaired as clinically indicated for the tear pattern using suture anchors (Arthrex, Speedbridge™, Naples, FL, USA). All patients were prescribed an opioid/acetaminophen combination medication postoperatively. Patients who
underwent RCR followed the same postoperative protocol with use of a sling for 3 weeks with daily pendulum exercises, followed by progression to active range of motion, then strengthening exercises at 10 weeks.

**Radiology methods**

Repair integrity was evaluated on a 3T MRI system (Skyra, Siemens Healthcare, Malvern, PA, USA) and a 15-channel dedicated knee coil (Tx/Rx Siemens Healthcare) with the same imaging protocol. The imaging protocol consisted of the following sequences; 2D fat saturated axial proton density, 2D fat saturated coronal T2, 2D coronal proton density, 2D fat saturated sagittal T2, and 2D sagittal T1. One fellowship trained musculoskeletal radiologist with 14 years of clinical experience reviewed the images using the classification of Sugaya to determine repair integrity. Repair integrity subtypes defined by Sugaya are as follows: type I, sufficient thickness with homogenous low T2 signal intensity; type II, considered statistically significant; type III, insufficient thickness without discontinuity; and type IV, presence of a minor discontinuity; type V, presence of a major discontinuity. Types I, II, and III were considered intact for the purposes of this study. Types IV and V were considered recurrent/persistent tears. In addition, assessment of the glenohumeral cartilage utilizing the Outerbridge classification and rotator cuff muscle atrophy utilizing the Goutallier classification was performed. The radiologist and principal investigator were blinded to the patient’s group. The radiologist’s findings were compiled by the research nurse coordinator; the surgeon and the members of the research team had no input with regard to MRI results.

**Outcome measures**

Primary outcome was healing of the rotator cuff as determined by MRI evaluation. Secondary outcome measures included pain (VAS) and clinical scores (SST, ASES, and UCLA scores). Range of motion (ROM) in forward elevation and strength testing of the supraspinatus (SS) and infraspinatus (IS) graded from 0–5 also was recorded. The groups were compared according to age, gender, comorbidities, and preoperative baseline scores to determine any baseline differences between groups.

**Statistical analysis**

For descriptive and clinical characteristics as well as for the secondary outcomes, continuous variables are presented as the mean ± standard deviation while categorical variables are presented as counts and percentages. The mean differences were compared by the Student t-test if the distribution was found to be normal, or the Wilcoxon Rank Sum test otherwise. Categorical data and agreed to participate in the 1-year follow-up (n = 45), 5 patients did not complete the MRI. For that reason, 45 patients had 1-year clinical data and 40 patients had MRI and clinical data at minimum 1 year (Figs. 2-5).

No significant differences at baseline occurred between patients who received active medication or placebo with regard to age, gender, smoking status, BMI, ASA classification, or medical comorbidities of diabetes or hypertension (P > .05 for all, Table I). Twenty of 22 patients (91%) who received celecoxib completed all doses of study medication, as did 17 of 23 patients (74%) who received placebo (P = .14). Thus, compliance with study medication was not statistically different between groups. Patients who received active medication had larger average tear size noted at the time of surgery (3.50 cm² vs. 2.25 cm² for placebo, P = .3).

No severe adverse events were recorded during the study period and the authors remained blinded to the groups throughout the study period. Eighteen patients stopped taking medication: 4 patients who received active medication experienced either rash or intolerance to the medication, and 14 patients who received placebo medication stopped for intolerance. Reasons cited for stopping medication (both active and placebo) included rash, nausea, syncopal episode, edema, headache, gastritis, eye irritation, calf cramping, facial swelling, increased heart rate, and elevated blood pressure. Of the 45 patients who agreed to participate in follow-up evaluation, 8 patients did not complete the study medication (2 on active medication, 6 on placebo, Table II).

After adjusting for tear size using multivariable logistic regression analysis, no statistically significant differences in healing rates were found between groups (Table II), with 10 of 20 patients (50%) who received celecoxib compared with 14 of 20 patients (70%) who received placebo showing intact rotator cuff repairs at 1 year (OR = 0.52, 95% CI: 0.14, 2.03, P = .35). Clinical results at 1 year for VAS, SST, and ASES scores, as well as ROM, SS, and IS strength testing values were equivalent for the groups (P > .05 for all, Table III). No differences appeared in clinical results at 1 year when patients with intact rotator cuff tears were compared with patients whose repairs were not intact at 1 year for VAS, SST, ASES, and SS strength testing (P > .05 for all, Table IV).

**Discussion**

Although differences between groups at 1 year postoperatively were not statistically significant, a nearly 20% difference occurred in rotator cuff healing rates after RCR for patients who received either...
celecoxib or placebo for 3 weeks after surgery. In patients taking celecoxib, 50% had a persistent or recurrent tear at the time of follow-up MRI. A recent study by Oh\textsuperscript{21} also found a 37% re-tear rate after use of celecoxib in treating RCR, which was significantly higher than in those patients who took ibuprofen or tramadol. They utilized both ultrasound and MRI to evaluate cuff integrity at a minimum 24 months after repair, and found much lower rates of re-tear, 4% and 7%, respectively, in the tramadol and ibuprofen groups.

Recurrent tears of the rotator cuff can occur in the absence of perioperative NSAIDs, and re-tear rates in the literature range from 13 to 94%.\textsuperscript{8,35} Risk factors for recurrent tear after rotator cuff repair are multifactorial, and not fully understood. Factors associated with recurrent tear include muscle atrophy, fatty infiltration, age, tear size, smoking status, and position of the musculotendinous junction preoperatively, among others.\textsuperscript{15,16,22,32} Despite no NSAID use in the placebo group, the re-tear rate was 30%, which is significantly higher than the rates reported by Oh et al.\textsuperscript{21} This re-tear rate is similar to other reported studies for suture bridge repair.\textsuperscript{33} A recent study found overall re-tear rates of 57.8% \textsuperscript{30} with degree of retraction and acromiohumeral interval predictive of re-tear.
Rehabilitation protocol has been examined as a risk factor for persistent or recurrent tears after RCR. A randomized, controlled trial comparing immobilization with early ROM demonstrated neither advantage nor disadvantage of early passive ROM after RCR. In our study, all patients followed the same postoperative rehabilitation protocol, which allowed for limited, passive early ROM. A recent systematic review suggested that early ROM may increase risk of recurrent tear after RCR, especially for larger tears. A recent meta-analysis found that the healing rates at long-term follow-up were not clearly affected by the type of rehabilitation.

At one-year follow-up, clinical results were similar between groups; no differences occurred between patients who received active or placebo medication (Table III), and no statistically significant differences between patients who had intact vs. non-intact repair (Table IV).

This study has several limitations. Although 87% of patients were available for follow-up at 6 weeks (69 of 79 patients), by 1 year almost half the study participants were lost to follow-up or declined follow-up MRI. This reduced the sample size and limited our ability to determine differences with statistical significance. This also limits the generalizability to the entire population, as only a subset of patients agreed to return for follow-up. It is possible that patients doing well clinically would be less willing to follow up at one year and obtain a follow-up MRI. However, a similar distribution of patients in both treatment groups remained at 1 year, suggesting no significant attrition bias.

One-year follow-up results are considered short term, and it is possible that clinical differences between groups including satisfaction and functional scores may diminish with time in patients with a persistent full-thickness rotator cuff tear. A recent retrospective cohort study noted that RCR remaining intact at 10 years was overall 48%, and those patients having intact repairs demonstrated superior abduction and flexion strength and lower grades of osteoarthritis.

Another limitation of the study includes lack of control for preoperative interventions. Many patients undergo a trial of nonoperative treatment before surgical intervention for rotator cuff pathology, which can include NSAID medications, physical therapy, and corticosteroid injections. In particular, preoperative injections were not evaluated or restricted but remain an option in our treatment algorithm for shoulder pain; current evidence suggests that preoperative injections may carry increased risk of infection or revision after RCR. However, it appears that we achieved a reasonable distribution of characteristics between groups as a result of randomization. Thus, we would not expect any differences between groups with respect to preoperative interventions.

The use of NSAID medications for study patients during the preoperative period and after the initial 6-week study period was not controlled, and NSAIDs are commonly utilized for musculoskeletal pain. Some reports suggest that use of preoperative NSAID medications may be correlated with inferior clinical outcomes after RCR. The effect of preoperative or long-term postoperative use of NSAIDs after RCR is not known. Current literature now indicates that the use of celecoxib after rotator cuff repair increases the risk for persistent or recurrent retear. At the time the original study
was conducted, this information was not available. Oh et al. also determined risk of recurrent tear after use of ibuprofen was only 7%, suggesting that nonselective NSAIDs may still play a role in multimodal pain relief after RCR.

Strengths of the study include the randomized design, which balanced potential confounders and decreased the likelihood of selection bias. We controlled for the possible confounding effect of tear size because groups at the baseline appeared to be markedly different. We also considered other factors known to influence risk of retear including advanced age with exclusion of patients aged >65 years. The rehabilitation protocol, which was the same for both groups, avoided any influence of rehabilitation protocol on retear rates. Additional strengths included the blinded clinical and radiologic evaluation of rotator cuff function and MRI appearance.

**Table I**

Demographic and clinical characteristics by treatment group

| Characteristic | Celecoxib (n = 22) | Placebo (n = 23) | P value
|----------------|-------------------|-----------------|----------|
| Demographics  |                   |                 |          |
| Age (years)   | 54.0 ± 7.1        | 56.8 ± 7.4      | .20      |
| Male gender   | 11 (50)           | 10 (43)         | .66      |
| Body Mass Index | 32.5 ± 7.5       | 32.5 ± 5.8      | .99      |
| Race           |                   |                 | .53      |
| White (n)     | 19 (86)           | 19 (83)         |          |
| Black (n)     | 4 (14)            | 4 (17)          |          |
| Sidedness     |                   |                 | .30      |
| Left (n)      | 11 (50)           | 8 (35)          |          |
| Right (n)     | 11 (50)           | 15 (65)         |          |
| Comorbidities |                   |                 |          |
| Diabetes (n)  | 1 (5)             | 5 (22)          | .10      |
| Hypertension  | 9 (41)            | 10 (43)         | .86      |
| Smoking status|                   |                 | .45      |
| Never (n)     | 13 (59)           | 15 (65)         |          |
| Former (n)    | 3 (14)            | 5 (22)          |          |
| Current (n)   | 6 (27)            | 3 (13)          |          |
| Other         |                   |                 |          |
| Completed study medication (n) | 20 (91) | 17 (74) | .14 |
| Tear size, cm² | 3.5 (2.25, 4) | 2.25 (1, 3) | .03 |
| Scores, preoperative | | | |
| VAS           | 50 ± 2.2          | 48 ± 1.9        | .65      |
| SST           | 7 (5, 9)          | 6 (3, 8)        | .26      |
| ASES          | 48.1 ± 19.0       | 50.8 ± 16.5     | .61      |
| UCLA          | 19.5 (13, 24)     | 16 (14, 18)     | .13      |
| Strength, preoperative | | | |
| SS strength   | 5 (4, 5)          | 4 (4, 5)        | .19      |
| IS strength   | 5 (5, 5)          | 5 (4, 5)        | .29      |
| AROM, preoperative | | | |
| Forward elevation | 170 (160, 170) | 160 (150, 170) | .16 |
| External rotation | 70 (70, 70) | 70 (60, 70) | .25 |

**Table II**

Adjusted odds ratios and 95% confidence intervals for MRI results

| Characteristic | n | OR | 95% Confidence interval | P value
|----------------|---|----|-------------------------|----------|
| Treatment group |   |    |                         | .35      |
| Celecoxib      | 20| 0.53| 0.14, 2.03              |          |
| Placebo        | 20| referent                   |          |
| Tear size (cm²) | 40 | 0.86 | 0.67, 1.10 | .22 |

P-values were obtained from multivariable logistic regression, adjusting for tear size.

**Table III**

Clinical assessments at one year by treatment group

| Assessment | Celecoxib (median (IQR)) | Placebo (median (IQR)) | P value
|------------|--------------------------|------------------------|----------|
| Scores     |                          |                        |          |
| VAS        | 0.5 (0, 2)               | 0 (0, 2)               | .56      |
| SST        | 12 (9, 12)               | 12 (10, 12)            | .86      |
| UCLA       | 31 (29, 33)              | 33 (27, 35)            | .77      |
| ASES       | 94 (85, 100)             | 95 (71, 100)           | .91      |
| Strength   |                          |                        |          |
| SS strength| 5 (5, 5)                 | 5 (5, 5)               | .32      |
| IS strength| 5 (5, 5)                 | 5 (5, 5)               | .51      |
| AROM       |                          |                        |          |
| Forward elevation | 170 (170, 170) | 170 (160, 170) | .14 |
| External rotation | 70 (70, 70) | 70 (60, 70) | .73 |

**Table IV**

Clinical assessments at one year by intact status

| Assessment | Not intact (median (IQR)) | Intact (median (IQR)) | P value
|------------|--------------------------|-----------------------|----------|
| Scores     |                          |                        |          |
| VAS        | 0.25 (0, 2)              | 0.25 (0, 1.5)          | .93      |
| SST        | 12 (10, 12)              | 11.5 (9, 12)           | .49      |
| UCLA       | 31 (29, 33)              | 31 (25, 33)            | .52      |
| ASES       | 94 (85, 100)             | 92.5 (75.5, 100)       | .84      |
| Strength   |                          |                        |          |
| SS strength| 5 (5, 5)                 | 5 (5, 5)               | .15      |
| IS strength| 5 (5, 5)                 | 5 (5, 5)               | .86      |
| Range of motion |                 |                        |          |
| Forward elevation | 170 (170, 170) | 170 (165, 170) | .33 |
| External rotation | 70 (65, 70) | 70 (60, 70) | .90 |

**Conclusions**

Patients who received celecoxib in the perioperative period had a lower healing rate at 1 year postoperatively. Although not statistically significant in this small study, larger studies are needed to clarify this important clinical concern. No clinical differences between patients who had received celecoxib or placebo were found at one year postoperatively, nor were clinical differences apparent between patients who had intact vs. nonintact repairs at 1-year postoperative follow-up. Currently, the authors do not recommend use of celecoxib for postoperative pain control after RCR.

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