Non-selective NSAIDs do not increase retear rates post-arthroscopic rotator cuff repair: A meta-analysis

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ABSTRACT

Background: Arthroscopic rotator cuff repairs (RCRs) are known to be associated with substantial pain and postoperative pain management is critical in overall patients' outcomes. Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used oral medications and can reduce opioid usage. However, controversies arise due to its postulated effect on postoperative tendon healing. As the evidence of safety and efficacy of NSAIDs remains unclear, this study aims to investigate the effect of NSAIDs on retear rates and clinical outcomes.

Methods: A systematic search of four databases (PubMed, EMBASE, Scopus, and Cochrane Library) was conducted, identifying studies that compared cohorts with post-RCR NSAIDs use versus control groups without NSAID use. Meta-analysis was conducted for retear rate as well as pain and functional outcomes (Visual Analogue Scale and American Shoulder and Elbow Surgeons Shoulder score). Subgroup analysis was conducted for retear rates to determine the overall treatment effect of including selective COX-2 inhibitors.

Results: Six studies were included in the meta-analysis. The total baseline cohort size was 916, with 443 (48.3%) patients in the NSAID group and 473 (51.6%) patients in the control group. There were no statistically significant differences in the baseline characteristics between the two groups. Meta-analysis between the two groups showed that there were no statistically significant differences in retear rates ($p = 0.70$), early and late post-operative Visual Analogue Scale score ($p = 0.10$ and $p = 0.10$, respectively) and latest American Shoulder and Elbow Surgeons Shoulder score ($p = 0.31$). However, subgroup analysis of retear rates revealed a statistically significant difference between the subgroup including COX-2 selective inhibitor versus non-selective COX inhibitor ($p < 0.01$).

Conclusion: NSAID use in post-arthroscopic RCR pain relief does not increase retear rates and can provide similar clinical outcomes compared to a non-NSAID regimen.

Level of evidence: Meta-analysis, level of evidence, 4.
What is already known?

- NSAID use post-arthroscopic rotator cuff repair is controversial, with concerns about potential effects on tendon healing.
- However, current standard-of-care has significant limitations.

What are the new findings?

- NSAID use post-arthroscopic rotator cuff repair does not increase retear rates and offers comparable clinical outcomes with the current standard of care.
- NSAIDs appear to be a safe and effective modality for pain-relief post-arthroscopic rotator cuff repair requiring oral analgesics, especially on discharge.

1. Introduction

Rotator cuff (RC) tears remain one of the most common shoulder conditions worldwide. While arthroscopic rotator cuff repair (RCR) has emerged as an effective form of treatment for reparable RC tears, it is associated with substantial postoperative pain with studies reporting pain levels to be as severe as that after gastrectomy or thoracic surgery [1–3]. Moreover, postoperative pain is also the most common reason for an emergency department visit after outpatient orthopaedic procedures. Hence, appropriate postoperative pain management can improve overall patients’ outcomes and reduce health-care costs [4–6].

Various methods of pain control such as regional nerve block and intravenous patient controlled analgesia has been increasingly used in recent years [3]. While interscalene brachial plexus block is very effective in managing pain immediately postoperatively, its effects wear off after approximately 6 h and it cannot be administered at home [7]. Given that most RCRs are day surgeries, oral analgesics are critical for postoperative pain management, especially after discharge. Nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids are among the most commonly used oral medications [1,3]. However, these medications have adverse side effects. For example, non-selective NSAIDs are known to cause gastrointestinal issues and bleeding [8,9]. On the other hand, opioid causes nausea, vomiting, constipation and, more importantly, they have a notable potential for abuse [3,4]. The opioid epidemic in the United States has caused a 200% increase in deaths due to opioid use in the United States has caused a 200% increase in deaths due to opioid use [3,4]. However, current standard-of-care pain relief which is typically opioids). We excluded studies that were (A) non-English; (B) without specific RCR or oral NSAID group; (C) non-clinical studies (including review articles, editorials, case reports or conference abstracts); (D) non-human studies; and (E) comprised overlapping cohorts/populations from the same institution.

The screening of titles, abstracts, and full-texts was conducted in a blinded manner by two independent reviewers (S.S and M.Y) using web-based platform Rayyan QCRI [16]. Any conflicts were resolved via consensus with another independent author (C.G).

2. Methods

2.1. Search strategy

This systematic review and meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [15]. An extensive literature search was conducted across PubMed, Embase, Scopus, and Cochrane Central Register of Controlled Trials (CENTRAL) from inception to 12 August 2022. Search terms that were used included RCR-specific terms (“rotator cuff repair,” “rotator cuff surgery,” “arthroscopic,” “shoulder arthroscopy”), NSAID-specific terms (“NSAIDs,” “non-steroid,” “anti-inflammatory,” “cyclooxygenase-2 inhibitor,” “COX-2 inhibitor,” “analgesia”) and terms specifying post-operative pain (“post-op,” “postop”). The citations of existing reviews and primary articles were searched to identify any additional articles.

2.2. Selection criteria

All studies were filtered using the following inclusion criteria: (A) clinical studies with post-arthroscopic RCR NSAID use; and (B) studies directly comparing outcomes of cohorts with post-RCR NSAID use versus the absence of NSAID use (i.e., reliant solely on the institution's standard-of-care pain relief which is typically opioids). We excluded studies that were (A) non-English; (B) without specific RCR or oral NSAID group; (C) non-clinical studies (including review articles, editorials, case reports or conference abstracts); (D) non-human studies; and (E) comprised overlapping cohorts/populations from the same institution.

The screening of titles, abstracts, and full-texts was conducted in a blinded manner by two independent reviewers (S.S and M.Y) using web-based platform Rayyan QCRI [16]. Any conflicts were resolved via consensus with another independent author (C.G).

2.3. Data extraction

Two authors (S.S and M.Y) independently extracted data using a predefined spreadsheet on Microsoft Excel (Microsoft Corporation, Redmond, Washington, United States). Any conflicts with data collection were resolved via consensus with an independent author (C.G). Study characteristics that were extracted include study period and design, sample sizes, follow-up duration, institution and country of study, institution's standard-of-care pain relief medication (including pre/post-operative analgesia and interscalene regional block if used), criteria for retear diagnosis, patient demographics (including sex, age, hand dominance, BMI, previous trauma, and comorbidities), and tear details (including tear size, tear morphology, specific tendons torn, or number of tendons involved). Outcome data that were extracted include retear rates, VAS score, ASES score as well as rescue medication/opioid use. All outcomes were reported at final follow-up only, except for VAS score where sufficient data were available for both early and late post-operative results.

2.4. Definition of NSAID and control groups

Groups that utilised post-RCR NSAIDs (“NSAID” group) were compared with groups that did not utilise NSAIDs (“control” groups). The respective institutions standard-of-care pain-relief medications (typically opioids) were given to all groups, even in control groups that were given placebo [3,4,10,17–19]. To specifically assess the effect of COX-2 inhibitors on retear rates, a subgroup analysis based on the use of COX-2 selective inhibitor versus non-selective COX inhibitors was conducted.

2.5. Follow-up durations for retear rates, VAS score, and functional outcomes

For retear rates, this study only included analysis for articles in which follow-up duration was >6 months as previous studies have shown that
time-to-failure for arthroscopic RC rarely exceed 6 months (24 weeks). Iannotti et al. demonstrated that retears primarily occurred between 6 and 26 weeks, while Miller et al. found that recurrent tears occur more frequently in the early post-operative period within 3 months [20,21]. Similarly, functional outcome (ASES score) was taken at final follow-up, with a minimum of 6-months duration for studies to be included.

As for VAS score, this study categorised pain assessment into two durations: early post-operative period (<3 months) and late post-operative period (≥12 months). Existing evidence has indicated that a significant proportion of pain improvement occurs in the first 3 months post-RCR, while pain recovery usually slows down at 12 months [22–24].

2.6. Statistical analysis

For study characteristics and patient demographics, this study obtained pooled Freeman-Tukey Double arcsine-transformed proportions of categorical variables as well as the raw means of continuous variables using the inverse variance method, via metamean and metaprop functions [25].

For outcomes, categorical outcomes were analysed via odds ratio between the NSAID and control groups (retear rates) while continuous data were compared between the two groups using absolute mean difference (VAS score and ASES score). Moreover, if continuous data were reported in multiple (>2) intervention groups, relevant subgroups were combined into a single comparator group (e.g., Ibuprofen and Celecoxib subgroups combined under “NSAID” group) using a validated formula from Cochrane [26]. For studies that reported median and interquartile range, the means and standard deviation (SD) were estimated using validated methods described by Wan et al. [27] Meta-analysis was not conducted for rescue medication/opioid use due to the heterogeneity and lack of data reported.

Meta-analysis was performed for all outcomes with ≥2 studies. To assess for heterogeneity across studies, we evaluated Forest plots, which reported Cochrane heterogeneity statistic and Higgins I² coefficient [28]). Two-tailed statistical significance was established at p value ≤0.05, while I² >50% represented moderate-high statistical heterogeneity. Where I² ≤50%, fixed-effects model was adopted. Otherwise, a random effects model was utilised in conjunction with the DerSimonian-Laird (DL) estimator to pool mean differences (MD) and odds ratios (OR) of the included studies [29].

To assess whether selective COX-2 inhibitor use influences the effect of NSAID use on retear rates, a subgroup analysis was conducted where studies were subgrouped based on the inclusion or exclusion of COX-2 inhibitor use. Studies that included selective COX-2 inhibitors included populations with either selective COX-2 only or both selective COX-2 and non-selective COX use. This study was unable to produce funnel plots due to the paucity of studies (<10). All data analyses were performed using R 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria) via the dmetar 0.0.9, meta 4.19-2, and metafor 3.0-2 packages.

2.7. Quality assessment

The risk of bias for each study was independently assessed by two independent reviewers (S.S and M.Y). Randomised controlled trials (RCTs) were evaluated using the RoB2 tool as outlined in “Chapter 8: Assessing risk of bias in a randomised trial, Cochrane Handbook for Systematic Reviews of Interventions” [26]. Each study was evaluated in terms of bias arising from randomisation process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result. Each potential source of bias was graded as “high,” “low,” or “some concerns.” On the other hand, non-RCTs were evaluated using the Newcastle–Ottawa Scale [30], where independent reviewers (M.Y and S.S) graded a scale that included 8 items using possible scores, which ranged from zero to nine. Studies with a score of seven of more were considered high quality. Studies that were deemed to be of “high” bias (RoB2) or of low quality (Newcastle–Ottawa Scale) were to be excluded. Disagreements were resolved by consultation with another author (C.G).

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-AnalysesRISMA 2020 flow diagram.
3. Results

3.1. Literature retrieval

The search strategy resulted in 5515 articles. No additional articles were identified through citation searching. After removal of duplicates, 3478 articles were screened based on title and abstract. This yielded 45 full-text articles that were assessed for eligibility and excluded based on criteria described in the PRISMA 2020 flow diagram (Fig. 1). Notably, we excluded the study by Jildeh et al. [31] as it did not report on outcomes relevant for this study such as retear rates or ASES scores. In total, six studies were included in this review [3,4,10,17-19].

3.2. Assessment of risk of bias

For the risk-of-bias assessment, the four RCTs had low risk in the various aspects of bias that were assessed (Supplementary Fig. 1) [3,4,10,17]. Meanwhile, the two non-RCTs assessed in the Newcastle-Ottawa scale scored 7 out of 9 [18,19] (Supplementary Fig. 2).

3.3. Study characteristics

In terms of study design, four RCTs and two non-RCTs were included in this systematic review. In terms of country/institution, one study originated from Korea [3], one from Iran [18], and the remaining four studies originated from USA [4,10,17,19]. Regarding the type of NSAIDs used, three studies (50%) utilised selective COX-2 inhibitors [3] [[17,18], specifically Celecoxib, while one study used Ketorolac [4] and three studies used Ibuprofen [3,10,19]. Notably, Oh et al. included the use of both Celecoxib and Ibuprofen [3], which were combined in this study under the NSAID group. For the control groups, three studies used placebo,10, 17, 18 one study used tramadol [3], and two studies did not give any additional medications [4,19]. All groups were prescribed the institutions’ standard-of-care prescription to be used as needed, with four studies using an opioid (hydrocodone/oxycodone) and acetaminophen combination [4,10,17,18], one study using oxycodone only [3], and one study not specifying the type of opioid used [19]. (Table 1).

3.3.1. Patient demographics and follow-up

Across all six studies, the total baseline cohort size was 916, with 443 (48.3%) patients in the NSAID group and 473 (51.6%) patients in the control group [3,4,10,17-19]. The pooled proportion of males was 53% (95%CI: 30 to 75) in the NSAID group and 53% (95%CI: 36 to 69) in the control group [3,4,10,17-19]. Pooled mean age was 55.8 years (95%CI: 51.4 to 60.2) in the NSAID group and 56.0 years (95%CI: 51.7 to 60.2) in the control group [3,4,10,17-19]. Across three studies, the pooled BMI (in kg/m²) was 31.0 (95%CI: 24.0 to 38.0) in the NSAID group and 29.9 (95%CI: 24.0 to 35.8) in the control group [4,17,19]. Across four studies, the pooled proportion of right hand dominance was 63% (95%CI: 0 to 100) in the NSAID group and 75% (95%CI: 5 to 100) in the control group [3,4,10,17]. Only Oh et al. reported the number of patients with previous trauma that consisted of 43/120 (35.8%) in the NSAID group and 25/54 (46.3%) in the control group [3]. (Table 1).

3.3.2. Tear details

Three studies reported mean tear or retraction size [3,17,18]. The pooled mean tear size was 20.0 mm (95%CI: 11.3 to 28.7) in the NSAID group and 18.3 mm (95%CI: 3.9 to 32.8) in the control group. The pooled proportion of large to massive tears across two studies was 14% (95%CI: 0 to 79) in the NSAID group and 13% (95%CI: 2 to 29) in the control group [4,10].

3.4. Outcome details

In terms of post-operative pain, follow-up duration ranged from 2 to 42 days for the earliest follow-up and 12–24 months for latest follow-up. VAS score ranged from 2.1 to 3.6 in the NSAID group and 2.5–5.1 in the control group. In terms of retear rates, the follow-up duration ranged from 7.5 to 24 months. Retear rates ranged from 16% to 50% in the NSAID group and 4–30% in the control group. The total sample size at final follow-up was 670, with 302 patients in the NSAID group and 368 patients in the control group. For the meta-analysis, all outcomes were analysed at final follow-up only except for VAS score, which had sufficient data for analysis at the earliest follow-up (immediately post-op) as well (Table 2).

3.5. Meta-analysis of retear rates

3.5.1. Retear rates (NSAID vs. control)

Four studies, involving 230 patients, compared retear rates between the NSAID and control groups [3,4,10,17]. For the diagnostic modality, one study used a mix of both magnetic resonance imaging (MRI) and ultrasonography (USG) [3], while two studies solely used MRI [4,17] and one study solely used USG [10]. The criterion for diagnosis was most commonly Sugaya Type IV or V tears on MRI or full/partial thickness tears on USG.

In the NSAID group, involving 131 patients, the pooled retear rate was 25% (95%CI 6 to 50), comprising of 32 retears. In the control group, involving 99 patients, the pooled retear rate was 21% (95%CI 3 to 49), comprising of 23 retears. Meta-analysis of odds ratio did not yield any statistical significance between the two groups (OR: 1.29, 95%CI: 0.18 to 9.10, p = 0.71) (Fig. 2).

3.6. Meta-analysis of pain outcomes

3.6.1. VAS score (early and late follow-up)

Four studies, involving 360 patients (207 in the NSAIDs group and 153 in the control group), compared VAS score between the NSAID and control groups at the early follow-up stage (<3 months) [3,4,10,18]. The pooled VAS was 2.9 (95%CI: 1.9 to 4.0) in the NSAID group and 3.8 (95%CI: 1.9 to 5.8) in the control group. There was no statistically significant difference in early VAS score between the groups (MD: −0.86, 95%CI: −2.03 to 0.31, p = 0.10) (Supplementary Fig. 3).

Four studies, involving 667 patients (302 in the NSAID group and 365 in the control group), compared VAS score between the NSAID and control groups at the late postoperative stage [3,10,17,19] (>12 months). The pooled VAS was 0.8 (95%CI: 1.2 to 1.5) in the NSAID group and 0.9 (95%CI: 0.5 to 1.3) in the control group. There was no statistically significant difference in the late VAS score between the groups (MD: 0.09, 95%CI: 0.02 to 0.16, p = 0.01) (Supplementary Fig. 4).

3.7. Meta-analysis of functional outcomes

3.7.1. ASES score

Four studies, involving 665 patients (300 in the NSAID group and 365 in the control group), compared ASES score between the NSAID and control groups at a minimum of 1 year postoperatively [3] [[10,17,19]. Notably, Sivasundaram et al. was excluded from the analysis as they only reported ASES score at a maximum of 6 weeks follow-up postoperatively [4]. The pooled ASES score was 90.4 (95%CI: 84.8 to 96.0) in the NSAID group and 87.5 (95%CI: 83.5 to 91.5) in the control group. There was no statistically significant difference in ASES score between both groups (MD: 0.46, 95%CI: −0.33 to 1.25, p = 0.31) (Fig. 3).

3.8. Subgroup analysis

Further subgroup analysis was conducted for retear rates between the NSAID and control groups to assess (1) whether the inclusion of COX-2 inhibitors influenced the effect of NSAID use on retear rates and (2) its
<table>
<thead>
<tr>
<th>Study</th>
<th>Study period</th>
<th>Study design</th>
<th>Group</th>
<th>Baseline sample size</th>
<th>Follow-up duration (months)</th>
<th>Institution (country)</th>
<th>Institution standard-of-care pain relief (pre-/intra/post-operative)</th>
<th>Rehabilitation protocol</th>
<th>Patient demographics</th>
<th>Tear details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rouhani et al., 2014</td>
<td>2009–2012</td>
<td>Case control study</td>
<td>Celecoxib (NSAID group)</td>
<td>30</td>
<td>0.07 (2 days)</td>
<td>Shohada Educational Hospital, Tabriz University of Medical Sciences, Tabriz, Iran</td>
<td>Pre-operative: Celecoxib (NSAID group only)</td>
<td>NR</td>
<td>Sex (Male): 24 (80%)</td>
<td>Age: 48.4 ± 11.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Placebo (Control group)</td>
<td>30</td>
<td>0.07 (2 days)</td>
<td></td>
<td>Post-operative: Acetaminophen 500mg/Hydrocodone 5 mg tablet as needed IV petidine as needed if severe</td>
<td>NR</td>
<td>Sex (Male): 22 (73.3%)</td>
<td>Age: 47.2 ± 12</td>
</tr>
<tr>
<td>Oh et al., 2017</td>
<td>2011–2012</td>
<td>RCT</td>
<td>Celecoxib</td>
<td>60</td>
<td>24</td>
<td>Seoul National University Bundang Hospital (Korea)</td>
<td>Pre-operative: None prescribed Post-operative: Subacromial patient-controlled analgesia (ropivacaine) Oxycodone as-needed</td>
<td>5 weeks abduction brace Passive ROM immediately after surgery</td>
<td>Sex (Male): 17</td>
<td>Age: 61.5 ± 8.4</td>
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<td></td>
<td></td>
<td></td>
<td>Sex (Male): 22</td>
<td>Age: 61.2 ± 9.5</td>
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<td></td>
<td></td>
<td></td>
<td>Sex (Male): 24</td>
<td>Age: 59.6 ± 9.2</td>
</tr>
</tbody>
</table>
|                            |              |               |                       |                      |                              |                                                                                       |                                                                      |                                      | Sex (Male): 94 (51%) | Age: 55.93 ± 9.72 | BMI: 27.9 ± 10.6 | Comorbidities: DM 9 (5%) | Tear size: Retraction (mm): 16.5 ± 7.6
|                            |              |               |                       |                      |                              |                                                                                       |                                                                      |                                      | No. of tendons involved: 1: 81 (44.5%) | 2: 72 (39.6%) | 3: 27 (14.8%) | 4: 2 (1.1%) |
|                            |              |               |                       |                      |                              |                                                                                       |                                                                      |                                      | Missing: 6 | |
| Kraus et al., 2020          | 2012–2016    | Retrospective study | Ibuprofen (NSAID group) | 182                  | 24                           | Tufts university school of medicine (USA)                                               | Pre-operative: NR Post-operative: Opioid medication as needed                                                     | NR                    | Sex (Male): 162 (58%) | Age: 57.01 ± 9.13 | BMI: 28 ± 8.73 | Comorbidities: DM 10 (4%) | Tear size: Retraction (mm): 16.1 ± 8.2
|                            |              |               |                       |                      |                              |                                                                                       |                                                                      |                                      | No. of tendons involved: 1: 82 (42.3%) | 2: 77 (39.7%) | 3: 31 (16%) | 4: 4 (2.1%) |
|                            |              |               |                       |                      |                              |                                                                                       |                                                                      |                                      | Missing: 89 | |
| Burns et al., 2021          | 2014–2018    | RCT           | Celecoxib              | 40                   | 12                           | SSM Health DePaul Hospital and University of Southern California (USA)                   | Pre-operative: NR Post-operative: Inter-scalene regional block Oxycodone/Hydrocodone/acetaminophen, codeine or tramadol as-needed | 3 weeks abduction sling Passive ROM immediately after surgery | Sex (Male): 11 | Age: 54 ± 7.1 | BMI: 32.5 ± 7.5 | Hand Dominance (Right): 11 Comorbidities: DM (1), HTN (9), Smoker (9) | |
|                            |              |               | Placebo                | 39                   |                               |                                                                                       |                                                                      |                                      | Sex (Male): 10 | Age: 56.8 ± 7.4 | (continued on next page) | |

(continued on next page)
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Intervention</th>
<th>Sex</th>
<th>Age (SD)</th>
<th>BMI (SD)</th>
<th>Comorbidities</th>
<th>Tear morphology (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sivasundaram et al., 2021</td>
<td>2019–2020 RCT</td>
<td>Ketorolac</td>
<td>20</td>
<td>55.7</td>
<td>32.5</td>
<td>DM (5), HTN (10), Smoking (8)</td>
<td>Tear size (mm): 14.04 ± 5.62a</td>
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<tr>
<td></td>
<td></td>
<td>Control</td>
<td>19</td>
<td>55.7</td>
<td>29.2</td>
<td>DM (1), HTN (4), CHF (1), Hypothyroidism (1), Depression (5)</td>
<td>Tear morphology (n): Partial-thickness (1), Full-thickness (6), Massive (2)</td>
</tr>
<tr>
<td>Tangtiphaiboontana et al., 2016–2019 RCT</td>
<td>Ibuprofen</td>
<td>51</td>
<td>12</td>
<td>57.7</td>
<td>29.2</td>
<td>DM (1), HTN (4), CHF (1), Depression (5)</td>
<td>Tear morphology (n): Small (21), Medium (24), Large (6), Massive (1)</td>
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<td></td>
<td></td>
<td>Placebo</td>
<td>50</td>
<td>56.9</td>
<td>29.2</td>
<td>DM (1), HTN (4), CHF (1), Depression (5)</td>
<td>Tear morphology (n): Small (19), Medium (24), Large (6), Massive (1)</td>
</tr>
</tbody>
</table>

NR: not reported; NSAIDs: non-steroidal anti-inflammatory drugs; RCT: randomised controlled trial; MRI: magnetic resonance imaging; USG: ultrasonography; DM: diabetes mellitus; HTN: hypertension; CHF: congestive heart failure; n: number; ROM: range of motion; SSP: supraspinatus; ISP: infraspinatus.

* Median IQR converted to mean ± standard deviation using formula by Wan 2014.
Table 2
Outcome scores of six studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Group</th>
<th>Analgesic used</th>
<th>Sample size at final follow-up</th>
<th>Retear rates (%)</th>
<th>Criteria for retear diagnosis</th>
<th>Follow-up duration for retear rates in months (≥6 months)</th>
<th>Pain outcomes</th>
<th>Function outcomes</th>
<th>Rescue medication/ opioid use (final follow-up)</th>
<th>Dosage/ number of pills</th>
<th>Rates (%)</th>
</tr>
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<tbody>
<tr>
<td>Rouhani et al., 2014</td>
<td>NSAID</td>
<td>Celecoxib</td>
<td>30</td>
<td>NR</td>
<td></td>
<td>3.6 ± 0.8 (n = 30) 0.3 week (2 days)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Control</td>
<td>Placebo</td>
<td></td>
<td>30</td>
<td></td>
<td></td>
<td>5.1 ± 1.4 (n = 30)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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</tr>
<tr>
<td>Oh et al., 2017</td>
<td>NSAID</td>
<td>Celecoxib</td>
<td>30</td>
<td>11/30 (37%)</td>
<td>Sugaya type IV or V on MRI or full/ partial-thickness tear on USG</td>
<td>24 months 2.8 ± 2.1 (n = 53) 2 weeks 0.9 ± 1.9 (n = 30) 12 months 92.9 ± 11.9 (n = 22)</td>
<td>NR</td>
<td>24 months 87.6 ± 11.4 (n = 30)</td>
<td>NR</td>
<td>18/30 (60%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ibuprofen</td>
<td></td>
<td>27</td>
<td>2/27 (7%)</td>
<td></td>
<td>3.2 ± 1.9 (n = 55)</td>
<td>NR</td>
<td>27/33 (51%)</td>
<td>No. of pills: 3.4 ± 1.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>Tramadol</td>
<td></td>
<td>25</td>
<td>1/25 (4%)</td>
<td></td>
<td>0.8 ± 1.5 (n = 25)</td>
<td>NR</td>
<td>30/55 (55%)</td>
<td>No. of pills: 3.9 ± 1.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Burns et al., 2021</td>
<td>NSAID</td>
<td>Celecoxib</td>
<td>22</td>
<td>10/20 (50%)</td>
<td>Sugaya type IV or V on MRI</td>
<td>12 months 0.86 ± 1.59 (n = 24)</td>
<td>NR</td>
<td>12 months 88.2 ± 22.9 (n = 23)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Control</td>
<td>Placebo</td>
<td></td>
<td>23</td>
<td>6/20 (30%)</td>
<td></td>
<td>1.58 ± 0.72 (n = 23)</td>
<td>NR</td>
<td>5/20 (25%)</td>
<td>No. of pills: 8.82 ± 3.65</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sivastundaram et al.,</td>
<td>NSAID</td>
<td>Ketorolac</td>
<td>20</td>
<td>2/11 (18%)</td>
<td>Full/partial-thickness tear on MRI</td>
<td>7.9 months 2.98 ± 2.50 (n = 20)</td>
<td>NR</td>
<td>13/19 (68.4%)</td>
<td>No. of pills: 19.42 ± 2.92</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2021</td>
<td>Control</td>
<td></td>
<td>19</td>
<td>3/11 (27%)</td>
<td></td>
<td>0.24 ± 0.46 (n = 19)</td>
<td>NR</td>
<td>104 MME</td>
<td>Dosage: 85.6 ± 4.2 (n = 281)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tangtiphaiboontana et</td>
<td>NSAID</td>
<td>Ibuprofen</td>
<td>51</td>
<td>7/43 (16%)</td>
<td>Full/partial-thickness tear on USG</td>
<td>12 months 2.1 ± 2.0 (n = 49)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>et al., 2021</td>
<td>Control</td>
<td></td>
<td>51</td>
<td>13/43 (30%)</td>
<td></td>
<td>0.4 ± 0.8 (n = 41)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>168.3 ± 96 MME</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td></td>
<td>50</td>
<td></td>
<td></td>
<td>0.7 ± 0.1 (n = 39)</td>
<td>NR</td>
<td>210.9 ± 104 MME</td>
<td>Dosage: 85.5 ± 4.5 (n = 182)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kraus et al., 2021</td>
<td>NSAID</td>
<td>Ibuprofen</td>
<td>182</td>
<td></td>
<td></td>
<td>2.5 ± 2.1 (n = 50)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Control</td>
<td>Opioids (not specified)</td>
<td>281</td>
<td></td>
<td></td>
<td></td>
<td>1.3 ± 0.4 (n = 182)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

NR: not reported; NSAIDs: non-steroidal anti-inflammatory drugs; VAS: Visual Analogue Scale; ASES: American Shoulder and Elbow Surgeons Standardised Shoulder Assessment Form; MME: Morphone Milligram Equivalents.

2. Baseline sample size (Celecoxib (N = 53), Ibuprofen (n = S5), Tramadol (n = 54)) differs from no. of patients included in RCT due to loss to follow-up.
3. Refers to medication refill rates.
4. SD calculated from DigitizeIt and converted to SD via Cochrane formulae, report number of pills taken.
contribution to heterogeneity in the primary analysis ($I^2 = 61\%$). The four studies were subgrouped based on inclusion of selective COX-2 inhibitors (“COX-2 only OR both” subgroup versus “non-selective COX only” subgroup) [3,10,18,19]. There was a statistically significant difference between the two subgroups ($p < 0.01$), indicating that the inclusion of COX-2 significantly affects retear with NSAID use, with the “non-selective COX only” subgroup having more favourable results (fewer retear rates) relative to the “COX-2 only OR both” subgroup (Fig. 4).

### 4. Discussion

Widespread opioid prescription in post-RCR pain management is a concern as opioid abuse is a national crisis in the United States. It has been found that 70% of abusers become addicted through an initial course of physician-prescribed medications [4]. While the use of opioid medications in orthopaedics remains higher than other surgical specialties, recent multimodal approaches to pain management have been adopted to reduce opioid usage [10,13]. NSAIDs play an important role in this approach, but controversies arose due to historical concerns on its potential effects on tendon-to-bone healing [10]. Hence, the aim of our study was to assess the effects of NSAID use on post-RCR retear rates, pain control, and functional outcomes. Our meta-analysis has demonstrated that using NSAIDs for post-RCR pain relief does not increase retear rates and offers comparable pain relief and satisfactory functional outcomes, as shown by the lack of statistically significant difference in VAS scores and ASES score, compared to a non-NSAID regime.

It is interesting to highlight the inclusion of selective COX-2 inhibitors such as Celecoxib in the NSAIDs arm in three of our included studies. In recent times, selective COX-2 inhibitors have received much attention since they provide a similar effect to traditional, non-selective NSAIDs.
One of the biggest concerns regarding NSAID use is its potentially detrimental effects towards tendon-to-bone healing and risk of retear. While animal studies have demonstrated that NSAIDs may lead to impaired tendon-to-bone healing, lower failure loads and reduced collagen organisation (predisposing to retears) [11,12], there is a lack of prospective clinical trials on humans. However, our analysis has shown that NSAID use does not lead to higher retear rates or worse functional outcome scores. Retear rates after arthroscopic RCR are multifactorial and range widely from 4% to 78% [35,36]. Risk factors include muscle atrophy, fatty infiltration, age, tear size, and smoking status [37,38]. Another possible risk factor for retear is the rehabilitation protocol, with Saltzman et al. concluding that early motion may result in greater retear rates [17,39,40]. Our study showed no statistically significant difference in comparable patient demographic factors such as age and tear size and the rehabilitation protocol was relatively standardised across both groups in all included studies. This demonstrates that the effects of these potential confounding factors are minimal in this study, which further strengthens this study’s finding that NSAID use does not increase retear rates.

To assess possible causes of high heterogeneity in the analysis of retear rates ($I^2 = 61\%$), we conducted a subgroup analysis which demonstrated that inclusion of selective COX-2 inhibitors (“COX-2 only OR both” subgroup) leads to higher retear rates when compared to non-selective COX inhibitors (“non-selective COX only” subgroup). Studies have postulated that COX-2 inhibitors impede soft-tissue healing due to the disruption of the COX-2/PGE-2 pathway, which is important in stimulating tenocyte proliferation, adhesion, and migration during the acute stages of tendon healing [3,41,42]. Su et al. reported a dose-dependent effect of celecoxib on the inhibition of fracture healing in contrast to non-selective NSAIDs, which delay rather than inhibit fracture healing [43]. This highlights that even though selective COX-2 inhibitors have proven advantage over traditional, non-selective NSAIDs in terms of side effects profile, the potential impact on healing outweighs the benefits it offers. Furthermore, co-prescription of proton-pump-inhibitors (PPIs) with NSAIDs can also mitigate the risk of gastritis and ulcers [44]. However, the conclusion drawn from the subgroup analysis should be taken with caution due to several reasons. First, this study recognises that although subgroup analysis can assess whether the inclusion of COX-2 inhibitors modifies the effect of NSAID on retear rates, it lacks statistical power to find significant differences in retear rates between the subgroups [45]. A primary meta-analysis comparing non-selective COX versus selective COX is required, which this study was unable to carry out due to the paucity of studies comparing the two (only Oh et al.). Second, the “COX-2 only OR both” subgroup had a component of non-selective NSAIDs from Oh et al.’s study although the effect of this is likely to be minimal since the Celecoxib group (COX-2 selective NSAIDs) contributed to majority of the retears (57%) compared to Ibuprofen (7%) [3]. Therefore, to verify the effects of COX-2 selective inhibitors, more studies comparing non-selective versus COX-2 selective inhibitors are required.

4.2. Pain outcomes

NSAIDs inhibit cyclooxygenase 1 and 2 enzymes which leads to reduced production of prostaglandins and reduced sensitivity of nerve terminals, thereby providing analgesia [46]. The use of NSAIDs in orthopaedic surgery for pain management is well-established. Studies by Barber et al. and Axelsson et al. demonstrated that post-operative ketorolac provided significantly greater pain reduction compared to the standard-of-care pain medications for anterior cruciate ligament reconstruction and Bankart repairs, respectively [47,48]. In this study, there was no statistically significant difference in pain control for both groups at both early and final follow-up. Moreover, the reported mean difference in VAS score was below the minimal clinical important difference (MCID) for VAS score in patients with RC disease [49]. Therefore, it can be concluded that NSAIDs are as effective as opioids in post-RCR pain relief, which is in concordance with studies by Rounhani et al. and Kraus et al. [18,19].

In terms of opioid rescue medication usage, both Tang et al. and Siva et al. reported that the use of NSAIDs reduces the need for opiate medication [4,10]. Similarly, Rounhani et al. found that patients taking Celecoxib did not require narcotics to manage pain at all [18]. However, we were unable to conduct meta-analysis on the rescue medication dosage due to the paucity of studies reporting this information and the heterogeneity in the studies’ rescue medication protocols.

4.3. Functional outcomes

This study found no statistically significant difference in ASES score between the NSAID and control groups. Moreover, for ASES, improvement in pre-operative score to post-operative score at final follow-up was greater than the MCID in all included studies, across both groups [50]. This shows that NSAIDs are as effective as the standard-of-care in providing sufficient pain control, which enables quicker rehabilitation and increased function post-surgery [19].

4.4. Limitations

This study is not without its limitations. First, there is heterogeneity to the type of NSAIDs included (Celecoxib, Ibuprofen, Ketorolac, etc.) as part of the analysis. However, attempts were made to differentiate non-selective NSAIDs and COX-2 selective NSAIDs via subgroup analysis. Second, there was heterogeneity in the diagnosis of a retear, with the included studies having varying diagnostic criteria and imaging modality. Lastly, this study solely evaluated postoperative use of NSAIDs following RCR surgery. However, there is evidence that preoperative NSAID can potentially influence long-term outcomes in RCR; hence, this is an area that could be further investigated [51].

Nonetheless, this study is, to the best of our knowledge, the first systematic review and meta-analysis comparing NSAID and non-NSAID regimen for post-RCR pain relief and demonstrating that NSAIDs do not have higher retear rates but allow effective pain control and functional outcomes to be achieved.

5. Conclusion

This study shows that NSAIDs use in post-arthroscopic RCR pain management does not increase retear rates and can provide similar clinical outcomes compared to a non-NSAID regime. However, subgroup analysis of retear rates revealed that the inclusion of COX-2 selective NSAIDs influenced the effect of NSAIDs on retear rates, contributing to higher retear rates as compared to traditional, non-selective NSAIDs. Hence, COX-2-selective NSAIDs should be used with greater caution. The authors recommend the use of non-selective NSAIDs for postoperative pain control after RCR.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.


