Review Article

Safety and Efficacy of Postoperative Nonsteroidal Anti-inflammatory Drugs in Sports Medicine

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ABSTRACT

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used for multimodal pain control after surgery. These medications work by selective or nonselective inhibition of cyclooxygenase, which has downstream effects on thromboxanes, prostaglandins, and prostacyclins. Clinical studies have shown beneficial effects for alleviating pain and reducing opioid consumption after surgery. Within hip arthroscopy, there is evidence that postoperative NSAIDs can also reduce the risk of symptomatic heterotopic bone formation. However, preclinical and animal studies have raised concern over the effect of NSAIDs on bone and soft-tissue healing. In addition, selective and nonselective cyclooxygenase 2 inhibitors may have different safety profiles regarding postoperative soft-tissue healing. The purpose of this review was to outline the mechanisms of action, efficacy, and effect on soft-tissue healing of postoperative NSAIDs and to provide evidence-based recommendations for appropriate use.

The pharmacologic management of pain and inflammation in orthopaedic surgery is a critical aspect of patient care, particularly in the early postoperative period. This topic has gained increased attention in the United States over the past decade because of more widespread recognition of the scope and severity of the opioid epidemic.[1] Calls for increased opioid stewardship have furthered the development of multimodal pain management protocols involving local or regional anesthesia and nonnarcotic pain medications. Many of these protocols use nonsteroidal anti-inflammatory drugs (NSAIDs) for their analgesic and anti-inflammatory effects. The addition of NSAIDs to postoperative pain management protocols has been effective in reducing opioid consumption. However, concerns have been raised about the risks of these medications of their effect on bone and soft-tissue healing. The effect of NSAIDs on bone healing has been reviewed previously, with concerning results that demonstrate delayed bone healing in the presence of NSAIDs, particularly in adult patients using higher doses for longer durations.[2,3] The purpose of this review was to outline the mechanisms of action, efficacy, and effect on soft-tissue healing of postoperative NSAIDs after arthroscopic sports medicine procedures and to provide evidence-based recommendations for appropriate use.

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J Am Acad Orthop Surg 2022;00:1-8

DOI: 10.5435/JAAOS-D-21-01228

Pharmacology

NSAIDs are a family of medications that inhibit cyclooxygenase (COX), a prostaglandin synthase that converts arachidonic acid to prostaglandin G_2 and H_2.[4] These parent compounds are subsequently converted by tissue-specific synthases into a variety of prostanoids, which include prostaglandins and thromboxanes.[5] Among these prostanoids, prostaglandin E_2 (PGE_2) and prostacyclin I_2 (PGI_2) contribute to increased peripheral pain sensitivity after tissue trauma or inflammation.[6] Increased PGE_2 within the spinal cord also has a role in central pain sensitization in response to tissue injury. The anti-inflammatory and analgesic effects of NSAIDs are thus the direct result of decreased PGE_2 synthesis by way of COX inhibition.[6]

There are two isoforms of COX: COX-1, which has widespread functions including systemic hemostasis and cytoprotection for gastric mucosa, and COX-2, which has a key role in prostanoid production for the inflammatory response. The nonspecific inhibition of both COX-1 and COX-2 is responsible for many of the commonly understood NSAID adverse reactions, including gastrointestinal upset, ulcer formation, and bleeding. This led to the development of selective COX-2 inhibitors, with the goal of improving the adverse effect profile while retaining the analgesic and anti-inflammatory benefits of traditional NSAIDs.

Although selective COX-2 inhibition has advantages in the prevention of gastrointestinal adverse reactions, this comes at a cost of a theoretical increase in cardiovascular risk. The mechanism behind this risk is an imbalance of prostacyclin I_2 (which inhibits platelet aggregation and is catalyzed by COX-2) and TXA_2 (which is prothrombotic and catalyzed by COX-1).[4] This risk may be further exacerbated by the inhibition of prostaglandins involved in chloride reabsorption, antidiuretic hormone activity, and renal medullary blood flow, which can increase systemic blood pressure. The clinical significance of this risk remains controversial, but a randomized trial comparing celecoxib with ibuprofen and naproxen found no increase in cardiovascular adverse events with celecoxib at mean dosages of 170 mg.[7]

A list of widely available NSAIDs in the United States is provided in Figure 1 with a focus on their relative COX-2 selectivity.[4] It should be noted that COX-2 selectivity is not limited to the "-coxib" family of medications; some traditional NSAIDs including diclofenac and meloxicam demonstrate similar selectivity and associated risk profiles.[8]

Effect of Nonsteroidal Anti-inflammatory Drug on Soft-tissue Healing

Early soft-tissue healing involves recruitment of macrophages and neutrophils to remove necrotic cell debris, which is stimulated in part by COX-mediated prostaglandin production.[9] Inhibition of this mechanism by NSAIDs has raised concerns that these medications may inhibit soft-tissue healing. Thus far, this effect has been most effectively studied in vitro. Ghosh et al[10] conducted a scoping review to summarize the positive and negative effects of NSAIDs on soft-tissue healing across the entire body of existing literature. In this review, eight in vitro studies investigating seven NSAIDs were identified. These studies made 12 total comparisons between NSAIDs and control subjects. NSAIDs had a negative effect on cell proliferation, cell migration, protein synthesis, or glycosaminoglycan synthesis in 83.3% of comparisons (10/12). When separated by COX-2 selectivity, selective COX-2 inhibitors showed a negative effect in 3 of 3 comparisons, while nonselective NSAIDs showed a negative effect in 7 of 9 comparisons. Molecular explanations for the negative effect included decreased DNA synthesis; decreased tenocyte differentiation, proliferation, or migration; decreased glycosaminoglycan synthesis; upregulation of matrix metalloproteinases; and altered gene expression.[10]

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Figure 1

	Category	Medication	Delivery	Notes
COX-2 Selective	Selective COX-2 Inhibitors	Celecoxib	100-200mg by mouth twice daily	Limited GI side effects Theoretical cardiovascular risk may not be clinically significant at typical drug dosages
	Traditional NSAIDs with COX-2 Selectivity	Diclofenac	50mg three times per day or 75mg twice daily	Also available in extended-release oral formulations and as a topical gel May accumulate in synovial fluid even after oral administration Similar risk profile to selective COX-2 inhibitors
		Meloxicam	7.5-15mg by mouth daily	Greater COX-2 selectivity at 7.5mg dose than 15mg dose
- - Non-selective - -	Non-selective COX-1 and COX-2 Inhibitors	Ibuprofen	200-800mg by mouth every 8 hours	Recommended to take with food to limit GI effects Discontinued by 10-15% of patients due to side effects
		Naproxen	220-550mg by mouth every 12 hours	Reaches peak anti-inflammatory effect after 2-4 weeks of use May be cardioprotective relative to other NSAIDs
	Traditional NSAIDs with COX-1 Selectivity	Aspirin	325-650mg every 4-6 hours	Irreversible inhibitor Pain relief requires higher doses than anti-platelet therapy
		Indomethacin	25mg 2-3 times per day or 75mg nightly	High potency leads to increased risk of GI side effects (20% discontinue) Other side effects include neutropenia and thrombocytopenia
COX-1 Selective		Ketorolac	15-30mg IV every 6 hours	Potent analgesic effects, limited anti-inflammatory effects Limit use to 5 days or less

Characteristics of commonly used NSAIDs in orthopaedic surgery.[4,5] COX = cyclooxygenase, GI = gastrointestinal

The in vitro effects of NSAIDs prompted additional investigation through animal models. At least 33 animal studies, most of which used rat and rabbit models, have been published.[10] Animal studies investigating nonselective NSAIDs found a negative effect on healing in only 11 of 30 comparisons (36.7%). The most commonly studied nonselective NSAID was indomethacin, which showed negative effects on healing in 3 of 10 comparisons (30%). Studies investigating selective COX-2 inhibitors found a negative effect on healing in 10 of 14 comparisons (71.4%). The most commonly studied selective COX-2 inhibitor was celecoxib, which had a negative effect on healing in 5 of 7 comparisons (71.4%). The most frequently identified negative effects were decreased tendon tensile strength, stiffness, and failure load.[10] Molecular mechanisms for the decreased mechanical properties of healing soft-tissue included decreased collagen organization[11] and decreased type I collagen percentage.[12]

Clinical studies investigating the effect of NSAIDs on soft-tissue healing have been less frequent. A systematic review done in 2019 identified only four studies that evaluated the effects of NSAIDs on musculoskeletal soft-tissue healing with the use of clinical outcomes and control groups.[9] Among those studies, only 1 of 4 (25%) found a negative effect. The one study that did find a negative effect showed decreased soft-tissue healing for a selective COX-2 inhibitor compared with a nonselective NSAID.[13] The methodology and findings of the specific clinical studies will be outlined in greater detail below.

Knee Arthroscopy

Knee arthroscopy with meniscectomy (APM) is one of the most commonly performed orthopaedic surgeries. Given that soft-tissue healing is less of a concern with this procedure, NSAID research has focused more on the efficacy of these medications in reducing opioid requirements and less on their effect on soft-tissue healing in the knee. Thus far, the results have shown inconsistent efficacy in that regard. Carrier et al[14] retrospectively studied 34 patients who underwent knee arthroscopy with partial meniscectomy or chondroplasty and were prescribed ibuprofen 800 mg every 8 hours for postoperative pain control without concurrent narcotic pain medication. Patients were surveyed at the 2-week follow-up regarding their satisfaction with pain control. Only six patients (17.6%) required opioids, with the most common reason being NSAID intolerance or contraindications. Of the 28 patients who took no opioids, only one patient (3.6%) reported that a narcotic would have been needed. This suggests that

ibuprofen may be adequate for postoperative pain control in most of the APM patients.

Pham et al conducted a nonrandomized study of 68 patients undergoing arthroscopic meniscectomy of whom 28 patients were prescribed ibuprofen (600 mg every 6 to 8 hours as needed) and 10 tablets of oxycodone/acetaminophen (5/325 mg) to be used every 6 hours as needed for breakthrough pain relief, while the remaining 40 patients were prescribed 30 or 40 tablets oxycodone/acetaminophen (5/325 mg every 6 hours as needed) without a concurrent NSAID.[15] The former group (concurrent NSAID prescription) consumed fewer opioid tablets on the day of surgery and between postoperative days 3 to 7. No differences were observed in total 1-week opioid use, visual analog scale (VAS) pain scores, or patient satisfaction between groups. However, these results should be interpreted with caution. Patients were not restricted in their NSAID use, and a similar amount of NSAID tablets were taken in both groups after the day of surgery (6.1 ± 5.9 total tablets in the NSAID group vs 1.6 ± 7.4 tablets in the opioid only group, $P = 0.360$).

When considering COX-2 selective NSAIDs, there are some data to support efficacy after nonreparative arthroscopic knee surgery. A placebo-controlled, randomized study by Ekman et al[16] investigated celecoxib 200 mg given preoperatively and as the first postoperative medication before any opioid use. Patients who received celecoxib were less likely to require opioids in the first 24 hours postoperatively without any associated increased risk for surgical or medical adverse events.

Knee arthroscopy with meniscal repair represents a different challenge because meniscal tissue is well known to have limited healing capacity and may thus be more susceptible to the effects of NSAIDs on soft-tissue healing observed in vitro. This was investigated by Proffen et al in a retrospective study of 107 patients, including 32 who received perioperative ketorolac. At minimum 5 years of follow-up, there was no difference between groups in repair failure rates defined as meniscal revision surgery (34% with ketorolac, 35% without, $P > 0.50$). This result suggests that limited perioperative NSAID use does not affect meniscal healing in vivo. However, this study is limited by the confounding effects of tear location, which was shown to be a notable predictor of revision surgery on multivariate analysis. Additional research into this area should seek to externally validate these results.

Similarly, knee arthroscopy with anterior cruciate ligament reconstruction relies on soft-tissue healing in the form of graft incorporation and ligamentization. Soreide and colleagues queried the Norwegian Knee Ligament Registry to investigate whether postoperative NSAID administration would affect graft survival, revision risk, or patient-reported outcomes.[17] A total of 4,144 patients who received NSAIDs were compared with 3,678 who did not. No increased risk of revision was observed among patients who took NSAIDs, the most common of which was diclofenac (91.5% of prescriptions).

Another area of interest to sports medicine knee surgeons is the safety and efficacy of NSAIDs around the time of open tendon repairs, such as with the quadriceps or patellar tendon. For quadriceps tendon repairs, heterotopic bone formation is common; this has been reported as high as 90% by Verdano et al[18] in a series of 20 patients. NSAIDs may have a role in postoperative pain control in these patients with the additional benefit of limiting heterotopic bone formation. However, there are no prospective or comparative trials thus far that investigate the safety regarding tendon healing and efficacy regarding pain control and heterotopic ossification (HO) prevention for these procedures. This area requires additional study.

In summary, the available clinical data suggest that NSAIDs do not impair soft-tissue healing in the knee, as evidenced by equivalent revision rates for both meniscal repair and anterior cruciate ligament reconstruction. Additional study in this area with a prospective design, the use of NSAID-restricted control groups, and comparisons between nonselective and selective NSAIDs is warranted.

Shoulder Arthroscopy

Within shoulder arthroscopy, NSAID efficacy (for pain control) and safety (defined as noninterference with healing) have been evaluated most specifically for arthroscopic Bankart repairs and arthroscopic rotator cuff repairs. Thompson et al[19] conducted a single-center prospective randomized trial with 80 patients undergoing arthroscopic Bankart repair to determine whether NSAIDs could reduce opioid consumption in this population. The authors compared two postoperative prescriptions: (1) 30 tablets of ibuprofen (600 mg every 6 to 8 hours as needed) and 10 tablets of oxycodone/acetaminophen (5/325 mg) to be used every 6 hours as needed for breakthrough pain relief and (2) 30 tablets of oxycodone/acetaminophen (5/325 mg every 6 hours as needed). There was significantly less total opioid tablet consumption in the NSAID group (7.9 ± 6.9 tablets vs. 11.7 ± 10.8 tablets, $P = 0.05$). No difference was observed in overall patient satisfaction.

Looking at safety regarding soft-tissue healing, a retrospective study examined 477 patients in the Norwegian shoulder instability register at a mean follow-up of 21 months.[20] NSAIDs were prescribed postoperatively to 155 patients (32.5%), and the remaining 322 patients were considered a control group. No difference was observed in Western Ontario Shoulder Instability score, recurrence rate, or revision surgery rates between groups. Owing to the retrospective nature, the effect of NSAIDs on early postoperative pain and satisfaction could not be elucidated. It should be noted that NSAID prescriptions were for a short course (only 9% of the patients were given greater than 1 week of the medication). Taken together, these studies suggest that nonselective NSAIDs are safe and effective for postoperative pain control after labral repair.

Rotator cuff repairs present a clinical challenge because of inconsistent healing rates. This has brought about a more extensive body of clinical research into the effect of NSAIDs on healing and surgical outcomes. First, looking specifically at efficacy, trials have investigated whether NSAID use after rotator cuff repair reduces opioid consumption without sacrificing patient satisfaction. Jildeh et al[21] conducted a small, randomized trial comparing multimodal pain control with opioid analgesia after arthroscopic rotator cuff repair. It should be noted that preoperative and intraoperative medications were administered as well. Patients indeterminate of the treatment group received the following medication preoperatively: celecoxib 400 mg, acetaminophen 975 mg, tramadol 50 mg, gabapentin 300 mg, and 8 mg dexamethasone intravenously. A regional block was done. Intraoperatively, all patients received a local infiltration of 30 mg (1 mL) ketorolac, 1 mg (1 mL) epinephrine, and 150 mg (30 mL) of 0.5% ropivacaine. Postoperatively, patients were prescribed 5 mg oxycodone (40 pills, 1 to 2 pills every 4 to 6 hours as needed) or a detailed nonopioid multimodal protocol.[22] Patients using multimodal nonopioid analgesia demonstrated lower VAS pain scores throughout the first week postoperatively, with fewer complaints of abdominal discomfort, and no decrease in patient satisfaction.

The safety of NSAIDs regarding tendon to bone healing and patient-reported outcomes has also been studied extensively for rotator cuff repairs. In a retrospective study by Kraus et al,[23] 281 patients who were advised to avoid NSAIDs after primary arthroscopic rotator cuff repairs were compared with 182 patients who were prescribed postoperative ibuprofen. No differences were observed between groups in VAS, American Shoulder Elbow Surgeons (ASES) score, Single Assessment Numeric Evaluation score, Simple Shoulder Test, and the Veterans Rand 12-Item Health Survey at 3 months, 6 months, 1 year, or 2 years after surgery.

The most recent and perhaps most impactful study of nonselective NSAID use in this population was a randomized, double-blind, placebo-controlled trial of postoperative NSAIDs done in 101 patients undergoing primary arthroscopic rotator cuff repair at a single institution.[24] Patients were prescribed ibuprofen (400 mg every 8 hours for 14 days continuously) or placebo (for the same duration) for postoperative pain control, in addition to opioid medication. Both patients and surgeons were blinded to the medications, and the pills were created to appear identical. Patients also received 60 pills of hydrocodone/acetaminophen (10 mg/325 mg) to be taken as needed. The ibuprofen group showed reduced VAS pain scores at all time points, with statistical significance at postoperative days 3 to 6. Patients in the ibuprofen group also required less opioid medication, as measured by morphine milligram equivalents (168.3 ± 96 MMEs vs. 210.9 ± 104 MMEs, $P = 0.04$). A statistically significant but clinically insignificant difference was observed in forward flexion and mean ASES score favoring the ibuprofen group at 6 months. No differences were observed in VAS pain score, remaining shoulder motion, SF-12 score, or DASH score preoperatively or at 6 weeks, 3 months, 6 months, or 1 year postoperatively. On ultrasonography at 1 year, seven patients (16.3%) in the ibuprofen group had evidence of tendon retears compared with 13 patients (30.1%) in the placebo group ($P = 0.20$).

Although nonselective NSAIDs seem to be safe and effective to administer after rotator cuff repair, there are two studies that raise concern about the use of selective COX-2 inhibitors in this population. The first is a landmark-randomized, controlled trial of 180 patients undergoing arthroscopic primary rotator cuff repair. In that trial, Oh et al randomly assigned patients to receive celecoxib, ibuprofen, or tramadol (n = 60 each).[25] No notable differences were observed among the three groups for VAS scores, pain intensity, adverse effects, or rescue medication use at 3 days or 2 weeks after surgery. Repair integrity was assessed with the Sugaya classification for 84 patients (n = 30 celecoxib, n = 27 ibuprofen, and n = 25 tramadol) who were available for the follow-up, MRI examination, and interview at 2 years postoperatively. The retear rate was 37% in the celecoxib group, 7% in the ibuprofen group, and 4% in the

tramadol group ($P = 0.009$). No notable differences in VAS, range of motion, Constant score, or ASES between groups. The authors concluded that celecoxib may have adverse effects on rotator cuff tendon healing. The second study is a recent randomized trial of 40 patients with a 1-year follow-up.[26] Burns et al randomized patients 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. Repair integrity was evaluated with MRI using the Sugaya classification at 1 year. Ten of the 20 patients in the celecoxib group (50%) had intact repairs at 1 year, while 14 of the 20 patients in the placebo group had intact repairs (70%). Although the absolute difference was concerning, there was no statistical difference in repair failure between groups ($P = 0.35$), which may be attributed to low sample sizes and insufficient power. The authors recommended against using celecoxib in this population.

Hip Arthroscopy

NSAIDs are frequently used after hip arthroscopy to reduce the risk of HO. In this capacity, several studies have shown efficacy. A systematic review conducted in 2016 found rates of HO to be 13.4% without NSAID prophylaxis and 3.3% with NSAID prophylaxis in the contemporary literature.[27] The authors concluded that NSAIDs were effective for lowering the risk of HO but recommended additional study regarding drug regimens, compliance, and adverse effects. One study of mention that was included in that review was a randomized, controlled trial of 108 patients randomized to either naproxen 500 mg twice daily or placebo for 3 weeks after surgery. The prevalence of HO was 46% in the placebo group versus 4% in the naproxen group ($P < 0.001$).[28] More recent studies have corroborated these results. Schaver et al[29] retrospectively analyzed 328 open and arthroscopic hip surgeries treated with postoperative NSAIDs (with naproxen being the most common medication at 84.4% of the cases). The rate of HO was only 1.5% (5/328), with no statistically significant differences between naproxen and other NSAIDs. Although there was no control group, this rate of HO is dramatically lower than reported rates for hip arthroscopy without postoperative NSAID use in the literature.

When looking at selective COX-2 medications, celecoxib has shown efficacy in reducing heterotopic bone formation. Dow et al[30] done a retrospective study of 454 cases in which 211 patients who were prescribed 400 celecoxib once daily for 6 weeks were compared with 241 who were not prescribed celecoxib. The celecoxib group had significantly lower rates of HO than control subjects (12.3% vs 29.4%, $P = 0.006$). No difference was observed in the percentage of patients reaching a minimal clinically important difference or substantial clinical benefit benchmark at any time point. Another study investigated etodolac, a selective COX-2 inhibitor, administered at 600 mg once daily for 2 weeks postoperatively.[31] In 63 patients treated with etodolac, no HO was identified; among 100 control subjects who were not prescribed an NSAID, the rate was 19.1% for Brooker grade ≥2 HO ($P < 0.0001$).

When considering efficacy for pain control, studies have investigated perioperative NSAID use on the day of surgery. Cunningham and Lewis[32] conducted a retrospective, observational study of opioid use, pain, and time spent in the postanesthesia care unit among opioid-naïve patients undergoing primary hip arthroscopy. Patients who received a dose of ketorolac at closure

Table 1. Recommendations for Appropriate Use of NSAIDs After Arthroscopic Surgery

1. The use of either selective COX-2 inhibitors or nonselective NSAIDs may be appropriate after knee arthroscopy with no controlled clinical studies demonstrating a negative effect. Additional study is warranted (Grade C).
2. The use of nonselective NSAIDs for multimodal pain control after shoulder arthroscopy may be appropriate, with ibuprofen being the most frequently studied medication (Grade A).
3. The use of selective COX-2 inhibitors after rotator cuff repair is rarely appropriate because of the risk of increased retear rates identified in two randomized controlled trials investigating celecoxib (Grade B).
4. The use of either selective or nonselective NSAIDs after hip arthroscopy is recommended for prevention of heterotopic bone formation and may reduce postoperative pain (Grade A).

COX = cyclooxygenase, NSAID = nonsteroidal anti-inflammatory drug

These recommendations can be made based on this literature and in accordance with the guidelines set forth by the American Academy of Orthopaedic Surgeons Appropriate Use Criteria Methodology.[36] Grade A indicates good evidence (Level-I studies with consistent findings) for or against recommending intervention, Grade B indicates fair evidence (Level-II or Level-III studies with consistent findings), Grade C indicates poor-quality evidence (Level-IV or Level-V studies with consistent findings), and Grade I indicates insufficient or conflicting evidence not allowing a recommendation for or against intervention.[37]

consumed less morphine equivalents (17.5 vs 22.5, $P = 0.01$), but there were no differences in pain scores or recovery time before discharge. Celecoxib, given in a single dose before surgery, has also shown efficacy for reducing early postoperative pain. Two placebo-controlled trials demonstrated reduced VAS pain scores on the first postoperative day after a single celecoxib dose of 200[33] or 400 mg.[34] Finally, a systematic review of 14 randomized, controlled trials sought to determine whether adjunctive analgesia (including NSAIDs or local anesthetics) was effective at reducing postoperative pain and facilitating shorter length of stay.[35] The authors concluded that adjunctive measures did indeed reduce pain on the first day, but results were inconclusive regarding the length of stay.

Summary

Nonsteroidal anti-inflammatory medications exist on a spectrum of COX-1 and COX-2 selectivity. Selective COX-2 inhibitors may reduce inflammation with fewer gastrointestinal adverse effects and equivalent analgesic effects. For knee arthroscopy, additional randomized, placebo-controlled trials are warranted to clarify the safety and efficacy of both selective and nonselective NSAIDs. Within shoulder arthroscopy, nonselective NSAIDs seem both safe and effective at reducing postoperative pain without adverse effects on soft-tissue healing. By contrast, two randomized clinical studies have raised concerns for decreased rotator cuff tendon healing in patients who were prescribed the selective COX-2 inhibitor celecoxib. In hip arthroscopy, efficacy of NSAIDs for reducing HO is well established and these medications may reduce postoperative pain. Recommendations for appropriate use of NSAIDs after arthroscopic knee, shoulder, and hip surgery are summarized in Table 1. T1

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