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Review Article

Do NSAID/COX-2 Inhibitors Increase Nonunion After Fracture Surgery? Dilemma and Consideration In Use

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ABSTRACT

Background: Nonunion accounts for 2% to 10% of fracture complications, diminishing quality of life and increasing mortality risk. Several factors, including smoking, metabolic disorders, dietary inadequacy, and nonsteroidal anti-inflammatory drugs (NSAIDs), may predict nonunion development. NSAIDs are frequently used to treat postoperative pain, including in orthopedic conditions, particularly for fracture pain management. However, NSAID/cyclooxygenase (COX)-2 inhibitor use has been controversial for many years. Many orthopedic surgeons avoid using them in fracture surgery due to their potential adverse effects on osteogenesis and subsequent nonunion risk.
Literature Review: An updated literature review was conducted using digital databases such as PubMed, Cochrane, Ovid-SP, Springer Link, and Science Direct, with the search terms "NSAIDs" OR "COX-2 inhibitor" AND "nonunion" AND "fracture surgery." Seven publications that met the inclusion criteria were summarized. This review revealed that while NSAIDs/COX-2 inhibitors have been shown to temporarily inhibit fracture union in some studies, the safety of NSAIDs following fracture fixation without notable interference in bone healing has been demonstrated in others. The association of COX-2 inhibitors or non-selective NSAIDs with nonunion remains unclear.
Summary: Prolonged NSAID use interferes with successful bone healing. Short-duration (<2 weeks of treatment) and low-dose NSAID use are considered safe and efficacious for postoperative fracture pain.

Keywords: COX-2 inhibitors; Fracture surgery; Human and medicine; Nonunion; NSAID

INTRODUCTION

Nonunion, the failure of the fracture healing process, contributes to 2% to 10% of fracture complications.[1,2] Nonunion is a common complication that decreases quality of life and increases mortality risk. The cost of nonunion fracture treatment is greater than that of union fracture. Prolonged disability and working absence further increase the financial burden.[3] Physicians should be aware of the protective and risk factors, both controllable and uncontrollable, for nonunion and thereby manage to prevent it. Several uncontrollable factors include sex, age, underlying diseases, type of injury, fracture pattern, location, displacement, and severity. In contrast, controllable factors include smoking, metabolic disease, nutritional deficiency, and nonsteroidal anti-inflammatory drug (NSAID) use.[2,4,5]

How medication affects nonunion has been a particular interest. NSAIDs are commonly prescribed for postoperative pain, including in orthopedic conditions, particularly for treating postoperative fracture pain.[3] NSAIDs have significantly reduced the need for opioids and their associated adverse effects (e.g., nausea/vomiting, constipation, and decreased mobilization), leading to their wide use in postoperative pain management.[3,6] Pain management is vital in healthcare, and physicians should be mindful of drugs' potentially harmful adverse effects.[7] NSAID/cyclooxygenase (COX)-2 inhibitor use has been controversial for many years.[1] Many

orthopedic surgeons avoid using these drugs for fracture surgery due to their potential interference with osteogenesis and subsequent nonunion risk.[3]

NSAIDs primarily act by inhibiting prostaglandin production. Prostaglandins are autocrine and paracrine lipid mediators that affect platelets, uterine and mast cells, and endothelial cells. Cyclooxygenase (COX), the initial enzyme in the prostaglandin production pathway, transforms arachidonic acid into thromboxane A2, prostacyclin, and prostaglandins. Two COX isoforms have been identified: COX-1 and COX-2.[8] Cyclooxygenase-1 is a constitutive enzyme that controls cellular physiology functions, including gastrointestinal cytoprotection, renal blood flow, platelet aggregation, and vascular hemostasis. Cyclooxygenase-2 is usually found in low levels. COX-2 upregulates the inflammatory system following the activation of inflammatory mediators and cytokines.[9]

Non-selective NSAIDs inhibit both COX-1 and COX-2. Suppression of COX-1 is responsible for the high occurrence of gastrointestinal adverse effects caused by NSAIDs. Cyclooxygenase-2 inhibitors were developed to reduce inflammation in a specific area while avoiding gastrointestinal side effects. Following tissue injury, cell membranes release arachidonic acid. When activated by inflammatory mediators and cytokines, COX-2 breaks down arachidonic acid into thromboxane A2 and prostaglandins. Prostaglandins can cause inflammation and discomfort when released at injury sites. Blocking the COX-2 enzyme leads to the anti-inflammatory effect of COX-2 inhibitors and NSAIDs.[8,9]

There are three phases of bone healing mechanisms: inflammatory, reparative, and remodeling.[1,8] In the inflammatory phase, prostaglandin production is stimulated by inflammatory mediators and cytokines. Osteoblasts produce prostaglandin E2, particularly in the presence of fracture callus formation. Osteoblasts create the most prostaglandin E2, which is the most prevalent prostaglandin. It enhances bone growth, bone mass, and strength by stimulating osteoblasts. Prostaglandin E2 increases bone resorption by acting as an agonist of osteoclasts. The quantity and activity of other prostaglandins also increase.[8,9] However, NSAIDs and specific COX-2 inhibitors suppress the inflammatory stage of bone healing. Several studies have shown the vital role of COX-2 in the early stages of bone healing. Inhibiting bone repair during the inflammatory stage has negatively affected animal experiments. The balance between bone resorption and absorption is disturbed in fracture healing when prostaglandin production is prevented.[8]

Animal studies have demonstrated the role of NSAIDs/COX-2 inhibitors in fracture healing impairment or delay.[2] Clinical studies involving humans have shown both the absence of an effect on fracture healing and the presence of an effect.[1] However, different studies have shown the safety of NSAIDs after fracture fixation with no remarkable effects on bone healing.[10] In clinical practice, pain caused by fractures leads patients to resort to NSAIDs/COX-2 inhibitors.[2] Therefore, controversy remains about using NSAIDs after fracture surgery due to the risk of nonunion. Our review's objective was to comprehensively assess: 1) the association between NSAIDs/COX-2 inhibitors and nonunion; 2) the consideration of safe doses and duration in NSAIDs/COX-2 inhibitor administration that can be used in clinical practice.

LITERATURE REVIEW

Medical databases, including PubMed, Cochrane, Ovid-SP, Springer Link, and Science Direct, were searched for studies published in English from January 2012 to June 2022. The initial search yielded 432 publications. Search terms and keywords are listed in Table 1.

Inclusion criteria were: 1) human clinical trials; 2) patients aged ≥18 years with fractures treated surgically; 3) NSAID/COX-2 inhibitor prescription following fracture surgery; 4)

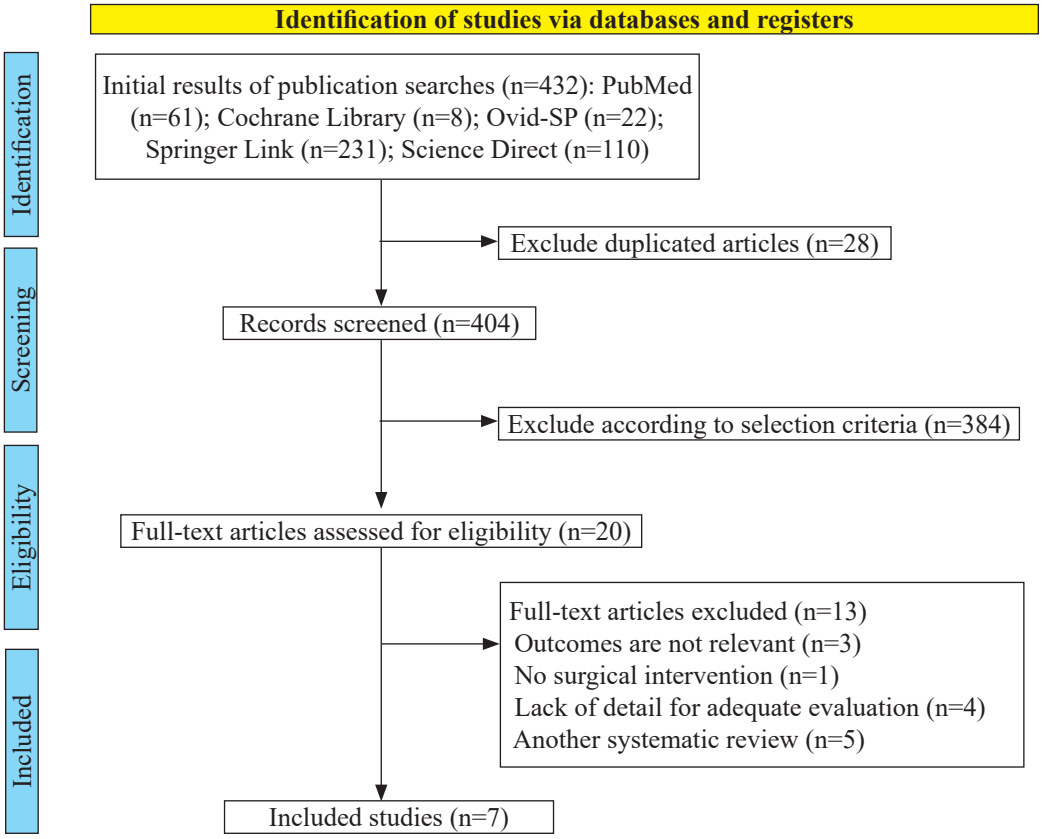

Figure 1. Prisma flow chart of the study selection process

Table 1. Search terms and Keywords

Key Words	Search terms
NSAIDs D32fwxOR	NSAIDs Nonsteroidal Anti-inflammatory Drugs
COX-2 inhibitor AND	COX-2 inhibitors Nonunion
Nonunion AND	Delay union Bone healing
Fracture Surgery	Fracture Surgery

Table 2. Study characteristics and results

Study	Study Design	No. of Subjects	Study Outcome	Type of Healing	NSAIDs Used, Dose, and Duration	Follow up Duration	Results
Kim et al. (2021)[11]	A Propensity score matching the Study (quasi-experimental method)	Total 8.693 (3.669 exposed to NSAIDs/ COX-2 inhibitor, 5.024 not exposed)	Non-union/delay union	Primary	Not specified, Standard dose, • ≤1 week • >1 and ≤3 weeks • >3 and ≤5 weeks • >5 and ≤7 weeks • >7 weeks	≥6 months after surgery	Although NSAIDs and COX-2 inhibitors have no immediate impact on healing long bone fractures, extended usage of >3 weeks may be associated with a higher nonunion or delayed union rate.

Table 2. Study characteristics and results

Study	Study Design	No. of Subjects	Study Outcome	Type of Healing	NSAIDs Used, Dose, and Duration	Follow up Duration	Results
Fader et al. (2018)[12]	Cohort retrospective study	190 exposed to NSAIDs	Healing time and fracture union on radiographic evaluation	Primary (Intramedullary nailing)	Not specified, Standard dose, Not specified	Not specified	NSAIDs might be safe and efficacious in managing fracture healing acute phase without significantly increasing the delayed union or nonunion risk.
George et al. (2020)[13]	Cohort retrospective study	22.590 exposed to non-selective NSAIDs 2.411 exposed COX-2-inhibitor	Nonunion	Not specified	Not specified, Standard dose, 30 days	91 to 365 days after fracture	Following a fracture, the nonunion risk was not increased by taking a single non-selective NSAID. Contrarily, COX-2 inhibitor was associated with a higher nonunion risk.
Hassan et al. (2019)[14]	Cohort prospective study	232 exposed to NSAIDs	Nonunion	Primary (screw, plates and screw, twiss of screws, K-wire, staples)	Acetaminophen 325–500 mg, (every 6 h) Ibuprofen 200–800 mg, (every 6 h), hydrocortisone-acetaminophen 5/325 mg, (every 6 h) Ketorolac 10 mg, (every 4–6 h), given for 14 days	12 weeks post-surgery	NSAID use and osseous nonunion did not significantly correlate ($p<0.05$). Fracture nonunion was not linked to short-term oral ketorolac and ibuprofen use after surgery.
Hunter et al. (2019)[15]	Cohort retrospective study	Total 506 (152 exposed to ASA and 354 did not)	Union or delay union	Primary (plate and screw)	Aspirin (325mg) per day for 6-8 weeks	Every 6,12, and 24 weeks after surgery	The use of ASA after surgery did not cause post-operative ankle fractures to take longer to heal, as observed in radiography, or affected the occurrence of post-operative DVT.

Table 2. Study characteristics and results

Study	Study Design	No. of Subjects	Study Outcome	Type of Healing	NSAIDs Used, Dose, and Duration	Follow up Duration	Results
McDonald et al. (2018)[6]	Cohort retrospective study	281 exposed to ketorolac	Fracture healing	Primary (ORIF)	Ketorolac 10 mg every 6 hours. Duration Not specified	Every 2, 6,12 weeks, three months, and six months after surgery	By 12 weeks, fracture union was associated with post-operative ketorolac prescription. There was no discernible change in the fracture patterns, healing, or problems. (P = .500).
Barnds et al. (2021)[16]	Cohort retrospective study	1.409 exposed to NSAIDs	Non-union/ delayed union	Primary and Secondary	Not specified. The standard dose for 60 days	60 days after surgery	In participants taking NSAIDs within 60 days of the initial diagnosis, the rate of 5th MT fracture nonunion/delayed union was considerably greater.

patients who continued or discontinued NSAID/COX-2 inhibitor use postoperatively for a specified duration; 5) study outcomes included fracture union or nonunion. Studies were screened in several steps. Initially, titles and abstracts were screened. Following this, studies underwent full-text screening. Finally, seven studies were included for narrative review. Study characteristics and results are summarized in Table 2.

Association between NSAIDs/COX-2 inhibitors and Fracture Nonunion

Numerous animal studies have demonstrated impaired or slowed fracture healing after NSAID/COX-2 inhibitor treatment.[1] An early study by Rø et al. on indomethacin use in rats with femur fractures showed a deleterious effect with significant pseudoarthrosis formation at 24 days.[17] Similarly, Pahlavanhosseini et al. reported that indomethacin delayed femur fracture healing in rats in a dose-related manner.[18] Additionally, White et al. showed a transient association between the selective COX-2 inhibitor valdecoxib and delayed fracture healing in rats.[1] While animal studies have demonstrated similar results, human studies have shown conflicting results.[11,13,19–21]

Kim et al. conducted a study involving 8,693 subjects who underwent surgery after a fracture from 1998 to 2018. Patients who received NSAIDs postoperatively were matched to patients who did not. The study demonstrated a statistically significant lower nonunion hazard than the matched patients who did not receive NSAIDs (p = 0.040) (hazard ratio: 0.69; 95% CI: 0.48 to 0.98). However, there were no significant differences for other outcomes. The study showed that NSAIDs and COX-2 inhibitors did not affect the healing of long bone fractures. However, long-term use may be linked to an increased likelihood of nonunion or delayed union (p = 0.001).[11] In line with these findings, Barnds et al. found a statistically significantly greater nonunion/delayed union of fifth metatarsal fractures in patients receiving NSAIDs within 60 days of the initial diagnosis.[16]

Fader et al. showed that NSAIDs are safe

in the acute phase of fracture healing. The fracture healing time in subjects who received NSAIDs was about 180.5 days (6 months). However, this study did not clarify the dose and duration of NSAIDs.[12] Similarly, George et al. showed that nonunion was not increased by administering non-selective NSAIDs after fracture. Conversely, there was a higher probability of nonunion when COX-2 inhibitor prescriptions were filled.[13]

Hassan et al. also showed a negligible correlation between NSAIDs and osseous nonunion ($p < 0.05$). However, 51 (21.98%) of the study participants were smokers, and the majority of the nonunion cases were among them. Excluding smokers from the study would reduce the sample size (232 subjects) and might not accurately reflect the entire population who underwent elective surgery. Further studies should control for such confounding factors.[14]

Hunter et al. conducted a large population study examining the impact of aspirin (ASA) as deep vein thrombosis (DVT) prophylaxis on ankle fracture healing time. The radiographic findings of healing at six weeks in the ASA and non-ASA groups were 95.9% (94/98) and 98.6% (207/210), respectively ($p = 0.2134$). There was no statistically significant difference in time to union between the groups. This implies that using ASA for DVT prevention in ankle fractures is safe. Aspirin is a widely accessible, easy-to-use, and affordable analgesic. This drug is becoming increasingly popular in postoperative orthopedic care.[15] In conclusion, there is a strong correlation between fracture nonunion and long-term postoperative use of NSAIDs and COX-2 inhibitors. Short-term use is considered relatively safe from the risk of fracture nonunion.

The consideration doses and duration of NSAIDs/COX-2 inhibitors

A Kaplan-Meier survival analysis conducted by Kim et al. evaluated treatment duration and how NSAIDs affect bone union. Lower nonunion/delayed union rates were seen for treatments lasting less than 3 weeks, and greater rates were seen for treatments lasting more than 3 weeks ($p = 0.001$). This highlighted the safety of NSAIDs/COX-2 inhibitors with <3 weeks of use. However, prolonged use of more than 3 weeks may be linked to an increased risk of nonunion or delayed union.[11]

According to George et al., NSAID effects on bone healing may be transient, quickly reversible, and dose- and duration-dependent. This study prescribed standard NSAID doses with a short duration (30 days after surgery); hence, they could not rule out the potentially harmful effects of high NSAID doses with prolonged use. Patients who received non-selective NSAIDs/COX-2 inhibitors for 60 days following fracture had a significantly higher nonunion rate. Reverse causation may be the best explanation: patients are more likely to continue using analgesics after the first month if they have serious injuries, ongoing pain after a fracture, or poor healing.[13]

A retrospective clinical investigation of 377 patients from England who received any NSAIDs after their injury showed a delay in fracture union and a greater incidence of fracture nonunion. The average time spent taking NSAIDs was 21.2 weeks (long-term use).[1] Similarly, Tucker et al. conducted a large study from a private insurance database and showed that postoperative NSAID use for 90 days increased the nonunion rate in tibial shaft, subtrochanteric femur, and humeral shaft fractures treated operatively.[20] In contrast, a study on posterior spinal fusion showed that 48 hours of postoperative ketorolac administration had no adverse effect on fusion rates.[21]

Further analysis by Hassan et al. showed no association between NSAIDs and fracture nonunion as of 14 days after the last NSAID use ($p < 0.05$). In this prospective cohort study, acetaminophen 325–500 mg (every 6 h), ibuprofen 200–800 mg (every 6 h), hydrocortisone-acetaminophen 5/325 mg (every 6 h), and ketorolac 10 mg (every 4–6 h) were given, beginning on the day of surgery for 14 days. Ibuprofen and oral ketorolac use after surgery for this period were not linked

to nonunion.[14] In another study, postoperative ketorolac use was linked to a high percentage of fracture healing after 12 weeks. There was no discernible relationship between fracture patterns and the healing process (P = 0.500). Aspirin (325 mg) use daily for 6 to 8 weeks after open reduction and internal fixation (ORIF) of ankle fractures does not delay radiographic union.[15]

CONCLUSION

For patients with a high risk of delayed fracture healing, limit the use of NSAIDs to 14 days or less and evaluate the risk/benefit ratio. Prolonged use of NSAIDs has been demonstrated to interfere with bone healing. Nevertheless, short-duration (less than 2 weeks of treatment) and low-dose use of NSAIDs (defined as indomethacin 150 mg/day, diclofenac 125 mg/day, aspirin 325 mg/day, or ketorolac 120 mg/day) are considered safe and efficacious in fracture postoperative pain management.

Several factors, including doses, exposure time, and treatment duration of NSAIDs/COX-2 inhibitors in humans, have yet to be studied and need further study. The majority of orthopedic surgeons practice caution in educating patients about the theoretical risks of NSAIDs. However, the abovementioned situations make changing the use of NSAIDs/COX-2 inhibitors in clinical practice challenging. A review of updated clinical research and randomized controlled trials has provided available evidence of the safety, doses, and duration of NSAIDs used clinically to reduce the risk of nonunion.

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