

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. It diminishes the quality of life and increases the risk of mortality. Several circumstances, including smoking, metabolic disorders, dietary inadequacy, and nonsteroidal anti-inflammatory drugs (NSAIDs), may predict the development of nonunion. In order to treat postoperative pain, NSAIDs are frequently used, including orthopedic conditions, particularly in the pain management of fracture. Using NSAIDs/cyclooxygenase (COX)-2 inhibitors has been controversial for many years. Many orthopedic surgeons avoid using them in fracture surgery due to the potential harmful effect on osteogenesis and subsequent nonunion risk.

Literature Review: We conducted an updated review of the literature using digital databases such as PubMed, Cochrane, Ovid-SP, Springer Link, and Science Direct, including “NSAIDs” OR “COX-2 Inhibitor” AND “nonunion” AND “fracture surgery”. In total 7 publications that met our inclusion criteria were summarized. This literature review revealed that some studies have proved that NSAIDs/COX-2 inhibitors are capable of inhibiting the fracture union temporarily; however, other studies have shown the safety of NSAIDs following fracture fixation without remarkable interference on bone healing. The association of COX-2 inhibitors or non-selective NSAIDs with nonunion remains unclear.

Conclusion: Prolonged use of NSAIDs interferes with the response to a successful bone healing. Short-duration (< 2 weeks of treatment) and low-dose use of NSAIDs are considered safe and efficacious for fracture postoperative pain.

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

INTRODUCTION

Nonunion, the failure of fracture healing process, contributes to 2% to 10% of fracture complications.^{1,2} Nonunion is a common fracture complication that decreases the quality of life and increases the risk of mortality. The cost of nonunion fracture treatment is greater than of union fracture. Prolonged disability and working absence further increase the financial burden.³ Physicians should aware of the protective and risk factors as well as controllable, uncontrollable factors of nonunion and thereby manage to prevent nonunion. Several uncontrollable factors include gender, age, underlying diseases, the type of injury, fracture pattern, location, displacement, and severity while the controllable factors include smoking, metabolic

disease, nutritional deficiency, and nonsteroidal anti-inflammatory drugs (NSAIDs) use.^{2,4,5}

It has been a particular interest of how the medication affects the nonunion. NSAIDs are common medication prescribed for postoperative pain, including orthopedic conditions, particularly in treating postoperative fracture pain.³ NSAIDs have significantly reduced the needs for opioid 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 a vital aspect of healthcare, and physicians should be mindful of the drugs' possible harmful adverse effects.⁷ Using NSAIDs/cyclooxygenase (COX)-2 inhibitors 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

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

Both COX-1 and COX-2 are inhibited by non-selective NSAIDs. The 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, the cell membranes release the arachidonic acid. Cyclooxygenase-2 breaks down arachidonic acid into thromboxane A₂ and prostaglandins when activated by inflammatory mediators and cytokines. Prostaglandins can cause inflammation and discomfort when they are released at damage sites. The blockage of the COX-2 enzyme leads to COX-2 inhibitors and NSAIDs anti-inflammatory effect.^{8,9}

There are three phases of bone healing mechanisms; inflammatory, reparative, and remodeling phases.^{1,8} In the inflammatory phase, prostaglandin production is stimulated by inflammatory mediators and cytokines. Osteoblasts act to 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, the inflammatory stage of bone healing is inhibited by NSAIDs and specific COX-2. Several studies have shown the vital role of COX-2 in the bone healing early stages. Inhibiting bone repair during the inflammatory stage has been shown to have negative effects in 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 human exhibited the absence of effect on fracture healing, while others exhibited otherwise.¹ However, distinct studies have shown the safety of NSAIDs after fracture fixation with no remarkable effects on bone-healing.¹⁰ In clinical practice, the pain caused by patients' fractures led to their resorting to NSAIDs/COX-2 inhibitors.² Therefore, there is still controversy about using NSAIDs after fracture surgery to consider 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 safety doses and duration in NSAIDs/COX-2 inhibitors administration that can be used in clinical practice.

LITERATURE REVIEW

Medical databases were searched, including PubMed, Cochrane, Ovid-SP, Springer Link, and ScienceDirect. The studies were included for further screening if they were released from January 2012 to June 2022, in English. The first search resulted in 432 literatures. Table 1 contains a list of the search terms and keywords.



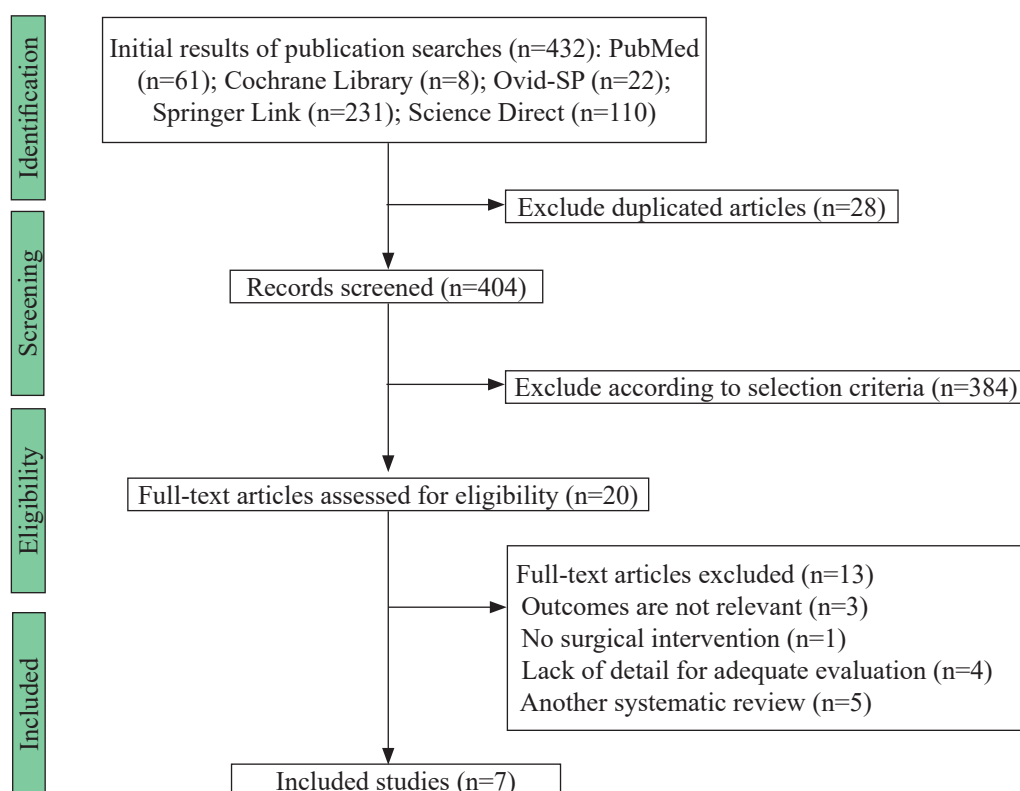


Figure 1. PRISMA flow chart of the study selection process

Table 1. Search terms and Keywords

Keywords	Search terms
NSAIDs	NSAIDs
D32fwxOR	Nonsteroidal Anti-inflammatory Drugs
COX-2 inhibitor	COX-2 inhibitors
AND	Nonunion
Nonunion	Delayed union
AND	Bone healing
Fracture surgery	Fracture surgery

The inclusion criteria were: 1) Human clinical trial study; 2) Involved patients aged ≥ 18 years with fractures that had undergone surgical treatment; 3) NSAIDs/COX-2 inhibitors prescription following surgery of fracture; 4) Patients who do or do not stop or the use of NSAIDs/COX-2 inhibitors postoperative care in a certain duration; 5) Study outcomes include fracture union or nonunion. The studies were screened in several steps. Initially, the title and the abstract were screened. Afterwards, the studies were then subjected to full text screening. Finally, seven studies were included for narrative review. The evidence for each study characteris-

tic and results are summarized below (Table 2).

Association between NSAIDs/COX-2 inhibitors and nonunion fracture

Numerous animal studies have demonstrated impaired or slowed fracture healing after NSAID/COX-2 inhibitor treatment.^{1,11,12} An early study conducted by Rø et al. on indomethacin use in rats with femur fracture showed a deleterious effect with significant formation of pseudoarthrosis at 24 days.¹² Similarly, indomethacin was reported to delay the femur fracture healing of rats in a dose-related manner in the study con-



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) ¹³	A propensity score matching study (quasi-experimental method)	Total 8.693 (3.669 exposed to NSAIDs/ COX-2 inhibitor, 5.024 not exposed)	Non-union/delayed 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.
Fader et al. (2018) ¹⁴	Cohort retrospective study	190 exposed to NSAIDs	Healing time and fracture union on radiographic evaluation	Primary (Intra-medullary 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) ¹⁵	Cohort retrospective study	22.590 exposed to non-selective NSAIDs 2.411 exposed COX-2-inhibitor	Non-union	Not specified	Not specified, Standard dose, 30 days	91 to 365 days after fracture	Following a fracture, the non-union 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) ¹⁶	Cohort prospective study	232 exposed to NSAIDs	Non-union	Primary (screw, plates and screw, twists 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 ($p<0.05$). Nonunion fracture was not linked to short-term oral ketorolac and ibuprofen use after 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
Hunter et al. (2019) ¹⁷	Cohort retrospective study	Total 506 (152 exposed to ASA and 354 did not)	Union or delayed union	Primary (plate and screw)	Aspirin (325mg) per day for 6-8 weeks	Every 6,12, and 24 weeks after surgery	Use of ASA after surgery did not cause post-operative ankle fractures to take longer to heal, as observed in radiography, or affect the occurrence of post-operative DVT.
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) ¹⁸	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 nonunion/delayed union fracture was considerably greater.

ducted by Hamid et al.¹¹ Additionally, Gerstenfeld et al.'s research showed a transient association between selective COX-2 inhibitor (valdecoxib) and fracture healing delay in rats.¹ While animal studies demonstrated similar results, human studies showed conflicting results.^{12,13,15,19,20}

A study involving 8.693 subjects who underwent surgery after a fracture from 1998 to 2018 was conducted by Kim et al. The patients who received NSAIDs postoperatively were matched to patients who did not. The study demonstrated a statistically significant lower nonunion hazard than the matched pa-

tients 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 had no effect on the healing of long-bone fractures. However, long-term use may be linked to an increased likelihood of nonunion or delayed union rates ($p = 0.001$).¹³ In line with the findings, subjects receiving NSAIDs within 60 days of the first diagnosis in patients, Bandon et al. found a statistically significant greater nonunion / delayed union of 5th MT fractures.¹⁸



In the acute phase of fracture healing, Fader et al. showed that NSAIDs are safe. The healing time of fracture in subjects who received NSAIDs is about 180.5 days (6 months). But this study did not clarify the dose and duration of NSAIDs.¹⁴ Similarly, George exhibited that nonunion was not increased by the administration of nonselective NSAIDs following fracture. Conversely, there was a higher probability of nonunion when COX-2 inhibitor prescriptions were filled.¹⁵

Hassan et al. also showed a negligible correlation between NSAID and osseous nonunion ($p < 0.05$). However, 51 (21.98%) of the study's participants were smokers, and the majority of the nonunion members were among them. Excluding the 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.¹⁶

A study involving large population conducted by Hunter et al. examined the impact of aspirin (ASA) as deep vein thrombosis (DVT) prevention on how quickly ankle fractures heal. The radiographic findings of healing at six weeks in ASA and non-ASA group were 95.9% (94/98) and 98.6% (207/210), respectively ($p = 0.2134$). There was no statistically significant difference in the time to union between the groups. This implies that using ASA for DVT prevention in ankle fractures is safe. Aspirin is a widely accessible, simple-to-use, and affordable painkiller. In postoperative orthopedic care, this drug is becoming more popular.¹⁷ In conclusion, there is a strong correlation between nonunion fracture and long-term postoperative use of NSAIDs and COX-2 inhibitors. The short-term use is considered relatively safe from risk of nonunion fracture.

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

A Kaplan-Meier survival analysis conducted by Kim et al. evaluated the duration of treatment

and how NSAIDs affect bone union. Lower and greater nonunion/delayed union rates were seen for treatments lasting less than three weeks and more than three weeks ($p = 0.001$), respectively. This highlighted the safety of NSAIDs/COX-2 inhibitors with <3 weeks use. However, prolonged use of more than three weeks may be linked to an increased risk of nonunion or delayed union.¹³

According to George et al., NSAID effects on bone healing may be transient, quickly reversible, and dose-duration-dependent. This study prescribed standard NSAID doses with a short duration (30 days after surgery), hence they cannot rule out the potential harmful effect of high dose of NSAID in prolonged use. The patients that received nonselective NSAIDs/COX-2 inhibitors for 60 days following fracture had significantly higher nonunion rate. The 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.¹⁴

A retrospective clinical investigation comprising 377 patients out of England who received any NSAIDs after their injury showed a delay in fracture union and a greater incidence of nonunion fracture. The average time spent taking NSAIDs was 21.2 weeks (long-term use).¹ In line with this, Tucker et al. conducted a large study from a private insurance database and showed that postoperative use of NSAIDs for 90 days increased the rate of nonunion in tibial shaft, subtrochanteric femur, and humeral shaft fractures treated operatively.¹⁹ In contrast, a study on posterior spinal fusion showed that 48 hours postoperative administration of ketorolac had no adverse effect on fusion rates.²⁰

Further analysis by Hassan et al. showed that as of 14 days after the last NSAID use, there was no connection between NSAID and nonunion fracture ($p < 0.05$). In this cohort prospective 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 used after surgery for a period of time were not linked to nonunion.¹⁶ In other study, use of postoperative ketorolac was linked to a high percentage of fracture healing after 12 weeks. There was no discernible relationship between fracture patterns and healing process ($P = 0.500$). Use of aspirin (325 mg) daily for six to eight weeks after ORIF of ankle fractures does not cause a delay in the radiographic union of the fractures.¹⁷

CONCLUSION

For patients with high risk of delayed fracture healing, limit the use of NSAIDs to 14 days or less and evaluate the risk/benefit ratio. NSAIDs' prolonged use has been demonstrated to interfere with bone healing. Nevertheless, short-duration (< 2 weeks of treatment) and low-dose use of NSAIDs (defined as indomethacin 150 mg/day, diclofenac 125 mg/day, aspirin 325mg/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 studies. The majority of orthopedic surgeons practice caution in patients' education on NSAID theoretical risks. However the abovementioned situations make the changes in NSAIDs/COX-2 inhibitors use in clinical practice challenging. A review of updated clinical research and randomized controlled trial has provided the available evidence of the safety, doses, or duration of NSAIDs used clinically to reduce the risk of nonunion.

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