Should Nonsteroidal Anti-Inflammatory Drugs Be Used to Provide Analgesia for Fractures?

Opposing authors provide succinct, authoritative discussions of controversial issues in emergency medicine. Authors are provided the opportunity to review and comment on opposing presentations. Each topic is accompanied by an Editor's Note that summarizes important concepts. Participation as at authoritative discussant is by invitation only, but suggestions for topics and potential authors can be submitted to the section editors.

Editor's Note: Nonsteroidal anti-inflammatory drugs provide excellent analgesia for orthopedic injuries, but their very mechanism of action, the reduction of inflammation, interferes with the normal injury response and may impair fracture healing. In this episode of Clinical Controversies, pro and con advocates discuss the risks and benefits of using nonsteroidal anti-inflammatory drug analgesics for orthopedic fractures.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS MAY BE CONSIDERED IN PATIENTS WITH ACUTE FRACTURES

Michael Gottlieb, MD
Department of Emergency Medicine
Rush University Medical Center
Chicago, IL

Stephen Alerhand, MD
Department of Emergency Medicine
Rutgers New Jersey Medical School
Newark, NJ

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Patients with acute fractures commonly present to the emergency department. Fractures are painful conditions, and it is important to obtain appropriate analgesia in this patient population. The ideal agent should adequately treat the pain, with minimal adverse events and no long-term addiction potential. Nonsteroidal anti-inflammatory drugs meet all of these criteria and should strongly be considered for acute pain management in appropriately selected patients during the early postreduction stage.

Traditionally, opioid medications have been commonly prescribed for pain management after an acute fracture.[1] Unfortunately, opioids are associated with significant adverse effects (eg, somnolence, delirium, respiratory depression, decreased ability to perform normal activities of daily living, and, most important, addiction and dependence), creating a need for other, better alternatives.[2] Several studies of both adult and pediatric patients have demonstrated that nonsteroidal anti-inflammatory drugs offer pain control similar to that of opioids for musculoskeletal injuries.[3-6] A study of pediatric patients with acute arm fractures found that ibuprofen had pain control equivalent to that of acetaminophen with codeine, with a significantly lower rate of adverse events, better functional outcomes, and higher patient and parent satisfaction.[3] Another study compared ibuprofen, oxycodone, hydrocodone, and codeine among adult patients with upper and lower extremity injuries and found no significant difference in pain reduction between all 4 medications.[4] An additional study comparing ibuprofen with oral morphine for uncomplicated extremity fractures also found no significant difference in analgesic efficacy, with nearly twice as many adverse events occurring in the opioid group.[5] A study of pediatric patients with isolated fractures found that ibuprofen actually provided superior pain control compared with opioids.[6]

Although some providers may avoid nonsteroidal anti-inflammatory drugs in fractures because of concern for delayed union or malunion, the actual evidence underlying this practice is fairly limited. Much of this concern is based on theoretic risks or observational data, which can be subject to a number of potential confounders.[7,8] For instance, many of the studies did not control for smoking, diabetes, mechanism of injury, or even fracture type, which are all known risk factors for malunion of fractures.[7,8] A randomized controlled trial directly comparing nonsteroidal anti-inflammatory drugs versus placebo among patients with a Colles' fracture found no difference in the rate of bone healing.[9] Moreover, many of the studies focused on the effect of long-term nonsteroidal anti-inflammatory drug use, rather than the short-term use more relevant for acute fractures.[7] Short courses of nonsteroidal anti-inflammatory drugs after an acute

fracture have been proposed to be less problematic because of the lower total exposure to prostaglandin suppression compared with long-term use.[7] In fact, a 2019 meta-analysis found that short-term nonsteroidal anti-inflammatory drug use was not associated with an increased risk of complications, prompting the authors to propose this as an alternate pain therapy for acute fractures.[7] The risk of nonunion does not increase significantly until after the initial 30 days, so nonsteroidal anti-inflammatory drug prescriptions should be limited to courses less than 30 days.[10]

Although there may be a risk of adverse events with long-term nonsteroidal anti-inflammatory drug use in select patient groups, the data do not currently suggest a risk with short-term use. Meanwhile, opioids carry a significant number of risks and a less favorable adverse effect profile. Although further studies would be beneficial, we believe that nonsteroidal anti-inflammatory drugs are a reasonable option for acute fractures in low-risk patients (eg, younger, no diabetes, nonsmoker, uncomplicated fracture) as pain medication with opioid-sparing properties.

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NON-STEROIDAL ANTI-INFLAMMATORY DRUG USE FOR MORE THAN 72 HOURS IN ADULT LONG-BONE FRACTURES: THE RISKS OUTWEIGH THE BENEFITS

Brit Long, MD
Michael D. April, MD, DPhil
Department of Emergency Medicine
San Antonio Uniformed Services Health Education Consortium
Fort Sam Houston, TX

Alex Koyfman, MD
The University of Texas Southwestern Medical Center
Department of Emergency Medicine
Dallas, TX

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Bone healing after a fracture is a complex process, including vascular development, prostaglandin production, and callus formation and remodeling. Many factors can affect bone healing, including older age, nutritional status, tobacco use, immunocompromise, and certain medications.[1] One medication class commonly used in the emergency department for analgesia includes nonsteroidal anti-inflammatory drugs. Although emergency physicians frequently prescribe these drugs to relieve pain and inflammation, previous evidence suggests a dose- and duration-related association with nonsteroidal anti-inflammatory drug use and delayed fracture healing.[1,2] Guidelines in regard to nonsteroidal anti-inflammatory drug use for analgesia do not currently exist, and practice patterns vary widely. According to the current literature, rather than using nonsteroidal anti-inflammatory drugs for greater than 72 hours, alternative medications should be considered for adults with long bone fractures including the tibia or humerus, fractures with nonunions, or spinal fractures requiring fusion.[1,2]

Fracture healing begins with release of cytokines and growth factors.[1,2] In the acute phase after fracture, prostaglandins affect bone production through triggering osteogenesis and increased bone mass.[1-4] Remodeling of the callus and bone formation compose final healing. The physiologic basis for nonsteroidal anti-inflammatory drug–mediated impairment of healing is inhibition of prostaglandin production through the cyclooxygenase-1 and -2 pathways.[1-4] Although nonsteroidal anti-inflammatory drugs can have analgesic and anti-inflammatory effects, reduced prostaglandin synthesis can potentially affect bone healing after a fracture.[3,4]

Multiple studies have demonstrated that nonsteroidal anti-inflammatory drugs reduce in vitro osteoblastic proliferation and osteogenesis.[3,4] These effects are time and dose dependent, suggesting increased complication risk with prolonged use. Specifically, although literature suggests ibuprofen is efficacious and comparable to the analgesic effect of morphine when used acutely,[5] adults with long bone fractures including the femur, humerus, tibia, and spine demonstrate more complications such as nonunion and need for reoperation with nonsteroidal anti-inflammatory drug use for greater than 72 hours.[6-10] A retrospective study including approximately 10,000 humeral shaft fractures found a 3.7-fold increased risk of nonunion for individuals who used nonsteroidal anti-inflammatory drugs within 90 days.[8] A study evaluating tibial fractures found increased time to bone union with nonsteroidal anti-inflammatory drugs used during several weeks.[9] In regard to spinal fusion, risk of incomplete union or nonunion was significantly higher among patients receiving ketorolac.[10] Further evidence suggesting that nonsteroidal anti-inflammatory drugs adversely affect long bone and spinal fracture healing is detailed in a 2019 meta-analysis.[11] This analysis of 19 studies including pediatric and adult patients found an odds ratio (OR) of 2.07 for delayed union or nonunion with nonsteroidal anti-inflammatory drug use, with adults demonstrating an OR of 2.93 and patients with long bone fractures demonstrating an OR of 2.34 and those with spinal fractures an OR of 4.90.[11] However, this meta-analysis was of poor quality because it combined randomized controlled trial data with cohort and case-control studies.[11] Another meta-analysis stated that the available data are conflicting and of insufficient quality, with high heterogeneity.[12]

Many of these studies were observational and retrospective, and thus could not control for confounding. Moreover, many of these studies comprised small sample sizes, were of low quality, evaluated postoperative nonsteroidal anti-inflammatory drug use, and included patients with factors that may affect bone healing, such as smoking, diabetes, and severe trauma.[1,11,12] To the extent that patients with these risk factors for poor bone healing were more likely to use nonsteroidal anti-inflammatory drugs, the relationship between such drug use and bone healing may be obscured. Nevertheless, in the absence of robust randomized controlled trials, the existing evidence suggests that although nonsteroidal anti-inflammatory drugs can improve analgesia and may not affect healing of smaller bones and minor, stable fractures if used for less than 72 hours, other patients with significant fractures involving long bones likely experience delayed healing and increased complications with nonsteroidal anti-inflammatory drug use of even minimal duration.[11] That said, although data are of relatively poor quality with multiple confounders, current meta-analyses suggest no effect with nonsteroidal anti-inflammatory drug use of short duration (less than 72 hours).[11,12] This finding may reflect less potent prostaglandin suppression in these patients.[11]

According to the available evidence, nonsteroidal anti-inflammatory drug use greater than 72 hours affects healing of tibial shaft fractures, humerus fractures, fracture nonunions, and spinal fractures requiring spinal fusion. Nonsteroidal anti-inflammatory drugs may also adversely affect fractures with comminution or those with severe instability. Consequently, emergency physicians should consider nonsteroidal anti-inflammatory drug use greater than 72 hours to be a risk factor for delaying fracture healing, comparable to the risk posed by poor nutritional status, immunocompromise, smoking, diabetes, or corticosteroid use.[1,2,11] Accordingly, further prospective, randomized studies are necessary to evaluate the effect of nonsteroidal anti-inflammatory drugs on bone healing among patients with these fractures, as well as those with other musculoskeletal injuries. In the interim, emergency physicians should consider alternative analgesic agents such as acetaminophen, regional nerve blocks, or lidocaine patches in adult patients with long bone fractures for prolonged therapy, although nonsteroidal anti-inflammatory drugs may be safe if used for less than 72 hours.

This review does not reflect the views or opinions of the US government, Department of Defense, US Army, US Air Force, Brooke Army Medical Center, or SAUSHEC EM Residency Program.

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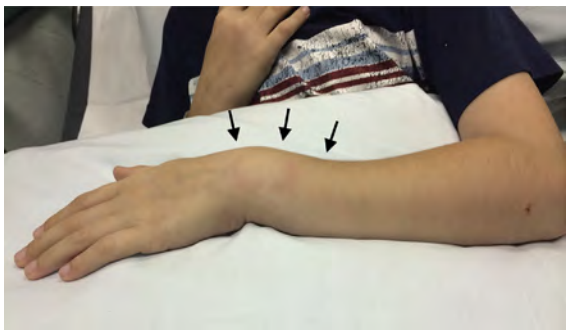

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