FPIN's Clinical Inquiries

NSAID Use and Effects on Bone Healing

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Clinical Question

Do nonsteroidal anti-inflammatory drugs (NSAIDs) prevent or delay fracture healing when used for pain management?

Evidence-Based Answer

The use of NSAIDs for more than three days at higher doses during the postoperative or acute phase of fracture healing may lead to increased rates of nonunion, delayed union, and pseudarthrosis in adults. (Strength of Recommendation [SOR]: B, based on multiple systematic reviews of randomized controlled trials [RCTs], cohort studies, and case-control trials.) NSAIDs do not appear to impair fracture healing in children younger than 11 years. (SOR: B, based on multiple systematic reviews of RCTs, cohort studies, and case-control trials.)

Evidence Summary

A 2019 meta-analysis (n = 14,887) of 16 studies that included RCTs, cohort studies, and case-control trials examined the adverse effects of NSAIDs on bone healing in the setting of fracture, osteotomy, or fusion surgery.[1] The primary outcomes were nonunion, delayed union, and pseudarthrosis with a minimum follow-up of six months. The pooled analysis included 15,242 bones, of which 3,283 were exposed to NSAIDs. In 512 patients with delayed union or nonunion fractures, 226 (6.9%) had been exposed to NSAIDs and 282 (2.4%) had not, showing an increased risk with NSAID use (odds ratio [OR] = 2.1; 95% CI, 1.2 to 3.6; number needed to harm [NNH] = 23). A subgroup analysis of retrospective cohort studies in children found that exposure to NSAIDs did not result in an increased risk of delayed union or nonunion (four trials; n = 2,017 bones; 13 of 37 cases of delayed healing exposed to NSAIDs; OR = 0.6; 95% CI, 0.3 to 1.2). A subgroup analysis of low-dosage or short-duration NSAID exposure (low dosage was defined as less than 125 mg per day of diclofenac, less than 150 mg per day of indomethacin, or less than 120 mg per day of ketorolac, whereas short duration was defined as less than two weeks of treatment) did not find an increased risk of delayed union or nonunion (four trials; n = 1,109; OR = 1.7; 95% CI, 0.6 to 4.5). This meta-analysis was limited by significant heterogeneity (I^2 = 77.3%) and significant bimodal age distribution of the included studies, with a large gap occurring at a mean age of 18 to 35 years.

A 2020 meta-analysis of 10 studies (eight retrospective cohort studies and two case-control trials; n = 14,556) examined whether the use of NSAIDs during the perioperative period is associated with an increased risk of bone healing complications across different bone types in trauma and elective spinal surgery settings.[2] The primary outcomes included delayed union, nonunion, and pseudarthrosis. Analysis of fair-quality observational studies of long bones in 1,900 adults exposed to NSAIDs found that 263 (13.8%) had poor bone healing outcomes compared with 405 (3.5%) of 11,529 who were not exposed to NSAIDs (OR = 2.9; 95% CI, 1.6 to 5.2; NNH = 10). Five moderate-quality observational studies of patients following spinal fusion surgery found an increased risk of poor bone healing after NSAID use. Bone healing complications occurred in 106 (15.0%) of 706

patients exposed to NSAIDs compared with only 19 (4.5%) of 421 patients with no NSAID exposure (OR = 5.2; 95% CI, 1.3 to 20.0; NNH = 10). Analysis of moderate-quality observational spinal studies revealed no significant risk of complications with NSAID use for a short duration (i.e., 48 to 72 hours) during the postoperative period (five trials; n = 706; OR = 1.9; 95% CI, 0.3 to 11.7). In contrast, NSAIDs administered for longer durations (i.e., more than 72 hours) by oral or parenteral routes demonstrated a statistically significant association with poor bone healing outcomes (three trials; n = 634; OR = 11.2; 95% CI, 2.3 to 53.0). An analysis of three retrospective cohort studies on children did not find an increased risk of bone healing complications with NSAID use (OR = 0.75; 95% CI, 0.4 to 1.4; $P = .36$). A meta-regression revealed that poor bone healing outcomes with NSAID therapy were associated with smoking status ($P < .00001$, data not provided), with a higher risk of complications in patients who smoked (OR = 2.6; 95% CI, 2.2 to 3.1). Increased age and diabetes mellitus did not affect the risk of bone healing complications after NSAID exposure. This meta-analysis was limited by statistically significant heterogeneity among the studies from each clinical group (i.e., long bone [$I^2 = 83\%$] and spine [$I^2 = 78\%$]), which the authors accounted for by using a random effects model and analyzing bone healing outcomes as a function of confounding factors.

A 2021 systematic review of eight studies (six retrospective cohort studies and two prospective RCTs) evaluated NSAID use and its effects on bone healing in children.[3] Data were not pooled because of study heterogeneity. Two studies investigated the short-term use of ketorolac postoperatively in children undergoing spinal fusion surgery for scoliosis and found no increased risk of pseudarthrosis with ketorolac administered, on average, for two days postsurgery. Another retrospective cohort study of 221 children with bone fractures requiring surgical repair (e.g., supracondylar humerus, lateral condyle, forearm, femur, tibia, ankle) did not identify any complications related to postoperative ketorolac or ibuprofen use. A retrospective cohort study of 237,033 fractures in children exposed to NSAIDs showed a low nonunion rate until 11 years of age, after which the risk of nonunion increased by 5% for every fracture location analyzed (tibia, fibula, femoral neck, scaphoid); the study did not specify which NSAIDs were used. A retrospective study of 808 children with fractures (e.g., tibia, femur, humerus, scaphoid, fifth metatarsal) did not find an association between ibuprofen use and bone healing complications in populations at high risk of fracture. An RCT evaluated weight-based acetaminophen (control group) vs. weight-based ibuprofen (intervention group) for 97 children with long bone fractures. There was no significant difference in fracture healing between the groups at six weeks, 10 to 12 weeks, or six months of follow-up. An RCT evaluated the use of ibuprofen vs. acetaminophen with codeine in 336 children with an upper extremity fracture and found that ibuprofen was associated with fewer cases of refracture, with no reports of nonunion. Overall, the authors of the systematic review concluded that NSAIDs provided adequate pain control without increasing the risk of nonunion in patients who were skeletally immature, particularly in long bone fractures and pseudarthrosis after spinal fusion. This review was limited by heterogeneity and the number of studies available.

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