

Do NSAIDs Increase the Risk of Non-Union? Results of the PAIN Study, A Three-Arm, Multicenter, Double Blind, Randomized Control Trial

METRC; Renan C. Castillo, MD

Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, UNITED STATES

Purpose: Despite increased awareness of the negative short and long-term consequences of poorly controlled pain, analgesic therapy among patients treated surgically for orthopaedic trauma remains inconsistent and often inadequate. In an effort to avoid the negative effects of opioids, pain medications such as nonsteroidal anti-inflammatory drugs (NSAIDs) and gabapentinoids may provide improved perioperative pain control. However, the effects of these medicines on orthopaedic outcomes such as nonunion have not been adequately studied. We hypothesized that a multimodal pain regimen would decrease postoperative pain without increasing nonunions.

Methods: This study was a 3-arm, double blinded, randomized, placebo-controlled multicenter phase III clinical trial to investigate the safety and efficacy of multimodal pain management among orthopaedic trauma patients. The study population includes patients aged 18 to 80 years with fractures known to have both postoperative pain issues as well as a reasonable chance of nonunion. These fractures included: proximal or distal humerus, supracondylar femur, femoral shaft, tibia plateau, tibia shaft, open ankle (with associated dislocation), tibia plafond, calcaneus, talus, or midfoot, which either occur in isolation or are treated surgically as a whole. Participants were block randomized (within centers) in a 1:1:1 ratio to either standard of care pain management plus placebo, NSAID, or pregabalin during the pre- and postoperative care around definitive fixation surgery. The study outcomes included surgery for nonunion, defined as unplanned nonprophylactic surgery for nonunion performed between 6 months and 1 year after injury, opioid utilization during the 48 hours after definitive fixation or discharge, and postinjury pain intensity, as measured by the Brief Pain Inventory (BPI) at 3 months. The modified intention-to-treat effect will be estimated, and the noninferiority on the nonunion outcome will be analyzed using survival analysis techniques.

Results: In this study, 435 patients were enrolled at 17 centers over 3 years (mean age, 40.6 years; 70% male) with 86% follow-up for nonunion at 1 year, 99.5% follow-up for 48-hour opioid utilization, and 82.5% follow-up for 3-month BPI. The final analysis of this study's main outcomes will be presented at the 2022 OTA Annual Meeting.

Conclusion: The results of this study will provide the much-needed evidence base that will inform pain management guidelines and impact care of orthopaedic trauma patients.