The Journal of Emergency Medicine, Vol. 52, No. 4, pp. 426–432, 2017

0736-4679/$ - see front matter

http://dx.doi.org/10.1016/j.jemermed.2016.09.027

Original Contributions

DOES THE USE OF IBUPROFEN IN CHILDREN WITH EXTREMITY FRACTURES INCREASE THEIR RISK FOR BONE HEALING COMPLICATIONS?

Kerrin C. DePeter, MD,* Stephen M. Blumberg, MD,* Sarah Dienstag Becker,† and James A. Meltzer, MD*

*Department of Pediatrics, Division of Emergency Medicine, Jacobi Medical Center, Bronx, New York and †Albert Einstein College of Medicine, Bronx, New York

Reprint Address: James A. Meltzer, MD, Jacobi Medical Center, 1400 Pelham Parkway South, 1B25, Building 6, Bronx, NY 10461

□ **Abstract—Background: Despite being an effective analgesic for children with fractures, some clinicians may avoid prescribing ibuprofen due to its potentially harmful effect on bone healing. Objective: To determine if exposure to ibuprofen is associated with an increased risk of bone healing complications in children with fractures. Methods: We performed a retrospective study of children aged 6 months to 17 years who presented to the pediatric emergency department (PED) with a fracture of the tibia, femur, humerus, scaphoid, or fifth metatarsus and who followed up with the orthopedic service. We chose these fractures due to their higher risk for complications. We classified patients as exposed if they received ibuprofen in the PED or during hospitalization or were prescribed ibuprofen at discharge. The main outcome was a bone healing complication as evidenced by nonunion, delayed union, or re-displacement on follow-up radiographs. Results: Of the 808 patients included in the final analysis, 338 (42%) were exposed to ibuprofen. Overall, 27 (3%) patients had a bone healing complication; 8 (1%) developed nonunion, 3 (0.4%) developed delayed union, and 16 (2%) developed re-displacement. Ten (3%) patients who were exposed to ibuprofen, and 17 (4%) who were not, developed a bone healing complication (odds ratio 0.8, 95% confidence interval 0.4–1.8; $p = 0.61$). There was no significant association between ibuprofen exposure and the development of a bone healing complication despite adjustment for potential confounders. Conclusion: Children with extremity fractures who are exposed to ibuprofen do not seem to be at increased risk for clinically important bone healing complications.**

□ **Keywords—ibuprofen; nonunion; delayed union; re-displacement; NSAID; fracture**

INTRODUCTION

Extremity fractures are common in children and often require analgesia both in the emergency department (ED) and as an outpatient. Although there can be considerable variation in the management of pain associated with fractures, most pediatricians and pediatric subspecialists report prescribing nonsteroidal anti-inflammatory drugs (NSAIDs) for children with musculoskeletal pain (1). NSAIDs have been shown to be as effective for children with acute fracture pain, and to provide better functional outcomes, when compared with opioids (2,3). Moreover, opioids are often associated with undesirable side effects, particularly in children, such as sedation, respiratory depression, nausea, vomiting, and constipation (2–4). Some clinicians, however, may avoid prescribing NSAIDs for fracture pain due to their potentially adverse effect on bone healing (5–9).

The current literature on the effect of NSAID exposure on fracture healing is inconsistent and remains

This study was presented in poster form at the 2015 Pediatric Academic Society's Annual Meeting, April 25–28, 2015, San Diego, California.

RECEIVED: 25 June 2016; FINAL SUBMISSION RECEIVED: 13 September 2016;
ACCEPTED: 15 September 2016

controversial. Several animal models suggest that NSAIDs adversely affect bone healing and report that the timing, duration, and dosing of NSAIDs are important predictors of fracture healing complications (7,10). Conversely, a study investigating a juvenile animal model reported no inhibitory effects on fracture healing from NSAIDs (11). In addition, studies on adult patients have yielded inconsistent results, showing both harmful effects and no effect on fracture healing with both the short-term and long-term use of NSAIDs (5,6,9,12,13).

The literature on NSAID use and fracture healing in the pediatric population is limited, primarily focusing on the effects of parenteral ketorolac in the inpatient setting (14,15). The purpose of this study is to determine if exposure to ibuprofen, the most commonly prescribed outpatient NSAID, is associated with an increased risk of a bone healing complication (16).

MATERIALS AND METHODS

Study Design and Setting

We performed a retrospective cohort study of children between the ages of 6 months and 17 years who experienced a fracture of the tibia, femur, humerus, scaphoid, or fifth metatarsus and who presented to an urban pediatric emergency department (PED) for their initial care between January 2003 and October 2014. We chose these particular bones because they have been noted in the literature to be at higher risk for bone healing complications (5,17–27). This study was granted exemption by the institutional review board of the Albert Einstein College of Medicine.

Measurements

We used International Classification of Diseases, 9th Revision codes to identify eligible patients and reviewed pediatric attending radiologist reports to confirm eligibility. One fracture was included and analyzed per patient. For patients with more than one eligible fracture, we analyzed only the largest of the fractured bones. We excluded patients from the study if they did not follow up with our orthopedic service, if they had a medical history placing them at increased risk for a bone healing complication (e.g., a history of osteogenesis imperfecta, osteomyelitis, neoplasm, diabetes, nutritional deficiencies requiring replacement therapy, or were exposed to corticosteroids or chemotherapy in the 3 months prior to sustaining the fracture), if they had an open or pathologic fracture, or if they had a prior fracture at the same site. We classified patients as being exposed to ibuprofen if they received ibuprofen in the PED or during their hospital admission, or received a prescription for ibuprofen at discharge.

Outcome Measures

The primary outcome was the presence of a bone healing complication as evidenced by nonunion, delayed union, or re-displacement on follow-up radiographs, as determined by an attending pediatric radiologist.

Statistical Analysis

We used STATA 14.0 (StataCorp, College Station, TX) for all statistical analyses. For categorical variables, we described data using frequencies and percentages, and compared groups using a chi-squared test or Fisher's exact test. For the continuous nonnormally distributed variable "age," we described data using a median and interquartile range (IQR), and compared groups using a Mann-Whitney test. We assessed normality using histograms. We used multivariable logistic regression to adjust for the following potential confounders: gender, age, race, year of ED visit, fracture reduction in the ED, initial hospitalization, initial surgery, and fracture type. We assessed and confirmed the assumption of linearity in the logit for the covariate "age" using a lowess curve and fractional polynomials. We assessed for clinically plausible effect modification of the association of ibuprofen exposure and fracture complication using a p value < 0.10 for the following variables: age, reduction, hospitalization, initial surgery, and fracture type. We considered a p value < 0.05 statistically significant for all analyses.

RESULTS

Overall, 1192 records of children with fractures at risk for bone healing complications were reviewed. Of these, 298 did not follow up with our orthopedic service after being seen in the PED, 28 had their initial care at an outside hospital, 24 had a medical history that put them at risk for fracture complications, 14 had an open fracture, 10 had a pathologic fracture, and 10 had a prior fracture at the same site.

In total, 808 patients (68%) were included in the final analysis. Of these, 508 (63%) were male, and the median patient age was 7 years (IQR 4, 12). Patient characteristics are demonstrated in Table 1 and are compared by ibuprofen exposure and fracture complication status. Eight (0.9%) of the patients had two eligible fractures, one of which had two fractures of the same bone. The distribution of fractured bones in the sample is shown in Table 2. Overall, 338 (42%) patients were exposed to ibuprofen. Twenty-seven (3%) patients had a bone healing complication; 8 (1%) developed nonunion, 3 (0.4%) developed delayed union, and 16 (2%) developed re-displacement (Table 3).