The Journal of Emergency Medicine, Vol. ■, No. ■, pp. 1–7, 2016

0736-4679/$ - see front matter

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

Original Contribution

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

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□ **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).

Table 1. Demographic and Clinical Characteristics of 808 Children with Extremity Fractures by Ibuprofen Exposure and Fracture Complication Outcome*

Variable	Exposed to Ibuprofen n = 338	Not Exposed to Ibuprofen n = 470	*p*-Value	Fracture Complication n = 27	No Fracture Complication n = 781	*p*-Value
Male	205 (61)	303 (65)	0.27	19 (70)	489 (63)	0.41
Age, years, median (IQR)	7 (3,13)	7 (4,12)	0.87	13 (8,16)	7 (4,12)	<0.001
Race			0.31			0.97
Black	107 (32)	132 (28)		8 (30)	231 (30)	
Latino	180 (53)	250 (53)		14 (52)	416 (53)	
White/Asian/Other	51 (15)	88 (19)		5 (19)	134 (17)	
Years			<0.001			0.31
2003–2005	36 (11)	87 (19)		3 (11)	120 (15)	
2006–2008	48 (14)	110 (23)		2 (7)	156 (20)	
2009–2011	90 (27)	183 (39)		12 (44)	261 (33)	
2012–2014	164 (49)	90 (19)		10 (37)	244 (31)	
Reduction in ED	140 (41)	167 (36)	0.09	14 (52)	293 (38)	0.13
Initial hospitalization	96 (28)	129 (28)	0.79	8 (30)	217 (28)	0.84
Initial surgery	67 (20)	86 (18)	0.61	2 (7)	151 (19)	0.12

IQR = interquartile range; ED = emergency department.
* Data are presented as frequency (percentage) unless otherwise indicated.

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; $p = 0.61$). Substantial effect modification was absent for all of the clinically plausible covariates examined. There was no statistically significant association between ibuprofen exposure and the development of a bone healing complication despite adjustment for potential confounders (Table 4).

We performed a post hoc power analysis of our data and found that, assuming a two-sided alpha of 0.05, this sample had 82% power to detect a clinically meaningful absolute increase of 5% in the probability of developing a bone healing complication over the baseline probability in the nonexposed.

DISCUSSION

Ibuprofen has been shown to be effective in treating children with acute fracture pain and to have fewer side effects when compared with other analgesics (2,3). Although other studies have proposed that NSAIDs may be detrimental to bone healing, we found no evidence to suggest that the use of ibuprofen for extremity fractures is unsafe for children. In our cohort collected from over a decade, children exposed to ibuprofen were not at any greater risk of a bone healing complication than children exposed to other pain medications.

This study specifically evaluated the effect of ibuprofen on bone healing in children with extremity fractures that were at a higher risk for complications. Although not the primary objective, Drendel et al., in a secondary analysis of their randomized control trial comparing the efficacy of two analgesics for fracture pain, also failed to find an association between nonunion or re-fracture and ibuprofen use (2). These results, however, were extracted from a sample of children with forearm fractures who did not require reduction, and thus, were at a lower risk for developing a bone healing complication. We chose to analyze several extremity fractures that have been cited in the literature to be at a higher risk for fracture healing complications (5,17–27). We hypothesized that these fractures would be more

Table 2. Distribution of Fractures in Sample by Ibuprofen Exposure and Fracture Complication Outcome*

Fracture Type	Exposed to Ibuprofen n = 338	Not Exposed to Ibuprofen n = 470	*p*-Value	Fracture Complication n = 27	No Fracture Complication n = 781	*p*-Value
Tibia	112 (33)	124 (26)	0.04	6 (22)	230 (29)	0.42
Femur	27 (8)	42 (9)	0.63	2 (7)	67 (9)	0.99
Humerus	160 (47)	242 (52)	0.24	12 (44)	390 (50)	0.58
Scaphoid	14 (4)	13 (3)	0.28	4 (15)	23 (3)	0.01
5th Metatarsus	25 (7)	49 (10)	0.14	3 (11)	71 (9)	0.73

* Data are presented as frequency (percentage).

Table 3. Clinical Characteristics of 27 Children Who Developed Fracture Complications

Location of Fracture	Gender	Age, Years	Race	Ibuprofen Exposure	Reduction in ED	Fracture Complication
Tibia	Female	17	Latino	No	Yes	Re-displacement
	Male	15	Latino	Yes	Yes	Re-displacement
	Male	14	Latino	No	Yes	Re-displacement
	Female	15	Black	No	Yes	Nonunion
	Male	8	Latino	No	Yes	Re-displacement
	Male	15	Latino	No	No	Delayed Union
Femur	Male	9	Latino	No	Yes	Re-displacement
	Female	4	Latino	No	Yes	Re-displacement
Humerus	Male	6	Latino	Yes	Yes	Re-displacement
	Female	4	Asian	No	No	Re-displacement
	Female	3	Latino	No	Yes	Re-displacement
	Male	10	Latino	Yes	Yes	Re-displacement
	Male	13	Asian	Yes	Yes	Re-displacement
	Female	17	Black	Yes	Yes	Re-displacement
	Female	9	Black	Yes	Yes	Re-displacement
	Male	16	Latino	Yes	Yes	Re-displacement
	Male	12	White	No	No	Re-displacement
	Male	7	Asian	No	No	Nonunion
	Male	5	Black	No	No	Delayed Union
	Male	9	Latino	No	No	Re-displacement
Scaphoid	Male	17	Latino	Yes	No	Nonunion
	Male	17	White	No	No	Nonunion
	Male	17	Black	No	No	Delayed Union
	Male	13	Black	Yes	No	Nonunion
5th Metatarsus	Female	11	Black	No	No	Nonunion
	Male	14	Black	No	No	Nonunion
	Male	18	Latino	Yes	No	Nonunion

ED = emergency department.

sensitive to medications that adversely affect bone healing. Certain extremity fractures, such as the scaphoid and the fifth metatarsal, have been noted to be at higher risk due to their tenuous blood supply (17,19,21). Other long bone fractures, including the humerus, femur, and tibia, are associated with increased risk of poor fracture healing because they often occur secondary to high-energy trauma, a well-known risk factor (18,20,22–28).

In an attempt to evaluate the potentially harmful effect of NSAIDs, many studies have used the outcome of nonunion or delayed union as evidence of inadequate healing (5,8,9,14,17,20,29). In addition to these outcomes, we used extremity fracture re-displacement as a marker for inadequate fracture healing. This is not without precedent. Other authors have similarly studied re-displacement as a bone healing complication in the setting of low bone density, infection, and, in one study, NSAID use (12,30,31).

Our results are comparable with those of Kay et al., who retrospectively studied the effects of parenteral ketorolac on children who had received operative care for a fracture of the humerus, femur, tibia, forearm, or ankle (14). Following the two groups until clinical and

Table 4. Association of Ibuprofen Exposure and Fracture Complication Adjusted for Clinical Covariates

	Odds of Fracture Complication if Exposed to Ibuprofen					
	Covariate Adjusted		Covariate + Age Adjusted		Covariate + Year of ED Visit* Adjusted	
Covariate	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
Gender	0.82 (0.37–1.82)	0.63	0.80 (0.36–1.79)	0.59	0.72 (0.32–1.61)	0.43
Age (years)	0.80 (0.36–1.79)	0.59	—		0.73 (0.32–1.64)	0.45
Race	0.81 (0.37–1.80)	0.61	0.81 (0.36–1.80)	0.61	0.71 (0.32–1.59)	0.41
Year of ED visit*	0.71 (0.32–1.60)	0.41	0.73 (0.32–1.64)	0.45	—	
Reduction in ED	0.78 (0.35–1.74)	0.55	0.77 (0.34–1.73)	0.53	0.70 (0.31–1.57)	0.39
Initial hospitalization	0.81 (0.37–1.79)	0.60	0.80 (0.36–1.79)	0.59	0.70 (0.32–1.57)	0.39
Initial surgery	0.82 (0.37–1.81)	0.62	0.78 (0.34–1.75)	0.55	0.70 (0.31–1.56)	0.38
Fracture type	0.78 (0.35–1.75)	0.55	0.76 (0.34–1.72)	0.52	0.69 (0.30–1.56)	0.37

ED = emergency department; OR = odds ratio; CI = confidence interval.
* Year of visit to emergency department dichotomized, 2003 to 2008 vs 2009 to 2014.

radiographic healing, their study found no cases of nonunion or delayed union. These results, however, were based on a relatively small number of patients who were exposed to a less commonly used NSAID in a different setting. Of note, 10 patients in our sample received ketorolac-9 in the hospital, and 1 as a prescription. This was the only other NSAID any patient was exposed to, and none of them developed a bone-healing complication.

Limitations

This study was limited by its retrospective design. We were therefore unable to quantify the patient exposure to ibuprofen in the outpatient setting. Although we were certain of the patient exposure in the PED and during hospitalization, we were unable to determine if the patients who were prescribed ibuprofen actually used it. Our study, however, used the principle of "intention to treat" and likely represents what commonly occurs in practice. In addition, we were unable to analyze any potential association between the duration of ibuprofen use and a bone healing complication. As some authors have suggested, the duration of the NSAID exposure may be an important factor in determining the probability of developing a fracture healing complication (10,29). Drendel et al. demonstrated, however, that a child's pain after an extremity fracture was greatest during the initial 48 h of injury, and analgesia was most commonly used for only 3 days (32). If these data are representative of our patient population, we may not have observed any effect on bone healing due to ibuprofen because the typical exposure for most children with extremity fractures is often short term.

Another limitation is that, although we collected all the variables that we believed, after a thorough literature search, could potentially affect our analyses; there may be residual confounding that we did not take into account. Lastly, although we attempted to adjust for clinical covariates using regression modeling, the number of independent variables allowed in the model at one time, and, therefore, the robustness of our adjustment, was limited by the number of outcomes in our sample (33). Despite this limitation, none of the regression models examined had any suggestion that there was a positive association between ibuprofen exposure and fracture complications.

We chose to use the pediatric radiology attending's final report to define the presence of nonunion, delayed union, and re-displacement. This simplified our data analysis and prevented the authors from introducing bias when reviewing patient data, as these terms are not well defined in the literature, particularly for children. There is no clear consensus, however, on the definition of these complications. Some sources define nonunion, for example, as the cessation of all reparative processes of healing without bone union in 3 to 9 months or twice the time in which one would expect the fracture to heal (34,35). The time frame may vary depending on the fracture site, severity, or other confounding variables, all potentially influencing the diagnosis and definition of nonunion, delayed, and fracture re-displacement (5,8,9,14,17–20,29–31). Moreover, these cited definitions are difficult to apply to children, as the average rate of healing varies by age.

CONCLUSIONS

Although ibuprofen has been shown to be an effective analgesic for children with extremity fractures, controversy exists as to whether its use may be detrimental to fracture healing. In this retrospective cohort collected from over a decade of children, we failed to find evidence to support this premise. Children with extremity fractures who are exposed to ibuprofen do not seem to be at increased risk for clinically important bone healing complications as evidenced by nonunion, delayed union, or re-displacement. Prospective randomized trials are needed to validate these findings.

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ARTICLE SUMMARY

1. Why is this topic important?

Ibuprofen is a common and effective analgesic used in the treatment of injured children. Several animal and adult studies, however, have suggested that nonsteroidal anti-inflammatory drugs are harmful to bone healing and should not be used for patients with fractures. This is problematic, as other commonly used medications, such as acetaminophen or opioids, may not be as effective or are associated with unpleasant side effects.

2. What does this study attempt to show?

This 12-year retrospective cohort study attempts to demonstrate whether there is an association between ibuprofen exposure and fracture healing complications such as nonunion, delayed union, or re-displacement.

3. What are the key findings?

Despite enrolling only patients with fractures at higher risk for complications, we failed to observe a significant association between ibuprofen exposure and fracture healing complications. Potential confounders (i.e., gender, age, race, year of emergency department [ED] visit, fracture reduction in the ED, initial hospitalization, initial surgery, fracture type) were adjusted for, yet this lack of association persisted.

4. How is patient care impacted?

Ibuprofen should be considered a safe analgesic in the treatment of children with fractures.