Effect of Ketorolac Administration on the Rate of Nonunion of Operatively Treated Pediatric Long-Bone Fractures

A Matched Cohort Analysis

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Background: Nonunion is a rare yet serious complication in pediatric fracture healing that can lead to patient morbidity and economic burden. The administration of nonsteroidal anti-inflammatory drugs (NSAIDs) has been associated with an increased risk of fracture nonunion in adults, but data are lacking in the pediatric population. This study examines the relationship between postoperative ketorolac administration and nonunion in operatively managed pediatric long-bone fractures.

Methods: A retrospective cohort study was conducted with use of TriNetX, a research network that encompasses data from the United States, Canada, and Western Europe. A total of 462,260 patients from 52 health-care organizations met the inclusion criteria. Patients <18 years old with operatively managed upper or lower-extremity long-bone fractures were included. The exposure of interest was ketorolac administration within 30 days postoperatively between 2003 and 2023. Nonunion was identified and verified with use of the pertinent medical codes. Absolute risks and hazard ratios (HRs) were calculated for both study groups. Significance was set at $p < 0.05$.

Results: After propensity score matching, 48,778 patients were identified per group. The incidence of nonunion was 2.19% in the ketorolac group and 0.93% in the non-ketorolac group (HR, 2.71; 95% confidence interval [CI]: 2.46, 3.21; $p < 0.0001$). Subgroup analyses demonstrated a higher risk of nonunion in patients with lower-extremity fractures (HR, 3.45; 95% CI: 3.14, 3.75; $p < 0.0001$) than in those with upper-extremity fractures (HR, 2.11; 95% CI: 1.84, 2.32; $p < 0.0001$). Among the fracture location subgroups, the greatest HR for nonunion was observed in patients with femoral fractures, followed sequentially by those with tibial and/or fibular fractures, humeral fractures, and radial and/or ulnar fractures.

Conclusions: To our knowledge, this is the largest study to date to explore postoperative ketorolac use and nonunion in the setting of operatively managed pediatric long-bone fractures. Nonunion in children was rare, occurring in <1% of all included patients. Ketorolac administration was associated with a 2 to 3-fold increase in nonunion risks, with pronounced implications for patients with lower-extremity fractures, particularly those with femoral fractures. Clinicians should weigh the therapeutic advantages of non-opiate analgesia with ketorolac against the risk of nonunion in order to optimize postoperative pain management and recovery.

Level of Evidence: Therapeutic Level III. See Instructions for Authors for a complete description of levels of evidence.

Nonunion signifies the inability of the body to heal a fracture as a result of an internal pathology or external influence[1,2]. Fracture nonunion is a rare occurrence in the pediatric population. A fracture that persists unhealed at 9 months after the injury, with no evident progression toward healing over a 3-month period, is a widely accepted definition for nonunion, although the precise definition can vary[3,4]. The incidence of pediatric nonunion is low relative to that in adults.

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For example, Shrader et al. documented only 43 pediatric nonunions over a span of 15 years at a Level-I trauma center[5]. Another investigation found a nonunion rate of 0.85% in a cohort of 237,033 pediatric fractures[6]. Despite the infrequency of nonunion in the pediatric population, several risk factors have been identified, including opioid prescription, vitamin-D deficiency, and surgical intervention[6-9]. The importance of understanding the leading causes of nonunion cannot be understated, as nonunions can lead to considerable patient morbidity, caregiver burden, and health-care cost[7-9].

The relationship between nonsteroidal anti-inflammatory drug (NSAID) administration and fracture nonunion is a topic of debate. NSAIDs are often administered following surgery in order to control acute postoperative pain. The proposed pathophysiology by which NSAIDs may promote nonunion is by inhibiting cyclooxygenase isozyme activity, which decreases prostaglandin production. Prostaglandins increase osteoblast activity and promote angiogenesis—both of which are essential for osseous healing[10-12]. Accordingly, studies have noted an increased nonunion risk with the postoperative administration of NSAIDs, particularly with prolonged use[10,13,14]. A common NSAID often utilized in the postoperative period is ketorolac (Toradol), as it offers strong analgesic effects when utilized as an adjunct to opiates and is well tolerated, especially in pediatric patients[15-17]. Despite various studies exploring the impact of NSAIDs on fracture healing, the evidence remains mixed: some studies have demonstrated delayed healing, whereas others have suggested that there is no impact when NSAIDs are utilized for short-term pain management in skeletally mature patients[18-24].

The effects of NSAIDs, particularly ketorolac, on surgically treated pediatric long-bone fractures remain poorly understood. The available studies on NSAID use following fracture treatment either focus on other medications, such as ibuprofen; have a mixed population of nonoperatively and operatively treated fractures; or are too underpowered to be generalizable given the rarity of nonunion in pediatric populations[25-28]. Our objective was to investigate the impact of ketorolac administration on the risk of nonunion in children undergoing surgical treatment for long-bone fractures and to discern whether risk patterns emerge based on the general fracture location.

Materials and Methods

Study Design and Data Source

We conducted a retrospective cohort study with use of TriNetX, a research network that encompasses data from approximately 110 million patients across the United States, Canada, and Western Europe. Within this dataset, 462,260 patients from 52 health-care organizations satisfied the inclusion criteria of our study. TriNetX, which aggregates data from various hospitals and public death registries, improves data quality by normalizing data formats and units across health-care organizations, which reduces errors when comparing data from different electronic health record (EHR) sources. The data import process employed by TriNetX converts diverse data types into standardized formats, enhancing their reliability for comparative analysis[25-28]. We chose this network to overcome the sample size limitations observed in previous studies. Although TriNetX enables indirect access to patient notes and imaging via natural language processing models, we did not use these resources. Lastly, we followed the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines to guide data extraction and analysis.

Complying with HIPAA (Health Insurance Portability and Accountability Act) and ISO/IEC (International Organization for Standardization and International Electrotechnical Commission) 27001:2013, TriNetX ensures rigorous safeguarding of health-care data. Datasets generated by the TriNetX platform are deidentified in accordance with the deidentification standard defined in Section 164.514(a) of the HIPAA Privacy Rule. As such, this study was exempt from full institutional review board approval (IRBHSC20230367NHR).

Usage of Codes

The use of EHR data, as opposed to claims data, helps to mitigate some database-related limitations. This approach facilitates patient tracking that extends beyond the initial hospital visit, allowing for the follow-up of patients across other inpatient, outpatient, and emergency room settings. The integration of Current Procedural Terminology (CPT) codes and International Classification of Diseases, Ninth Revision (ICD-9) and Tenth Revision (ICD-10) codes, coupled with General Equivalence Mapping 2 (GEMS2), effectively bridged ICD-9 codes from 2015 and earlier to their corresponding ICD-10 codes. This enhanced the precision of searches across different health-care contexts and related codes, and amplified the sensitivity of the search algorithms[29-34].

Index Event, Study Population, and Outcome

Children <18 years old with surgically managed upper or lower-extremity long-bone fractures (i.e., excluding those in the hands and feet) were identified. Patient groups were delineated by ketorolac exposure within the 30-day postoperative window. Nonunion, our outcome of interest, was identified and defined according to the diagnostic coding documented in the EHR by orthopaedic surgeons, trusting their adherence to standard criteria for diagnosis. Operative management, or the index event, was utilized as the starting point of the follow-up period for each patient. The dataset spans from 2003 to 2023 and includes surgeries performed no later than 2021 in order to facilitate 2 years of comprehensive follow-up. Follow-up for nonunion began at 90 days post-exposure in order to capture all diagnosed cases, accounting for anticipated variations in the timing of a nonunion diagnosis.

Statistical Analysis

Propensity Score Matching (PSM)

An initial regression model was conducted to identify the factors influencing ketorolac administration. This model revealed significant ($p < 0.001$) differences in age, sex, race, body mass index (BMI), specific fracture patterns, and use of other analgesics between the 2 groups. These variables were integrated into our PSM model, enhancing the subsequent analysis. Furthermore, patients in the ketorolac and non-ketorolac groups

were matched according to their respective dates of surgery, which had to be no more than 2 months apart. Matching was performed with use of a greedy matching algorithm with a caliper of 0.1. Balance between the groups after matching was verified with use of standardized mean differences. An additional analysis was conducted to compare the incidences of open versus closed fractures between the groups. We provide both the pre- and post-matching data. Patient characteristics prior to matching can be found in the Appendix.

Statistical Tools, Models, and Measures of Association

Absolute risk identifies the probability of an event occurring in each group, which is equivalent to the incidence of the condition within the targeted cohort[35,36]. Conversely, hazard ratios (HRs), which we derived from our Cox regression models, convey the risk over time, thereby representing the instantaneous risk[35,37]. Absolute risks provide a clear perspective on the proportion of a group that experienced a specific event, whereas HRs reveal details regarding event timing, survival, or event history and the relationship between 2 groups[35,37-40]. Hence, we calculated both the absolute risk (also referred to as incidence), which is presented as the count and corresponding percentage, and the HR.

By utilizing daily patient data in our analysis, we were able to conduct analyses with day-to-day precision. This mitigated the risk of errors by ensuring that outcomes such as nonunion occurred after the index surgery, thereby enhancing our ability to establish causality. Specifically, the cumulative incidence and event rate were calculated with use of the single-factor Aalen-Johansen estimator (AJE) of the cumulative incidence curve in order to depict the progression and estimated time to outcome. Additionally, HR significance was tested with use of the log-rank test, and proportionality tests ensured adherence to Cox proportional hazards model assumptions. Assumptions for all statistical tests were verified before their use initially. Significance testing utilized the Fisher exact test or chi-square test with Kendall tau C for categorical variables and t-test statistics for continuous variables. HRs are presented with 95% confidence intervals (CIs) and associated p values. Significance was set at $p < 0.05$.

Software Suite for Testing, Visualization, and Validation

Data compilation and analysis were accomplished with use of TriNetX LIVE, Python (version 3.11.3; Python Software Foundation), and Stata MP 18 (24-core) (StataCorp). Visuals and illustrations were crafted through Adobe Illustrator Cloud, Adobe Creative Suite, BioRender, Adobe InDesign, and Microsoft Excel. All analytical procedures underwent validation by 2 independent statisticians, and critical project stages were affirmed by at least 1 senior author.

Results

Demographics

A total of 462,260 pediatric patients with operatively managed upper or lower-extremity fractures were identified; of

TABLE I Post-Matching Characteristics

Characteristic	Ketorolac (N = 48,778)*	No Ketorolac (N = 48,778)*	P Value	SMD†
Age *(yr)*	9.66 ± 4.62	9.67 ± 4.61	0.775	<0.0001
Sex†				
Male	30,411 (62.35)	30,448 (62.42)	0.949	0.002
Female	18,367 (37.65)	17,920 (36.74)	0.939	0.019
Race and ethnicity				
Hispanic	8,392 (17.20)	8,401 (17.22)	0.981	0.001
Asian	1,528 (3.13)	1,521 (3.12)	0.902	0.001
American Indian or Alaskan	351 (0.72)	256 (0.52)	0.261	0.004
Black	5,831 (11.95)	5,851 (12.00)	0.850	0.002
Native Hawaiian	276 (0.57)	269 (0.55)	0.349	0.003
White	30,612 (62.76)	30,603 (62.74)	0.949	0.000
Unknown race	9,914 (20.32)	10,132 (20.77)	0.070	0.011
BMI percentile	63.51 ± 33.23	63.44 ± 31.22	0.207	<0.0001
Lower-extremity fracture†	13,787 (28.26)	13,998 (28.69)	0.886	0.010
Femur	3,922 (28.45)	4,075 (29.11)	0.722	0.015
Tibia and/or fibula	9,864 (71.55)	9,923 (70.89)	0.649	0.015
Upper-extremity fracture†	34,991 (71.73)	34,780 (71.30)	0.829	0.010
Humerus	19,465 (55.63)	18,875 (54.27)	0.663	0.027
Radius and/or ulna	15,525 (44.37)	15,905 (45.73)	0.576	0.027

*Values are given as the mean ± standard deviation or as the number of patients, with the percentage in parentheses. †SMD = standardized mean difference. ‡Totals may not equate to 100% of the cohort size due to missing data.

TABLE II Nonunion Rates and Hazard Ratios, Overall and by Location

Fracture Subgroup	Nonunion* *(no. [%])*		Hazard Ratio (95% CI)	P Value
	Ketorolac	No Ketorolac		
Overall, pre-matching	1,066 (2.19)	2,822 (0.68)	3.49 (3.23, 3.82)	<0.0001
Post-matching				
Overall	1,066 (2.19)	453 (0.93)	2.71 (2.46, 3.21)	<0.0001
Lower extremity	545 (3.95)	206 (1.47)	3.45 (3.14, 3.75)	<0.0001
Femur	191 (4.87)†	64 (1.57)†	3.76 (3.61, 3.92)	<0.0001
Tibia and/or fibula	354 (3.59)†	142 (1.43)†	2.99 (2.85, 3.17)	<0.0001
Upper extremity	521 (1.49)	247 (0.71)	2.11 (1.84, 2.32)	<0.0001
Humerus	229 (1.18)†	101 (0.54)†	2.24 (1.92, 2.54)	<0.0001
Radius and/or ulna	292 (1.88)†	146 (0.92)†	1.89 (1.65, 2.11)	<0.0001

*Values are given as the number of patients, with the percentage in parentheses. Except as noted, percentages are based on the total number of patients in that category for that group (as described in Table I). †Percentages are based on the total number of patients with the specified fracture location in that group, as described in Table I.

these patients, 48,778 had been administered ketorolac and 413,482 had not. An initial regression model identified age, sex, race, BMI, fracture patterns, and other analgesic use as key factors affecting ketorolac use, as these variables differed significantly between the groups ($p < 0.001$). These variables were subsequently incorporated into our PSM model. After matching, the total population was 48,778 per group. The follow-up rate was 100% at 1 year and 86% at 2 years. In the ketorolac group, the mean age (and standard deviation) was 9.66 ± 4.62 years, with 30,411 (62.35%) male and 18,367 (37.65%) female patients. A total of 30,612 patients (62.76%) were White and 5,831 (11.95%) were Black. The mean BMI percentile was 63.51 ± 33.23. Similar findings were observed in the matched comparison group, which are presented in Table I along with a further demographic breakdown of the study population. Pre-matching characteristics are available in the Appendix.

Incidence of Nonunion Following Ketorolac Administration

In the pre-matching analysis of the 48,778 patients who received ketorolac and the 413,482 who did not, we observed nonunion rates of 2.19% (1,066 patients) in the ketorolac group and 0.68% (2,822 patients) in the non-ketorolac group, yielding an HR of

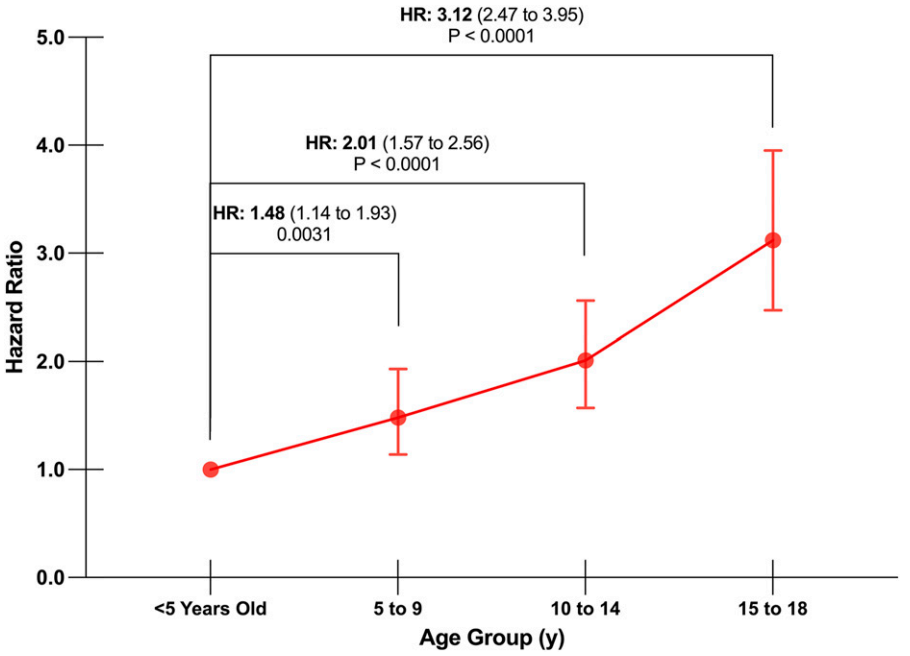

Fig. 1

Plot of the hazard ratios for nonunion in the ketorolac group, stratified by age group. The whiskers represent the 95% CI.

TABLE III Nonunion Rates and Hazard Ratios in the Ketoralac Group, by Age

Age	Nonunion* *(no. [%])*	Hazard Ratio (95% CI)	P Value
<5 years	138 (1.19)	1 (reference)	—
5 to 9 years	226 (1.47)	1.48 (1.14, 1.93)	0.0031
10 to 14 years	306 (2.68)	2.01 (1.57, 2.56)	<0.0001
15 to 17 years	396 (3.85)	3.12 (2.47, 3.95)	<0.0001

*Values are given as the number of patients, with the percentage in parentheses. Percentages are based on the total number of patients in each age group.

3.49 (95% CI: 3.23, 3.82; $p < 0.0001$; Table II). After matching, we found that nonunion developed in 2.19% (1,066) of the patients who received ketorolac versus 0.93% (453) of the patients who did not receive ketorolac, with an HR of 2.71 (95% CI: 2.46, 3.21; $p < 0.0001$; Table II). When stratifying nonunion data in the ketorolac group by age, we found that, among patients 5 to 9 years of age, the HR for nonunion versus <5-year-olds was 1.48 (95% CI: 1.14, 1.93; $p = 0.0031$); among those 10 to 14 years of age, the HR for nonunion increased to 2.01 (95% CI: 1.57, 2.56; $p < 0.0001$); and among those 15 to 17 years of age, the HR increased further to 3.12 (95% CI: 2.47, 3.95; $p < 0.0001$; Fig. 1, Table III).

Fracture Location

When focusing on lower-extremity fractures, we observed a nonunion rate of 3.95% (545 patients) in the ketorolac group and 1.47% (206 patients) in the non-ketorolac group, yielding an HR of 3.45 (95% CI: 3.14, 3.75; $p < 0.0001$). Upon further stratification of patients with lower-extremity fractures, the incidence of femoral nonunion was 4.87% (191 patients) in the ketorolac group and 1.57% (64 patients) in the non-ketorolac group (HR, 3.76; 95% CI: 3.61, 3.92; $p < 0.0001$). For tibial and/or fibular nonunion, the incidence was 3.59% (354 patients) with ketorolac and 1.43% (142 patients) without ketorolac (HR, 2.99; 95% CI: 2.85, 3.71; $p < 0.0001$). When investigating upper-extremity fractures, the incidence of nonunion was 1.49% (521 patients) in the ketorolac group and 0.71% (247 patients) in the non-ketorolac group, with an HR of 2.11 (95% CI: 1.84, 2.32; $p < 0.0001$). The incidence of humeral nonunion was 1.18% (229 patients) among those who received ketorolac, whereas the incidence was 0.54% (101 patients) among those who did not (HR, 2.24; 95% CI: 1.92, 2.54; $p < 0.0001$). For radial and/or ulnar nonunion, the incidence was 1.88% (292 patients) in the ketorolac group and 0.92% (146 patients) in the non-ketorolac group (HR, 1.89; 95% CI: 1.65, 2.11; $p < 0.0001$). This information is represented in Figure 2 and Table II. No significant differences were found in the incidences of open versus closed fractures between the ketorolac and non-ketorolac groups ($p > 0.05$).

Discussion

Effective pain management is crucial following surgical treatment of long-bone fractures, with narcotics and NSAIDs being the most commonly administered analgesics. However, the association between ketorolac, a commonly utilized NSAID, and pediatric nonunion is debated. This study demonstrated that nonunions, although rare in pediatric patients with surgically treated fractures, were more common in pediatric patients who received ketorolac than in those who did not, especially among those with lower-extremity fractures.

In contrast with our findings, a study by Kay et al. that explored the impact of ketorolac use on 221 pediatric patients with upper and lower-extremity fractures demonstrated no increased complication risk or incidence of nonunion associated with ketorolac administration[41]. Similarly, a systematic review by Choo and Nuelle showed that NSAID use during the acute phase of bone healing did not precipitate higher rates of nonunion[42]. However, the studies on ketorolac that were utilized in that review often focused on spinal fusions or had limited power due to the rarity of nonunions and small sample sizes[41,43]. Given the rarity of nonunions within pediatrics, smaller sample sizes might inadequately discern differences in nonunion data as nonsignificant. The rate of pediatric nonunion has been reported in the literature as 0.85%[6], whereas the present study found a 0.68% incidence of nonunion in the non-ketorolac group prior to matching. In our post-matching analysis of the association between ketorolac use within 30 days postoperatively and nonunion in pediatric long-bone fractures in 97,556 patients, we identified a significantly higher incidence of nonunion in the ketorolac group (2.19%) than in the non-ketorolac group (0.93%) and significantly elevated HRs among the subgroups. The increased risk of nonunion associated with ketorolac use was greater for patients with lower-extremity fractures than for those with upper-extremity fractures; this finding is notable given that lower-extremity fractures have been shown to affect function, activity, and overall conditioning more severely than upper-extremity fractures[44]. The elevated risk of nonunion in patients with lower-extremity fractures, particularly those with femoral fractures, following ketorolac administration underscores the importance

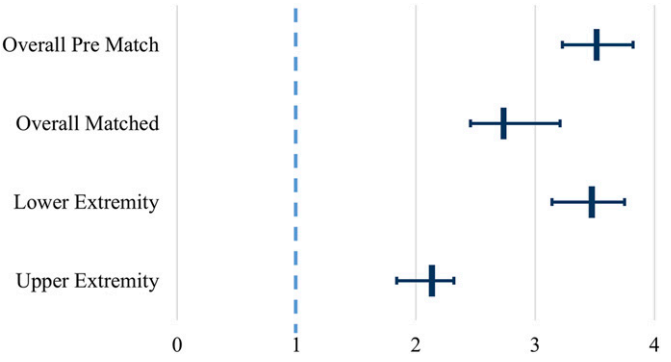

Fig. 2

Forest plot of the hazard ratios for lower and upper-extremity fractures. The rectangles represent the estimate, the whiskers represent the 95% CI, and the dashed line is the reference line indicating no difference in risk.

of carefully evaluating postoperative pain management strategies in these patients.

The ability of our study to identify these associations stems partly from our robust dataset, which contrasts with prior studies, which were limited by their datasets. Furthermore, we employed PSM to minimize the comparative age-related factors between the groups, recognizing that the threshold of skeletal maturity, which is often marked by physeal closure, can influence bone-healing expectations. Our study also accounted for a potential association between open fractures and increased nonunion rates. Our finding of no significant differences in the incidences of open versus closed fractures between the groups further strengthens the validity of our results. Additionally, our selection of a 30-day time frame for ketorolac exposure reflects the nuanced use of ketorolac in pain management, capturing the variability in both patient-experienced pain and healing trajectories that exists even among patients with similar conditions[45].

Although the differences in the absolute risks of nonunion between the study groups were not markedly large, they were nonetheless significant, highlighting the need for careful, individualized consideration of ketorolac use. NSAIDs, including ketorolac, are valuable for reducing opioid dependency and managing pain and inflammation, but they come with associated risks[46]. However, completely forgoing NSAIDs is neither a realistic nor a safe approach. Furthermore, alternative pain management strategies such as local blocks are not uniformly implemented at various institutions[47]. Given the array of pain management strategies, it is crucial for physicians to holistically evaluate the needs of each patient, judiciously weighing every risk and benefit that has been substantiated by rigorous research in order to tailor the postoperative care regimen to the individual[46,48]. Future research should not only focus on understanding how NSAIDs might obstruct bone healing in biomechanical and pharmaceutical studies but also explore the role of NSAIDs in various surgical treatments and specific fracture locations and compare ketorolac with alternative postoperative analgesics.

Limitations

Our study has limitations. Its retrospective nature made it vulnerable to biases, and the utilization of an extensive network might have resulted in unaccounted-for outcome measures. Moreover, despite comprehensive data, multi-code verification, and detailed data-cleaning to minimize errors, the possibility of coding inaccuracies and clinical misattributions could not be completely eliminated. Additionally, the TriNetX database primarily consists of individuals seeking medical care from large academic medical centers, which introduces a potential discrepancy in the incidences of ketorolac administration and/or nonunion between the database and the general population[25]. Furthermore, the present study did not delineate the percentage of nonunion diagnoses made at the initial hospital visit versus at other treatment facilities, which is a key factor in understanding the continuity of care and resource utilization. Another limitation is that patient notes and radiographs were not utilized to confirm nonunion, potentially leading to some uncertainty in the definitive assessment of fracture-healing outcomes. Moreover, our data did not include detailed information on ketorolac dosage and duration. Finally, we were not able to account for fracture severity or the type of surgery received, which may explain the confounding that we observed in the differences between subgroups, namely between the upper and lower-extremity subgroups. Matching patients by age and fracture type was intended to standardize comparisons as much as possible, with the assumption that matched pairs would likely have received age and fracture-appropriate surgical interventions. However, this does not guarantee uniformity in treatment.

Conclusions

In this study encompassing >400,000 operatively treated fractures, we explored the relationship between ketorolac administration within 30 days after surgery and the incidence of nonunion among pediatric patients. Although the overall rate of postoperative pediatric nonunion was low, the administration of ketorolac was correlated with a 2 to 3-fold increase in nonunion rates. The hazard was particularly elevated in patients with lower-extremity fractures. Therefore, the benefits and risks of the administration of ketorolac for symptomatic pain management in these groups should be carefully considered. These findings accentuate the importance of cautious use of ketorolac in postoperative analgesia and support a patient-centered approach that considers individual risk. Our results call for further robust research to refine analgesic protocols with the aim of optimizing fracture healing and minimizing nonunion risk in pediatric orthopaedic care.

Appendix

eA Supporting material provided by the authors is posted with the online version of this article as a data supplement at jbjs.org (http://links.lww.com/JBJS/I255). ■

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