JPPT | Single Center Retrospective Study

Ketorolac Dose Ceiling Effect for Pediatric Headache in the Emergency Department

Brian Lefchak, MD, MPH; Danielle Morgan, PharmD; Mike Finch, PhD; Manu Madhok, MD; and Mike Raschka, PharmD

OBJECTIVE This study sought to demonstrate a non-inferiority analgesic ceiling effect previously demonstrated within adults for pediatric patients receiving a maximum ketorolac dose of 15 mg.

METHODS We conducted a retrospective cohort study of pediatric ED patients weighing at least 60 kg treated with 30 mg (pre-intervention) or 15 mg (post-intervention) intravenous (IV) ketorolac for headache. The primary outcome included patient-reported pain scores. Additional outcomes included demographic variables, adjunct medication use and adverse effects. Categorical data were evaluated using a χ^2 test, and numerical data were evaluated using an ANOVA F test and Welch 2-sample *t* test.

RESULTS The pre- and post-intervention groups included 216 and 62 patients, respectively. Overall demographics were similar between the groups (72.3% female, 49.3% White/Caucasian, mean age 15.5 years, mean weight 79.2 kg, and mean baseline 10-point pain score 7.5). Twelve (5.6%) in the pre-intervention group required rescue analgesic compared with 2 patients (3.2%) in the post-intervention group (p = 0.416). In the pre-intervention group, 198 patients (91.7%) received nausea medication compared with 52 patients (83.9%) in the post-intervention group (p = 0.087). Mean 10-point pain scores following ketorolac administration decreased by 3.9 in the pre-intervention group compared with 5.1 in the post-intervention group (p = < 0.001). Common (0.9%) or rare (0.9%) side effects were infrequent and only seen in the pre-intervention group patients.

CONCLUSIONS Truncating the maximum intravenous ketorolac dose in pediatric patients at least 60 kg in weight to 15 mg compared with 30 mg results in effective analgesia in pediatric patients with headache. Future research could explore differences in admission rates, treatment of other indications, or treatment with multiple-dose regimens.

ABBREVIATIONS COX-1, cyclooxygenase-1 enzyme; COX-2, cyclooxygenase-2 enzyme; ED, emergency department; ICD, *International Classification of Diseases*; IV, intravenous

KEYWORDS dose; emergency department; headache; ketorolac; migraine; pediatric

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Introduction

Ketorolac is a nonsteroidal anti-inflammatory drug that has been extensively studied for the treatment of moderate-to-severe pain.[1] The antipyretic, analgesic, and anti-inflammatory properties of ketorolac result from reversible inhibition of cyclooxygenase (COX)-1 and COX-2 enzymes, thereby decreasing the formation of prostaglandin precursors.[2] The side effect profile is often considered favorable to the withdrawal or dependency concerns associated with other forms of analgesia, such as opioids. Adverse effects of ketorolac can include interstitial nephritis, renal failure, hypersensitivity reactions, and gastrointestinal hemorrhage.[2,3]

Historically, a maximum dose of 30 mg given by the intravenous (IV) route has been used to achieve analgesia; however, more recent studies have demonstrated an equivalent analgesic ceiling effect at smaller doses among adult patients.[3–9] A randomized, double-blind trial assessing the analgesic efficacy of different IV ketorolac doses (10, 15, and 30 mg) for moderate-to-severe acute pain in adult emergency department (ED) patients found no significant differences in pain reduction, need for additional analgesia, or serious adverse events.[4] The most common side effects reported were mild and transient, including dizziness, nausea, and headache.[4] As IV ketorolac vials are only available in 15, 30, and 60 mg doses in the United States, many adult institutions now use the 15 mg amount as the maximum dose.[10]

Like other institutions, Children's Minnesota often uses IV ketorolac as a first-line agent for headache and migraine pain control within the ED. In pediatric patients, ketorolac has been typically administered using weight-based dosing of 0.5 mg per kilogram per dose, with a

maximum dose of 30 mg.[11] Currently, to our knowledge, no data exist evaluating whether the analgesic ceiling effect of 15 mg seen in adult patients is also observed in pediatric patients. Therefore, the primary aim of this study was to compare the efficacy and safety profiles of a maximum ketorolac dose of 15 mg with those of the previously used maximum dose of 30 mg.

Methods

Study Design. We conducted a retrospective chart review of pediatric ED visits between January 1, 2018, and December 31, 2021, to Children's Minnesota with chief complaint of migraine or headache and administration of IV ketorolac. *International Classification of Diseases* (ICD)-10 codes that met inclusion criteria included G43 (Migraine), G44 (Other headache syndromes), and R51 (Headache), along with all subcategories for both of these indications (i.e., G43.909: Migraine, unspecified, not intractable, without status migrainosus).[12] Exclusion criteria included body weight less than 60 kg, chief complaint other than headache or migraine, inadequate or missing pain scores, lack of caregiver documented research participation consent form (provided routinely to patients as part of their clinical visit and not specific to this study), hospital admission, or receipt of analgesics listed in Appendix 1 within 30 minutes before or after ketorolac administration. This time frame was selected to account for the onset of action of ketorolac and to ensure that post-administration pain scores were reflective of ketorolac rather than concomitant analgesia treatment. Hospital admission was excluded to minimize confounding from potentially more complicated or alternate diagnoses that may not have been apparent within the ED setting. Patients meeting inclusion criteria who visited between January 1, 2018 and December 31, 2020 received a maximum ketorolac dose of 30 mg ("pre-intervention group"), whereas patients who visited between January 1, 2021 and December 31, 2021 received a maximum dose of 15 mg ("post-intervention group"). Maximum doses for both groups were truncated automatically within the electronic medical record at the time of ordering.

Data Collection. Data were obtained retrospectively from the Children's Minnesota electronic medical record using inclusion criteria ICD-10 diagnosis codes and also included the following elements: ED visit date, date of birth, sex, ethnicity, body weight, ketorolac dose, and route and time of ketorolac administration. Manual chart review of nursing and provider documentation was conducted to obtain baseline and follow-up 10-point pain scores, using a Likert-type numeric pain score with a score of zero representing no pain and a score of 10 representing the worst pain possible. The manual chart review also collected pertinent information including pain score timestamps, reported side effects, additional analgesic medications (Appendix 1) received at least 30 minutes prior to ketorolac, additional analgesic medications (Appendix 1) administered between 30 minutes and 6 hours after ketorolac, and nausea medications (Appendix 2) administered at the same time and up to 6 hours after ketorolac administration. This time frame was also selected to account for the onset and duration of the action of ketorolac. Adverse events evaluated for included "common" (headache, gastrointestinal pain, dyspepsia, nausea) and "rare" (acute kidney injury, allergic reaction, anemia, bleeding, constipation, diaphoresis, diarrhea, dizziness, drowsiness, edema, flatulence, gastrointestinal fullness, gastrointestinal perforation, gastrointestinal ulcer, hypertension, pruritis, skin rash, stomatitis, tinnitus, and vomiting) categories as labeled in the ketorolac package insert.[2] Adverse effects were included if noted during the ED visit.

Statistical Analysis. Categorical data were analyzed using a χ^2 test unless otherwise noted as Fisher exact test. Numeric data was analyzed using an ANOVA F test and Welch 2-sample *t* test. All numeric data were examined for normality, and p values less than 0.05 were considered significant. A margin of +0.5 was utilized to demonstrate non-inferiority.

Results

Study Population. Two hundred ninety-four patients met the inclusion criteria in the pre-intervention group and 80 in the post-intervention group. Among pre-intervention patients, 3 (1.0%) were excluded due to a lack of study consent, and 75 (25.5%) were excluded due to a lack of adequate baseline or follow-up pain scores. Among post-intervention patients, 2 (2.5%) were excluded due to a lack of study consent, and 16 (20%) were excluded due to a lack of adequate pain scores. The final pre- and post-intervention groups included 216 and 62 patients, respectively (see Supplemental Figure).

Demographic and baseline characteristics were generally similar between the 2 groups (Table 1). Both groups were predominantly female (overall 72.3%, p = 0.560) and White/Caucasian (overall 49.3%, p = 0.464), with similar mean age (overall 15.5 years, p = 0.590) and weight (overall 79.2 kg, p = 0.710). The mean baseline pain score in the pre-intervention group was 7.6 vs 7.2 in the post-intervention group (p = 0.248). The rate of analgesic exposure at least 30 minutes prior to ketorolac administration was higher among post-intervention patients (22.6%) than pre-intervention patients (13.4%; p = 0.079; Table 2). The mean baseline pain scores after alternate analgesic administration but prior to ketorolac administration, however, were similar between the pre-intervention and post-intervention groups (7.7 vs 7.2, p = 0.475). The mean time between the baseline pain score and ketorolac administration was longer in the post-intervention group (84.0 minutes) compared with the pre-intervention group (68.2 minutes; difference of 15.8 minutes, p = 0.039). The time between ketorolac

Table 1. Demographic and Baseline Characteristics*

	Ketorolac 30 mg (N = 216)	Ketorolac 15 mg (N = 62)	p value
Age, mean (yr)	15.50 (15.28–15.72)	15.63 (15.41–16.08	0.590
Weight, mean (kg)	78.96 (76.45–81.47)	79.94 (77.43–84.26)	0.710
Female, %	73% (67%–79%)	69% (63%–81%)	0.560
Race			
White/Caucasian	50% (44%–57%)	45% (33%–58%)	0.464
Black/African American	20% (15%–26%)	32% (21%–44%)	0.074
Hispanic/Latino	16% (11%–21%)	11% (3%–19%)	0.305
Asian	5% (2%–7%)	0% (0.0%–0.0%)	0.001
Other/Unknown/Declined	1% (0%–2%)	5% (0%–10%)	0.170
ICD-10 code			
G43 - Migraine	12.5% (8.1%–16.9%)	4.8% (−0.5% to 10.2%)	0.033
G43.1 - Migraine with aura	0.5% (−0.4% to 1.4%)	0.0% (0.0%–0.0%	0.593
G43.901- Migraine, unspecified, with status migrainosus	0.0% (0.0%–0.0%)	1.6% (−1.5% to 4.8%)	0.321
G43.909 - Migraine, unspecified, without status migrainosus	43.5% (36.9%–50.1%)	41.9% (29.6%–54.3%)	0.825
G44.221 - Chronic tension-type headache, intractable	1.4% (−0.2% to 3.0%)	0.0% (0.0%–0.0%)	0.353
R51 - Headache	42.1% (35.5%–48.7%)	29.0% (17.6%–40.4%)	0.054
R51.9 - Headache, unspecified	0.0% (0.0%–0.0%)	22.6% (12.1%–33.1%)	<0.001
Received an analgesic medication prior to ketorolac	13% (9%–18%)	23% (18%–33%)	0.079
Baseline pain score, mean	7.56 (7.31–7.80)	7.24 (7.00–7.75)	0.248
Patients who did not receive an analgesic prior to ketorolac	7.604 (7.346–7.862) (n = 187)	7.104 (6.520–7.688) (n = 48)	0.097
Patients who received a pain medication prior to ketorolac	7.241 (6.496–7.986) (n = 29)	7.714 (6.699–8.730) (n = 14)	0.475
Mean time between baseline pain score and ketorolac administration, min	68.19 (61.35–75.04)	84.03 (77.19–98.52)	0.039
Mean time between ketorolac administration and follow-up pain score, min	80.37 (72.93–87.80)	108.63 (101.19–125.00)	<0.001

ICD, International Classification of Diseases

* Reported as mean (95% CI).

Table 2. Additional Analgesics Received Prior to or After Ketorolac Administration

	Ketorolac 30 mg (N = 216)		Ketorolac 15 mg (N = 62)	
	Pre-Ketorolac N = 29 (13.4%)	Post-Ketorolac N = 12 (5.6%)	Pre-Ketorolac N = 14 (22.6%)	Post-Ketorolac N = 2 (3.2%)
Acetaminophen	23	6	13*	2
Fentanyl	1	1	0	0
Ibuprofen	1	0	1	0
Morphine	0	1	0	0
Naproxen	3	0	0	0
Tramadol	1	4	0	0

* One patient received a dose of acetaminophen, aspirin and caffeine.
Other medications reviewed for but not received by any patients in either group included amitriptyline, gabapentin, hydromorphone, lidocaine patch, meloxicam, methadone, and oxycodone.

administration and the follow-up pain score was also shorter in the pre-intervention group (80.4 minutes) compared with the post-intervention group (108.6 minutes; difference of 28 minutes, p = <0.001).

Efficacy. In the pre-intervention group, 12 patients (5.6%) required rescue analgesic medication within the 6 hours following ketorolac administration compared with 2 patients (3.2%) in the post-intervention group (p = 0.073). One hundred ninety-eight patients in the pre-intervention group (91.7%) and 52 patients in the post-intervention group (83.9%) received concomitant medication therapy for nausea and vomiting at the same time or up to 6 hours from ketorolac administration (p = 0.087). The average number of nausea medications administered per patient in the pre-intervention group was 1.6 vs 1.4 in the post-intervention group (p = 0.128). In the pre-intervention group, the mean pain score following ketorolac administration decreased by 3.87, whereas in the post-intervention group the mean pain score decreased by 5.11 (p = < 0.001) (Table 3). Changes in mean pain scores were larger among the post-intervention group compared with the pre-intervention group for both the subgroup of patients who did not receive analgesics prior to ketorolac (4.9 vs 3.9, p = 0.023) and the subgroup of patients receiving both ketorolac and at least 1 pain medication prior to the ketorolac (6.0 vs 3.7, p = 0.011). All patients in each group received a 10- to 20-mL per kilogram bolus 0.9% sodium chloride upon arrival to the ED.

Safety. In the pre-intervention group, 2 patients (0.9%) reported a common side effect associated with ketorolac compared with 0 patients in the post-intervention group (p = 1.00). Two patients (0.9%) in the pre-intervention group also reported a rare side effect associated with ketorolac compared with 0 patients in the post-intervention group (p = 0.60). Of the common side effects reported, both patients reported a new onset of headache pain. The reported rare adverse effects included dizziness in 1 patient and tingling of the lips and fullness in the throat in the second patient, which was treated with diphenhydramine and resolved.

Discussion

This single-institution retrospective chart review study is the first study evaluating the potential ceiling effect of analgesic properties in the pediatric population. This study demonstrated non-inferiority in pain reduction with the utilization of a maximum ketorolac dose of 15 mg compared with a maximum dose of 30 mg using a +0.5 margin. This suggests that a ceiling effect likely also exists in the pediatric population, similar to what has been demonstrated in adult studies. There was no statistically significant difference between the need for or amount of nausea medication administered or the need of rescue analgesic treatment after ketorolac administration. While the rate of analgesic exposure prior to ketorolac administration was higher among post-intervention than pre-intervention patients, this difference was not significant, and changes in pain scores were larger among post-intervention patients receiving either ketorolac only or ketorolac with additional analgesia, thus supporting our overall conclusion and clinical practice of ketorolac dose capping.

In terms of safety, very few patients (less than 2% of the entire combined sample) experienced a side effect. This result is not surprising given that these patients only received a one-time dose of ketorolac and were monitored for a short period of time in the ED. Given that all reported side effects, while uncommon, occurred in the larger-dose group, it may be possible that lower maximum dosing on a scheduled basis could limit unintended side effects over time, as certain ketorolac adverse effects have been considered dose-response related, including gastrointestinal bleeding and acute kidney injury.[13–15]

Table 3. Efficacy Data*

	Ketorolac 30 mg (N = 216)	Ketorolac 15 mg (N = 62)	p value
Need for rescue analgesic medication	5.6% (n = 12)	3.2% (n = 2)	0.416
Nausea medication administration	91.7% (n = 198)	83.9% (n = 52)	0.087
Number of nausea medications per patient	1.58 (1.47–1.69)	1.42 (1.20–1.64)	0.128
Change in mean pain scores	−3.87 (−4.21 to −3.52)	−5.11 (−5.77 to −4.45)	<0.001
Patients who did not receive an analgesic prior to ketorolac	−3.89 (−4.26 to −3.51) (n = 187)	−4.85 −5.59 to −4.11) (n = 48)	0.023
Patients who received a pain medication prior to ketorolac	−3.72 (−4.67 to −2.78) (n = 29)	−6.00 (−7.38 to −4.62) (n = 14)	0.011

*Reported as mean (95% CI).

Interestingly, there was a significant difference between the time the baseline pain score was obtained and the time that ketorolac was administered between the 2 groups, with the pre-intervention group receiving a dose of ketorolac approximately 15.8 minutes earlier on average compared with the post-intervention group. Similarly, there was a significant difference in the time between ketorolac administration and the assessment of a follow-up pain score. On average, the pre-intervention group had a follow-up pain score 28 minutes earlier than those in the post-intervention group. Considering the pharmacokinetics of ketorolac, the analgesic effect of the drug typically begins approximately 30 minutes after IV administration, with maximum effects in 1 to 2 hours.[2] As both the pre-intervention and post-intervention groups were followed up on average between 1 and 2 hours post-administration of ketorolac, it is unlikely that this difference in follow-up time between the 2 groups had a significant impact on the follow-up pain scores, but remains a possibility given the findings in this study of superiority with a maximum dose of 15 mg compared with 30 mg.

In regards to the statistical tests utilized, an ANOVA F test and Welch 2-sample *t* test were used for the numerical data. Although both tests are widely held to be robust, they are sensitive to heavily tailed asymmetric distributions.[16] While the Shapiro-Wilk rejected the null in a majority of the cases, in all cases the median was well within the 95% CI of the mean. Likewise in all cases, the 95% CI of the skewness between groups was non-significant, suggesting that while slightly skewed the distributions were not heavy tailed.

There were several limitations to our study. Major limitations include the subjective nature of both pain scores and decision-making for need of rescue analgesic. Another limitation is that the post-intervention sample size was smaller than the pre-intervention group size, which may have resulted in an underestimation of significant differences between the 2 dosing groups, although this seems unlikely to have altered the non-inferiority conclusion. Several patients were excluded due to a lack of documented pain scores, and it is unknown as to why these pain scores were not adequately documented in the electronic medical record. The study only included patients within the ED setting, and although we attempted to collect information on pre-ED medication use that otherwise may have been expected to be similar between the 2 groups, it is possible that differences in such medication use may be underreported given the dependence on chart documentation. Additionally, we were unable to investigate the efficacy or safety profile of repetitive ketorolac use at different doses or over longer periods of time. It has been speculated that a smaller dose of ketorolac may still provide appropriate pain control initially but may not provide pain control for the same duration as the historical 30 mg dose.[17]

Furthermore, our study was unable to include objective measures related to adverse effects or adverse effects outside the timeframe of the ED visit and thus may underreport these frequencies. Objective measures, including laboratory serum creatinine, were initially considered as part of analysis, but ultimately unable to be included because laboratory studies were not routinely obtained. While the low rates of

adverse effects in our population is encouraging, comparison of adverse effect differences may therefore be limited. Also, due to the retrospective nature of this study specific to adverse events is that the authors were unable to determine whether the 2 patients who reported experiencing headaches were experiencing new ketorolac-induced headaches or experiencing breakthrough pain of the headache they presented to the ED for.

There are various opportunities for future research regarding the potential ceiling effect of ketorolac. To our knowledge, this is the only pediatric study comparing 15 vs 30 mg ketorolac in children weighing 60 kg or greater for any indication. Future study could explore differences in the treatment of other indications such as sickle cell pain. For example, there is currently no published evidence to our knowledge of ketorolac dose capping for sickle cell crisis for adult or pediatric patients. Other areas of inquiry could include differences in admission rates and treatment with multiple-dose regimens.

Conclusion

This study found that truncating the maximum IV ketorolac dose to 15 mg compared with 30 mg in children weighing 60 kg or greater resulted in effective analgesia in pediatric patients with headache. Further, there was no significant difference in adjunct medication use or safety profile between the 2 study groups. To our knowledge, this is the only pediatric study comparing these ketorolac doses for any indication and supports the clinical practice of dose capping. Future studies should focus on whether this lower maximum dose has an impact on admission rates or whether the maximum dose has any effect on pain scores when utilized with multiple-dose regimens.

Article Information

Affiliations. Department of Pediatric Emergency Medicine (BL, MM), Children's Minnesota, Minneapolis, MN; Pharmacy Department (DM, MR), Children's Minnesota, Minneapolis, MN; Children's Minnesota Research Institute (MF), Children's Minnesota, Minneapolis, MN.

Correspondence. Mike Raschka, PharmD; mike.raschka@childrensmn.org

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Ethical Approval and Informed Consent. Given the nature of this study, institutional review board/ethics committee review and informed consent were not required. However, permission was still obtained from the institutional review board at Children's Minnesota (Protocol number 2021-011).

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