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# Intranasal ketorolac versus intravenous ketorolac for treatment of migraine headaches in children: A randomized clinical trial

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## Abstract

**Background:** Intravenous ketorolac is commonly used for treating migraine headaches in children. However, the prerequisite placement of an intravenous line can be technically challenging, time-consuming, and associated with pain and distress. Intranasal ketorolac may be an effective alternative that is needle-free and easier to administer. We aimed to determine whether intranasal ketorolac is non-inferior to intravenous ketorolac for reducing pain in children with migraine headaches.

**Methods:** We conducted a randomized double-blind non-inferiority clinical trial. Children aged 8– 17 years with migraine headaches, moderate to severe pain, and requiring parenteral analgesics received intranasal ketorolac (1 mg/kg) or intravenous ketorolac (0.5 mg/kg). Primary outcome was reduction in pain at 60 min after administration measured using the Faces Pain Scale-Revised (scored 0– 10). Non-inferiority margin was 2/10. Secondary outcomes included time to onset of

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AUTHOR CONTRIBUTIONS

Daniel S. Tsze and Peter S. Dayan conceptualized the study. Daniel S. Tsze, Shannon E. Babineau, Benjamin W. Friedman and Peter S. Dayan designed the trial. Daniel S. Tsze and Peter S. Dayan obtained research funding. Daniel S. Tsze supervised the conduct of the trial and data collection. Daniel S. Tsze, Weijia Fan and Peter S. Dayan conducted the statistical analyses for the study. Daniel S. Tsze, Tamar R. Lubell, Robert C. Carter, Lauren S. Chernick, Kerrin C. DePeter, Son H. McLaren, Maria Y. Kwok, Cindy G. Roskind, Ariana E. Gonzalez and Peter S. Dayan undertook recruitment of participating patients. Daniel S. Tsze drafted the manuscript, and all authors contributed substantially to its revision. Daniel S. Tsze takes responsibility for the paper as a whole.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

CONFLICTS OF INTEREST

None of the authors have any conflicts of interest to disclose.

clinically meaningful decrease in pain; ancillary emergency department outcomes (e.g. receipt of rescue medications, headache relief, headache freedom, percentage improvement); 24-h follow-up outcomes; functional disability; and adverse events.

**Results:** Fifty-nine children were enrolled. We analyzed 27 children who received intranasal ketorolac and 29 who received intravenous ketorolac. The difference in mean pain reduction at 60 min between groups was 0.2 (95% CI −0.9, 1.3), with the upper limit of the 95% CI being less than the non-inferiority margin. There were no statistical differences between groups for secondary outcomes.

**Conclusions:** Intranasal ketorolac was non-inferior to intravenous ketorolac for reducing migraine headache pain in the emergency department.

## INTRODUCTION

Ketorolac is an analgesic commonly used to treat migraine headaches in children in the emergency department (ED).[1] Ketorolac is a nonsteroidal anti-inflammatory drug (NSAID) frequently given by the intravenous (IV) route, which requires a needle-stick for administration. Needle-related procedures are one of the most feared medical experiences reported by children and are associated with pain and distress that, when inadequately managed, can result in both short-and long-term consequences.[2–12] In addition, the placement of an IV line can be technically challenging and time consuming; analgesics may take longer to administer when using the IV route compared to other routes that do not require IV access.[13]

Ketorolac can be given by the intranasal (IN) route, which does not require a needle-stick or IV access for administration.[14–18] Analgesics and sedatives administered by the IN route have been shown to have comparable efficacy and time to onset of action compared to IV administration.[19–23] The IN route takes advantage of the highly-vascularized respiratory epithelium in the nasal cavity for systemic absorption and transports medications directly to the brain through the olfactory and trigeminal nerves, also known as the “nose-brain pathway.”[24] This allows some medications administered by the IN route to produce both faster central nervous system effects and higher drug concentrations in the central nervous system than after IV administration alone.[17,19,25–27]

Intranasal ketorolac may be an effective alternative to IV ketorolac that is both needle-sparing and easier to administer. However, these benefits are immaterial if the analgesic effectiveness of IN ketorolac is not comparable to IV ketorolac. Therefore, the primary aim of our study was to determine if IN ketorolac is non-inferior to IV ketorolac for reducing pain intensity in children with migraine headaches. Our secondary aims were to identify differences in time to onset of a clinically meaningful reduction in pain intensity; ancillary ED outcomes (i.e. receipt of rescue medication, headache relief, headache freedom, percentage improvement); 24-h follow-up outcomes; functional disability; and adverse events.

# METHODS

## Study design and setting

We conducted a prospective, double-blind, randomized, parallel, 1:1, non-inferiority clinical trial comparing IN ketorolac with IV ketorolac. We enrolled patients presenting to a single tertiary-care children's hospital ED during one of three recruitment periods between June 2015 and March 2021. Enrollment was paused from May 2016 to March 2018 due to funding limitations, and from March 2020 to September 2020 due to hospital-wide COVID-19 restrictions on research activities. The study was closed March 2021 due to a persisting decline in eligible patients associated with an overall reduction in pediatric ED visits.[28,29] The decision to close the study was made prior to unblinding and data analysis. Our institutional review board approved this study with written informed consent and assent. This trial was registered at clinicaltrials.gov (NCT02358681).

## Selection of participants

We enrolled children who were aged 8– 17 years; presented with a migraine headache as defined by the modified Irma's ED Criteria (Table S1); had a self-reported pain score of ≥4/10 (representing moderate to severe pain); and required any IV analgesic for the headache pain as per the treating physician.[30] Exclusion criteria included any contraindication to receiving ketorolac; receipt of any NSAID within previous 6 h; presence of IN obstruction that could not be readily cleared; inability to complete self-report measures of pain or questionnaires (e.g. developmental delay, autism spectrum disorder, neurological impairment); history of intracranial surgery, structural abnormalities, or risk factors for intracranial abnormality (e.g. coagulopathy; pseudotumor cerebri; pregnancy); chronic disease associated with pain other than migraine headaches (e.g. sickle cell disease, fibromyalgia); underlying medical condition necessitating multiple painful procedures (e.g. malignancy, complex congenital heart disease); known liver or kidney problems; critical illness; use of any medication for headaches on more than 10 days per month; or did not speak English or Spanish.

## Interventions

Patients were randomized to receive either IN ketorolac (1 mg/kg) and IV normal saline (placebo) or IV ketorolac (0.5 mg/kg) and IN normal saline (placebo), with a maximum ketorolac dose of 30 mg. The dose of IN ketorolac was chosen based on its bioavailability and in consultation with a clinical pharmacologist.[15] A 30 mg/ml concentration of ketorolac was used for both IN and IV administration. Intranasal medications were administered first using a mucosal atomization device (Wolfe-Tory Medical, Inc.). Total volumes were divided into two equal aliquots, with each aliquot administered into a different nostril. With the maximum dose and concentration used, the largest possible volume of administration for each nostril using this technique was 0.5 ml. The IV medication was administered over 30–60 s immediately after completing IN administration, followed by a 20 ml/kg normal saline bolus (maximum 1 L) over 60 min. All IVs were placed before any study medications were administered. No other analgesics (e.g. dopamine antagonists) were administered in the ED before or concurrently with the study medications. Treating clinicians administered rescue

medications (i.e. additional parenteral analgesics administered in response to inadequate improvement in pain) when deemed clinically indicated.

We randomized patients using computer-generated blocks of eight. Allocation was concealed using sequentially numbered, sealed, opaque envelopes. The random allocation sequence was created and maintained by a research administrator not involved with study procedures, and was not available to the investigator or study team until completion of the study. We ensured blinding of treatment assignment by using syringes with identical volume, color and odor. The treating clinicians, study team members who assessed outcomes, patient, and family members were all blinded to the treatment assignment.

## Measurements and outcomes

Outcomes were measured by a study team member at 10, 30, 60, and 120 min after completion of the IV study medication administration. Pain associated with IN administration was assessed immediately after completing IN administration of study medication (i.e. ketorolac or placebo). Pain intensity was measured at 10, 30, 60, and 120 min after study medication administration. Qualitative descriptors of pain intensity (i.e. none, mild, moderate, or severe), functional disability, and adverse events were assessed at 60 and 120 min.[31] Twenty four-hour follow-up outcomes were assessed via telephone by a study team member within 24–48 h after study medication administration.

The primary outcome was the difference in pain intensity reduction 60 min after study medication administration, measured using the Faces Pain Scale – Revised (FPS-R).[32,33] The FPS-R is a self-reported pain scale scored from 0 to 10 and comprised of 6 faces, each representing an increasing degree of pain intensity. The FPS-R has strong validity and reliability for assessing pain intensity in children aged 4– 17 years and is recommended for research in children.[33,34] The 60-min time point was chosen based on International Headache Society (IHS) recommendations for the study of parenteral medications for treating migraine headaches.[31] Secondary outcomes included: (a) difference in pain intensity reduction 10, 30, and 120 min after administration; (b) time to onset of clinically meaningful reduction in pain; (c) ancillary ED outcomes (i.e. receipt of rescue medication, headache relief, headache freedom, percentage improvement); (d) 24-h follow-up outcomes; (e) functional disability; and (f) adverse events.[35,36]

Time to onset of clinically meaningful reduction in pain intensity was determined by identifying the time that pain was first observed to have decreased by a minimum clinically significant difference (i.e. 2 on the FPS-R) and by performing a Kaplan-Meier distribution analysis.[35,36] As per IHS recommendations, ancillary ED outcomes included: (a) receipt of rescue medications in the ED after study medication administration; (b) headache relief, defined as change within 120 min of the patient's headache from severe to moderate to either mild or none, without receipt of rescue medications; (c) headache freedom, defined as achieving a headache level of none within 120 min, without receipt of rescue medications; and (d) percentage improvement in pain intensity between baseline and 60 min, defined as: (baseline pain intensity – 60 min pain intensity) / baseline pain intensity. We also evaluated treatment success as a reduction of 50% or greater in pain intensity at 30 or 60 min after study medication administration, or complete resolution of pain.[37] Degree of pain intensity

associated with IN administration was assessed immediately after administration of the IN medication using the FPS-R.

Twenty four-hour follow-up outcomes included: (a) patient's overall assessment of efficacy and tolerability, expressed as a dichotomous response to the question, "The next time you come to the emergency department with a headache or migraine, do you want to be given the same medication?"; (b) sustained headache relief, defined as achieving headache relief and maintaining this level for 24 h without the use of rescue medications after ED discharge; (c) sustained headache freedom, defined as achieving headache freedom, and maintaining this level for 24 h without the use of rescue medications after ED discharge; and (d) use of outpatient rescue medications during the 24-h period after ED discharge.[31]

Functional disability was assessed using a question standard in headache research but modified for the pediatric population (Table S2).[31] Responses were categorized as none, mild, moderate, and severe functional disability. Functional disability was assessed at baseline, 60 and 120 min after study medication administration, and during the 24-h follow-up assessment. Adverse events were assessed at the same three time points.

### Missed eligible patient review

We identified missed eligible patients (i.e. eligible but not enrolled) by reviewing the electronic medical record and identifying patients with a chief complaint of headache or migraine who received a parenteral analgesic (e.g. ketorolac, metoclopramide, prochlorperazine). Data collected for comparison to enrolled patients included the patient's age, sex, initial pain score, receipt of rescue medications, and disposition.

### Data analysis

For our primary outcome, we compared the difference in FPS-R score reduction between IN and IV ketorolac 60 min after study medication administration using the independent samples t-test. The predetermined margin of non-inferiority was 2, which represents a minimum clinically significant difference in pain intensity in children when using the FPS-R.[35,36] A margin of 1.8 was used for the sample size determination, which was based on reducing our predetermined margin by 10% in order to be conservative. Using a standard deviation of 2.725, a planned sample size of 40 patients per group was chosen to provide 90% power to detect non-inferiority using a one-sided independent sample t-test with an alpha of 0.05.[38,39] All enrolled randomized patients with outcomes measured were analyzed. To evaluate our secondary outcomes, we used the independent samples t-test to compare continuous variables and the chi-square test to compare categorical variables. Kaplan-Meier curves were compared using a log rank test. P values $<0.05$ were considered statistically significant. Analyses were conducted using SPSS (version 26; IBM Corporation).

## RESULTS

### Characteristics of study participants

We assessed 525 children for eligibility and excluded 466 (Figure 1). Fifty-nine patients were enrolled and randomized. Three patients were withdrawn before study medication

administration due to either resolution of headache prior to study medication administration or identification of an exclusion criterion after randomization; no outcome measures were assessed for these patients. The patient characteristics of the 56 children analyzed are shown in Table 1. Missed eligible patients were similar to those enrolled in age, sex, headache pain intensity at ED presentation, proportion who received rescue medications, and ED disposition (Table S3).

### Main results

The decrease in pain intensity associated with IN and IV ketorolac at 60 min is shown in Figure 2, with IN ketorolac being non-inferior to IV ketorolac for reducing pain intensity ($p < 0.001$) (Figure 3).[40] Table 2 shows the decrease in pain intensity associated with IN and IV ketorolac at 10, 30, and 120 min. Intranasal ketorolac was also non-inferior to IV ketorolac at 30 and 120 min, but the non-inferiority determination was inconclusive at 10 min (Figure 3). There was no statistical difference between groups in time to onset of a minimum clinically significant difference in pain, and ancillary ED outcomes (Table 2, Figure S1). No patients received rescue medications prior to the 60-min assessment. All patients achieved at least a minimum clinically significant difference in pain by 60 min. Treatment success, defined as a reduction of 50% or greater in pain intensity at 30 or 60 min after study medication administration, or complete resolution of pain, was achieved by 24 (88.9%) and 27 (93.1%) patients who received IN and IV ketorolac, respectively; the mean difference between groups was −4.2% (95% CI −19.2, 10.8).

There was no statistical difference between groups for the 24-h follow-up outcomes, although the group that received IV ketorolac had a larger proportion of children with sustained headache relief and headache freedom and a smaller proportion who used rescue medications after ED discharge (Table 2). There was no difference between groups in proportion of children who experienced none or mild functional disability when assessed at 60 and 120 min after study medication administration and when assessed at 24-h follow-up. There were very few children who reported moderate or severe functional disability in either group at these same time points (Table 2).

There were no serious adverse events, including no upper or lower gastrointestinal bleeding. Four children who received IN ketorolac reported 5 adverse events; 6 who received IV ketorolac reported 6 adverse events (Table 3). The most common adverse events were nausea and dizziness. The mean pain intensity associated with IN administration of ketorolac and placebo was 6.7 (95% CI 6.5, 6.9) and 0.6 (95% CI 0.5, 0.7), respectively; the mean difference between groups was 6.1 (95% CI 4.8, 7.3).

## DISCUSSION

In this randomized clinical trial, we found that IN ketorolac was non-inferior to IV ketorolac for treating pain in children with migraine headaches at 60 min after medication administration. Ketorolac administered by either route was effective in treating migraine headaches in children when assessed using a number of clinically important headache-related outcome measures.

This is the first randomized clinical trial of IN ketorolac in children, and the first trial comparing IN ketorolac to a parenteral analgesic for treating migraine headaches. This is also the first study of which we are aware utilizing the parenteral formulation of ketorolac for IN administration outside of the dental and post-operative setting.[41,42] The vast majority of prior studies of IN ketorolac have utilized an IN formulation that combines ketorolac with lidocaine, the latter of which may also have analgesic effects.[16,43–52] This lidocaine-containing formulation has been shown to be superior to placebo and non-inferior to IN sumitriptan for reducing migraine headache pain in adults.[16,48] Our findings further support the effectiveness of IN ketorolac for treating migraine headaches, specifically in the pediatric population and when using the parenteral formulation of ketorolac that does not include lidocaine and is readily available in the ED setting.

Ketorolac, when given by either route, appeared to be effective in our study for treating migraine headaches in children based on a number of clinically important headache-related outcomes. A percent reduction of pain intensity at 60 min of ~70% was greater than percent reductions associated with an ideal clinically significant difference (i.e. 60% reduction) and children declining additional analgesia because of adequate pain relief (i.e. 40% reduction).[36] Ketorolac treatment was also associated with headache relief in ~90% and mild or no functional disability in greater than 90% of patients. Approximately 20% of patients who received IN or IV ketorolac received rescue medications and between 40 and 60% achieved headache freedom within 2 h, which are proportions comparable to those described in four prior studies evaluating other parenteral analgesics in children. These studies of ketorolac, prochlorperazine, propofol, and a combination of ketorolac/dopamine antagonist/diphenhydramine/IV fluids reported that 5– 37% of patients received rescue medications, and 7– 60% experienced headache freedom at similar time points.[37,53–55] Our results are comparable to those reported in the randomized clinical trial comparing ketorolac and prochlorperazine for treating migraine headaches in children: the proportion of patients in our study who achieved treatment success with both IN and IV ketorolac was no less than that reported for IV ketorolac (55.2%) and IV prochlorperazine (84.8%).[37] In addition, we observed that both IN and IV ketorolac were comparable to a combination of ketorolac/dopamine antagonist/diphenhydramine/IV fluids with regard to percent pain reduction 60 min after administration (59%) and proportion of children who received ED rescue medications (22.2%).[53]

The implementation of IN ketorolac may be limited by the moderate degree of nasal pain associated with IN administration. Pain associated with IN administration has also been described with IN midazolam, which is commonly used for anxiolysis for children in the ED setting.[56–59] This associated pain, however, has not precluded the use of IN midazolam. Rather, it has prompted the study of different strategies for treating this pain so that children can still benefit from its favorable properties (e.g. rapid onset, needle-free administration, effective anxiolysis), such as with the pre-treatment or co-administration with lidocaine.[57,60–63] The administration of the IN formulation of ketorolac containing lidocaine has been associated with nasal pain in 5– 20% of patients, with the degree of pain intensity rated as “mild” in one study.[14,48,49,51] However, further research is necessary to better describe the effect of lidocaine or other strategies for decreasing the pain associated with IN administration of ketorolac in children. Until then, there should be shared decision-

making with patients and families weighing the benefits and drawbacks of IN administration with those associated with IV administration of ketorolac.

This study demonstrated non-inferiority of IN ketorolac compared to IV ketorolac, but it does not address whether IN ketorolac alone is non-inferior to a regimen consisting of IV ketorolac and a normal saline bolus. Intravenous fluids are commonly given to children as part of their migraine headache treatment in the ED.[64] Since one of the advantages of using IN ketorolac would be to avoid placing an IV line, patients receiving IN ketorolac would be unlikely to receive a normal saline bolus. Although hydration could be achieved orally, nausea and vomiting associated with migraine headaches could potentially be prohibitive. Therefore, clinical practice could be informed by future studies comparing IN ketorolac alone to a regimen of IV ketorolac and a normal saline bolus. However, the benefit of a normal saline bolus for decreasing pain in patients with migraine headaches is unclear. To date, there are only two prospective trials of a normal saline bolus for treating migraine headaches in patients presenting to the ED. One study of children aged 5– 17 years demonstrated that the overall decrease in pain associated with a 10 ml/kg normal saline bolus was small and not clinically significant.[65] Similarly, one study of adults showed no difference in pain intensity improvement between patients who received a one-liter normal saline bolus and those who did not.[66]

## LIMITATIONS

First, we were unable to achieve our planned sample size. However, we were able to enroll a sufficient number of patients to provide adequate power to achieve our primary aim and demonstrate non-inferiority due to the conservative estimates used when calculating the sample size. Specifically, we determined the sample size using a standard deviation (2.725) that was larger than those actually observed in the IN ketorolac and IV ketorolac groups (1.695 and 2.353, respectively). Second, we did not include patients who used medications for more than 10 days a month, which may limit generalizability by excluding patients who may have a more established or refractory history of migraine headaches. This decision was based on IHS recommendations to avoid enrolling patients who may be taking excessive medications for headaches and, therefore, have altered pathophysiology and response to treatment.[31] Finally, our sample size was not powered to identify differences between groups for secondary outcomes. Although a number of these outcomes were clinically similar between groups (e.g. percentage improvement at 60 min, proportion who experienced headache relief and received rescue mediations, time to achieve a minimum clinically significant decrease in pain), there were potentially meaningful differences between groups that did not achieve statistical significance but may favor IV ketorolac (e.g. proportion who experienced headache freedom, sustained headache relief or headache freedom, use of rescue medications after ED discharge, and wanting same medication again). Further study is required to definitively determine whether there are differences in these headache-related outcomes.

## CONCLUSION

Intranasal ketorolac was non-inferior to IV ketorolac for reducing pain intensity in children with migraine headaches at 60 min after medication administration. Ketorolac administered by either route was effective in treating migraine headaches in children when assessed using a number of clinically important headache-related outcome measures.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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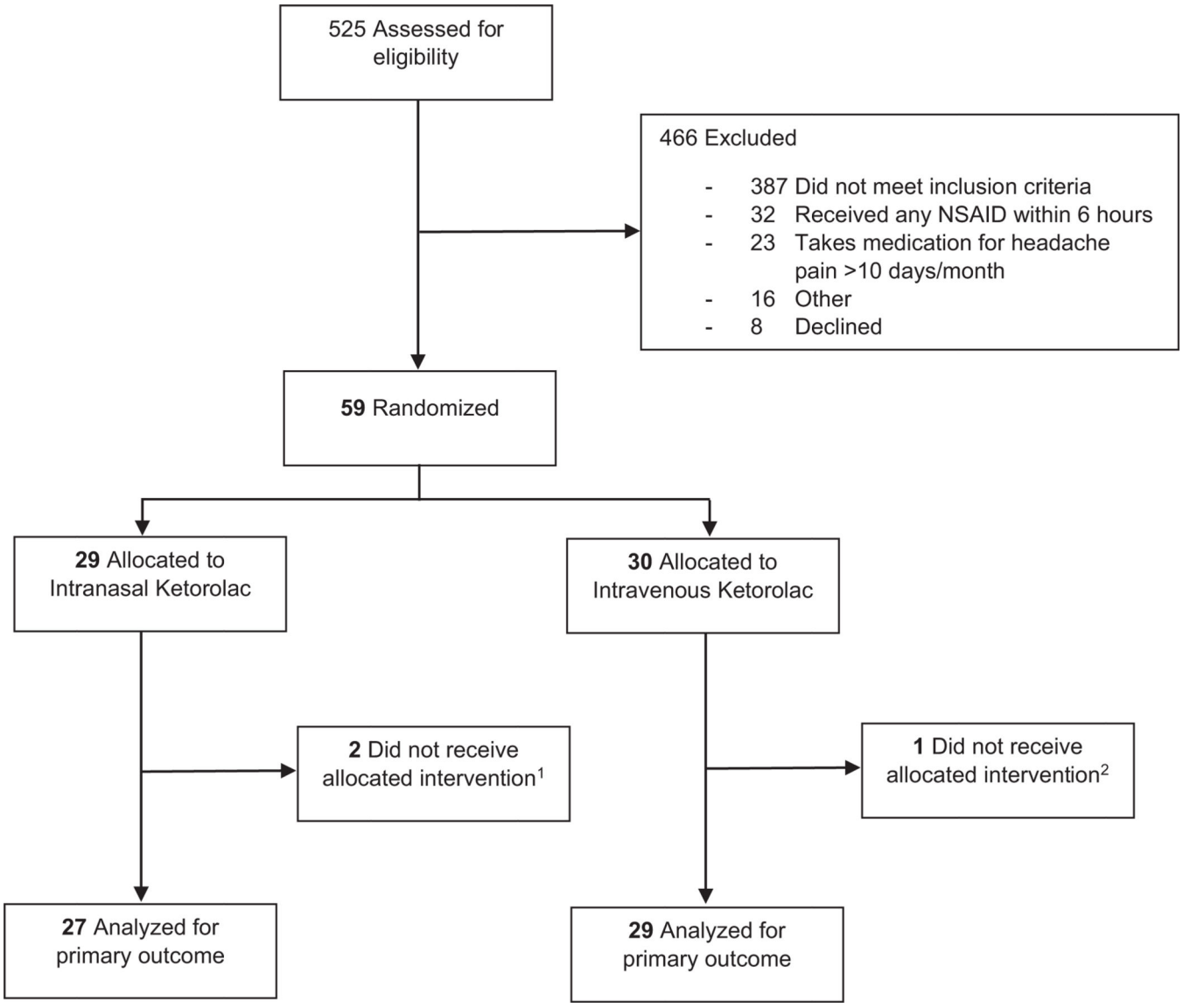


**FIGURE 1.**

Enrollment flow diagram. [1]One patient did not receive allocated intervention because headache pain resolved prior to study drug administration; the other patient had an exclusion criterion identified after enrollment and intervention was not administered. [2]Patient did not receive allocated intervention because headache pain resolved prior to study drug administration

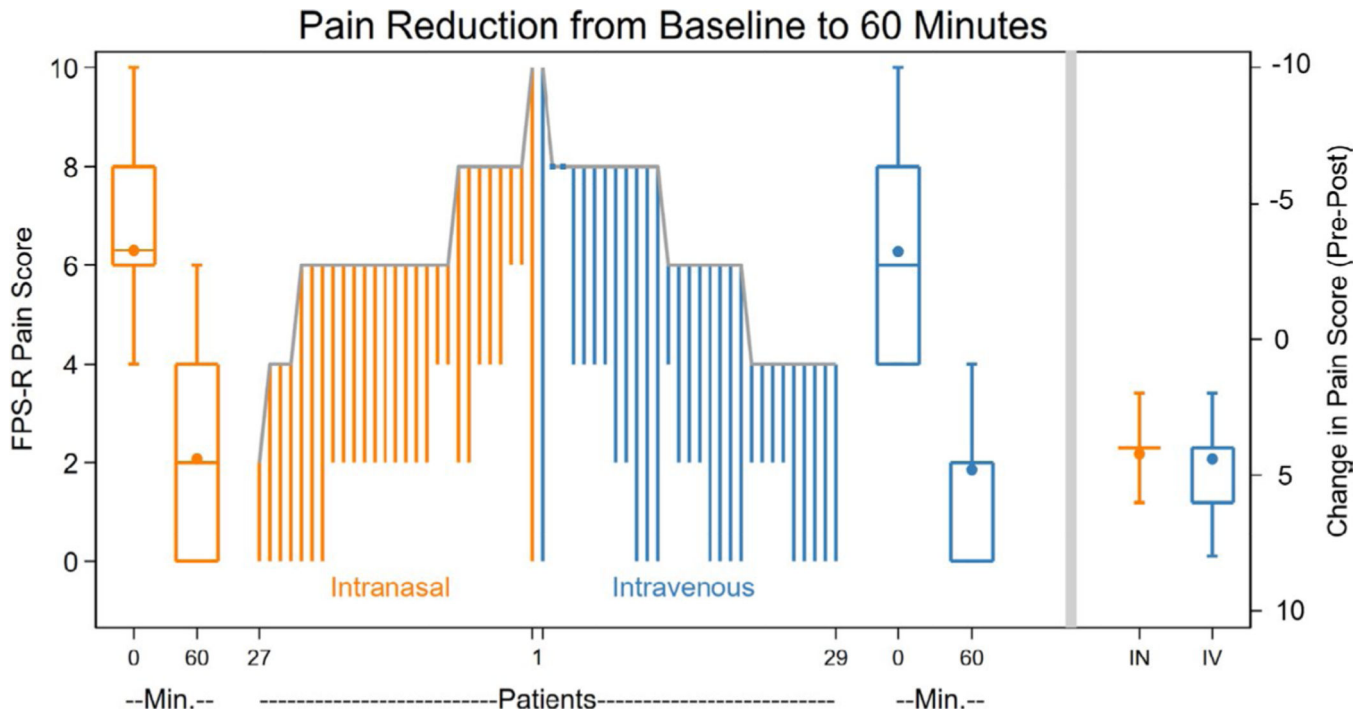


**FIGURE 2.**

Pain reduction associated with intranasal ketorolac and intravenous ketorolac at 60 min after study medication administration. The length of lines in the parallel line plot represents the magnitude of change in pain intensity for each patient. The boxplots to the left and right of the parallel line plot represent the pain scores at 0 and 60 min, with the middle line of each box representing the median, the box representing the interquartile range, the whiskers representing the range, and the dot representing the mean. The box plots on the far right represent the change in pain score from baseline to 60 min; a single line is portrayed for the IN group because of overlapping median and quartiles. FPS-R, Faces Pain Scale – Revised; IN, intranasal; IV, intravenous; Min., Minutes

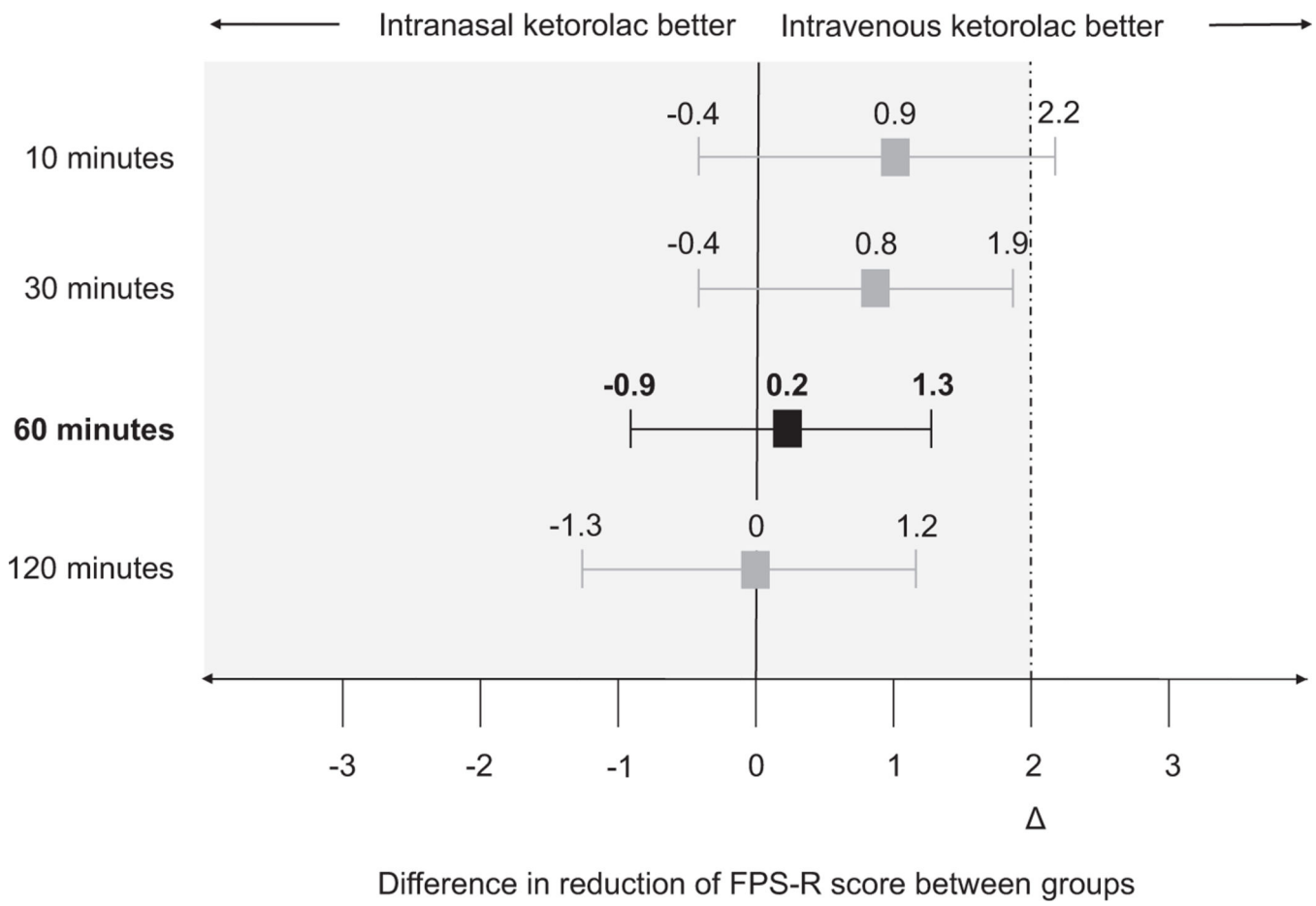


**FIGURE 3.**

Differences in pain reduction between intranasal and intravenous ketorolac. Pain intensity was measured using the FPS-R (scored 0–10). The upper limit of the 95% confidence interval for differences in mean pain reduction at 30, 60, and 120 min were less than the non-inferiority margin of 2, demonstrating non-inferiority(primary outcome = difference in pain reduction at 60 min). Non-inferiority determination at 10 min was inconclusive. Δ, Non-inferiority margin; FPS-R, Faces Pain Scale-Revised

**TABLE 1**

Patient characteristics

| | Intranasal Ketorolac n = 27 | Intravenous Ketorolac n = 29 |
|---|---|---|
| Age, median (IQR), years | 14 (11, 16) | 15 (11, 16) |
| Female, No. (%) | 17 (63) | 21 (72.4) |
| Weight, mean (SD), kg | 57.7 (16.9) | 63.7 (26.8) |
| Ethnicity/race, No. (%) | | |
| Hispanic | 24 (88.9) | 26 (89.7) |
| Black | 2 (7.4) | 0 |
| White | 0 | 3 (10.3) |
| Don't know | 1 (3.7) | 0 |
| Primary language, No. (%) | | |
| English | 24 (88.9) | 28 (96.6) |
| Spanish | 3 (11.1) | 1 (3.4) |
| Headache history, No. (%) | | |
| First headache of life | 5 (18.5) | 5 (17.2) |
| Headaches for <1 year, not first headache of life | 8 (29.6) | 9 (31.1) |
| Headaches for ≥1 year | 14 (51.9) | 15 (51.7) |
| Number of days per month with a headache, median (IQR)[a] | 3 (1, 6) | 3 (2, 6) |
| Number of days per month requiring medication for headache pain, median (IQR)[a] | 1 (1, 4) | 2 (1, 4) |
| Type of medication taken at home for headache prior to ED presentation No. (%) | | |
| Over-the-counter analgesic only | 26 (96.3) | 28 (96.6) |
| Prescription analgesic (+/− over-the-counter analgesic)[b] | 1 (3.7) | 1 (3.4) |
| Headache pain intensity at ED presentation, mean (SD)[c] | 6.3 (1.6) | 6.3 (1.8) |
| Functional disability at ED presentation, No. (%) | | |
| None | 3 (11.1) | 0 |
| Mild | 9 (33.3) | 9 (31) |
| Moderate | 9 (33.3) | 12 (41.4) |
| Severe | 6 (22.3) | 8 (27.6) |
| Family history of migraine headaches, No. (%)[d] | 20 (74.1) | 21 (72.4) |

Abbreviations: ED, emergency department; IQR, interquartile range; SD, standard deviation.

[a]Does not include patients with first headache of life; intranasal n = 22, intravenous = 22.

[b]Over-the-counter analgesics include acetaminophen, ibuprofen, naproxen, and combination analgesics (e.g. aspirin/acetaminophen/caffeine). Prescription analgesics include sumitriptan, metoclopramide, and topiramate.

[c]Measured using the Faces Pain Scale – Revised.

[d]First-or second-degree relatives (parents, siblings; grandparents, uncles, aunts) with migraine headaches.

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**TABLE 2**

Secondary headache-related outcomes

| | Intranasal Ketorolac | Intravenous Ketorolac | Difference in Means or Proportions |
|---|---|---|---|
| Decrease in pain intensity, mean (95% CI), units[a] | | | |
| 10 min | 1.7 (0.9, 2.5) | 2.6 (1.6, 3.6) | 0.9 (−0.4, 2.2) |
| 30 min | 2.9 (2.2, 3.6) | 3.7 (2.9, 4.5) | 0.8 (−0.4, 1.9) |
| *60 min (Primary outcome)* | *4.2 (3.6, 4.8)* | *4.4 (3.5, 5.3)* | *0.2 (−0.9, 1.3)* |
| 120 minutes[b] | 4.9 (4, 5.8) | 4.9 (4.1, 5.7) | 0 (−1.3, 1.2) |
| Time to minimum clinically significant decrease in pain, mean (95% CI), min[a] | 21.9 (15, 28.8) | 18.6 (12.7, 25) | −3.3 (−12.5, 6) |
| Ancillary ED outcomes[a] | | | |
| Receipt of ED rescue medications, No. (%) | 6 (22.2) | 5 (17.2) | −5 (−25.8, 15.8) |
| Headache relief, No. (%)[c] | 25 (92.6) | 26 (89.7) | −2.9 (−17.7, 11.9) |
| Headache freedom, No. (%)[d] | 11 (40.7) | 17 (58.6) | 17.9 (−7.9, 43.7) |
| Percentage improvement at 60 min, mean (95% CI)[e] | 69.8 (60.6, 78.9) | 71.8 (60.7, 82.9) | 2 (−12.7, 16.9) |
| 24-h follow-up outcomes[f] | | | |
| Want same medication again, No. (%)[g] | 19 (79.2) | 21 (95.4) | 16.2 (−2.3, 34.7) |
| Sustained headache relief, No. (%)[h] | 7 (29.2) | 12 (52.2) | 23 (−4.3, 50.3) |
| Sustained headache freedom, No. (%)[i] | 5 (20.8) | 8 (34.8) | 14 (−11.4, 39.4) |
| Use of rescue medications after ED discharge, No. (%)[j] | 12 (66.7) | 8 (42.1) | −24.6 (−52.2, 3) |
| Functional disability[k] | | | |
| 60 min, No. (%)[a] | | | |
| *None or mild* | *25 (92.5)* | *28 (96.5)* | *4 (−8, 16)* |
| None | 15 (55.6) | 13 (44.8) | −10.8 (−36.9, 15.3) |
| Mild | 10 (37) | 15 (51.7) | 14.7 (−11, 40.4) |
| Moderate | 2 (7.4) | 1 (3.5) | −3.9 (−15.8, 8) |
| Severe | 0 | 0 | NA |
| 120 min No. (%)[l] | | | |

| | Intranasal Ketorolac | Intravenous Ketorolac | Difference in Means or Proportions |
|---|---|---|---|
| *None or mild* | *18 (94.7)* | *22 (100)* | *5.3 (−4.8, 15.4)* |
| None | 11 (57.9) | 16 (72.7) | 14.8 (−14.2, 43.8) |
| Mild | 7 (36.8) | 6 (27.3) | −9.5 (−38.1, 19.1) |
| Moderate | 0 | 0 | NA |
| Severe | 1 (5.3) | 0 | −5.3 (−15.4, 4.8) |
| 24-h follow up, No. (%)[m] | | | |
| *None or mild* | *7 (100)* | *12 (100)* | *NA* |
| None | 7 (100) | 11 (91.7) | −8.3 (−23.9, 7.3) |
| Mild | 0 | 1 (8.3) | 8.3 (−7.3, 23.9) |
| Moderate | 0 | 1 (8.3) | 8.3 (−7.3, 23.9) |
| Severe | 0 | 0 | NA |

Abbreviations: CI, confidence interval; ED, emergency department; NA, not applicable.

The use of italicized values for functional disability were to distinguish the composite values from the non-composite values.

[a]Times listed are number of minutes after study drug administration at which pain intensity was assessed. Intranasal ketorolac = 27, intravenous ketorolac = 29.

[b]Analyzed patients who did not receive rescue medication or were not discharged prior to 120-minute assessment. Intranasal ketorolac = 20, intravenous ketorolac = 23.

[c]Change within 2 h of the patient's description of headache from severe or moderate to either mild or none, without the use of ED rescue medications.

[d]Achieving a headache description of none within 2 h, without the use of ED rescue medications.

[e](Baseline pain intensity – 60 min pain intensity)/baseline pain intensity.

[f]Patients who completed 24-h follow-up. Intranasal ketorolac = 24, intravenous ketorolac = 23.

[g]One patient in intravenous ketorolac group who completed follow-up did not give an answer to this question, so only 22 patients in intravenous ketorolac group analyzed.

[h]Patients whose headaches changed to either mild or none in the ED without the use of ED rescue medications, and maintained this level of relief (or better) without use of ED rescue medication or rescue medication after ED discharge.

[i]Patients who achieved a level of "none" within 2 h of study medication administration, and maintained this level for 24 h without use of ED rescue medication or rescue medication after ED discharge.

[j]Analyzed patients who completed 24-h follow-up and did not receive a rescue medication in the ED. Intranasal ketorolac = 18, intravenous ketorolac = 19.

[k]Assessed using standardized question detailed in Table S2.

[l]Patients removed from analysis if data missing, discharged home, or received ED rescue medications prior to 120-minute assessment. Intranasal ketorolac = 19, intravenous ketorolac = 22.

[m] Analyzed patients who completed 24-hour follow-up and did not receive ED rescue medication or rescue medication after ED discharge. Intranasal ketorolac = 7, intravenous ketorolac = 12.

**TABLE 3**

Adverse events

| | Adverse Events, No. | | | | | |
|---|---|---|---|---|---|---|
| | Total[a] | | Emergency Department[b] | | 24-hour Follow-Up | |
| **Symptoms** | **Intranasal Ketorolac** | **Intravenous Ketorolac** | **Intranasal Ketorolac** | **Intravenous Ketorolac** | **Intranasal Ketorolac** | **Intravenous Ketorolac** |
| Nausea | 2 | 1 | 0 | 1 | 2 | 0 |
| Dizziness | 1 | 1 | 0 | 0 | 1 | 1 |
| Sleepiness | 0 | 1 | 0 | 1 | 0 | 0 |
| Other[c] | 2 | 3 | 2 | 3 | 0 | 0 |
| Total | 5 | 6 | 2 | 5 | 3 | 1 |

[a]For the intranasal ketorolac group, 4 patients reported 5 adverse events. For the intravenous ketorolac group, 6 patients reported 6 events. Adverse events documented were not present prior to initial assessment at 60 min after study medication administration.

[b]Includes adverse events identified at 60 and 120 min after study medication administration.

[c]Other includes “feeling cold”, “less focus, feel off”, transient extremity sensory complaints.