Analgesic Efficacy of Intranasal Ketamine Versus Intranasal Fentanyl for Moderate to Severe Pain in Children
A Prospective, Randomized, Double-Blind Study

Kellie Quinn, DO,* Sabina Kriss, MD,* Jefferson Drapkin, BS,* Antonios Likourezos, MA, MPH,* Illya Pushkar, MPH,* Jason Brady, PharmD,† Matthew Yasavolian, MD,* Salil S. Chitnis, MD,* Sergey Motov, MD,* and Christian Fromm, MD*

Purpose: This study aimed to compare analgesic efficacy of intranasal (IN) ketamine to IN fentanyl for moderate to severe pain in children in a pediatric emergency department.

Methods: A prospective, randomized, double-blinded, noninferiority study evaluating children aged 3 to 17 years in a pediatric emergency department with acute moderate to severe pain was conducted. Patients received either 1 mg/kg of IN ketamine or 1.5 μg/kg of IN fentanyl and were evaluated after 10, 20, 30, and 60 minutes. The primary outcome was the degree of pain reduction after 20 minutes.

Results: Twenty-two patients were enrolled (11 in each group). Underlying pain conditions represented were musculoskeletal injury (73%) and abdominal pain (27%). At 20 minutes after analgesia, there was no significant difference in pain scores between the fentanyl (median, 2; range, 0–8) and ketamine groups (median, 4; range, 0–7; P = 0.20). The ketamine group showed a significantly greater rate of adverse effects, 73% versus 9% (P = 0.002), and throughout the course of the study period, 7 patients in the ketamine group (64%) showed some degree of sedation versus no one in the fentanyl group (P = 0.004).

Conclusions: There was insufficient power to support the analgesic noninferiority of IN ketamine at a dose of 1 mg/kg compared with IN fentanyl at a dose of 1.5 μg/kg in children experiencing painful conditions at 20 minutes after administration. Intranasal ketamine was found to be inferior to IN fentanyl in relieving pain at 10 minutes and was found to have significantly greater rates of sedation and dizziness.

Key Words: pain, analgesia, ketamine

Intranasal (IN) delivery of analgesic agents can provide relatively rapid and simplified drug administration. For children experiencing significant pain, the placement of an intravenous (IV) catheter to provide parenteral analgesia often increases patient anxiety and pain, is time consuming, and can be technically challenging requiring multiple attempts. As such, the IN route of medication administration is particularly advantageous in the setting of a busy emergency department (ED), particularly for children.

Intranasal delivery of fentanyl has become more commonly used in children’s pain management in many settings, including prehospital and ED scenarios. Over the past decade, ED studies have demonstrated that IN fentanyl is as effective as IV morphine to treat acute moderate to severe pain, making the use of IN fentanyl more commonplace in pediatric EDs. Likewise, ketamine, when used at subdissociative doses, has recently been reported to successfully treat pain in both children and adults. This information suggests that IN ketamine can readily provide an efficacious, nonopioid alternative for pain management in pediatric emergency care. Nonetheless, medical literature on pediatric usage of IN ketamine for analgesia, rather than sedation, is limited.

Intranasal delivery is optimized with low-volume, high-concentration medications for absorption through the highly vascular surface area of the nasal mucosa. Intranasal fentanyl is frequently given in a concentration of 50 μg/mL, making the IN efficacy decrease with larger volumes required for patients of increasing weight. Ketamine has the advantage of being available at a higher concentration (100 mg/mL), thus providing a lower-volume option than fentanyl for patients of equivalent weight.

In this study, we hypothesized that IN ketamine (dose of 1 mg/kg) provides equivalent analgesia versus IN fentanyl (dose of 1.5 μg/kg) in the treatment for pediatric patients with acute moderate to severe pain in the ED.

METHODS

Study Design

Our study was a prospective, randomized, double-blinded noninferiority active control trial comparing the analgesic efficacy of IN ketamine with IN fentanyl for acute moderate to severe pain for pediatric patients in the ED. This study was approved by the Maimonides Medical Center Institutional Review Board and registered with ClinicalTrials.gov (NCT02388321). The study was performed and was reported according to the CONSORT statement.

Study Setting and Population

The study was conducted at a 711-bed community teaching hospital with an annual ED census of more than 120,000 visits, approximately 36,000 of which are pediatric visits. Study investigators performed patient screening, enrollment, and data collection. The patient randomization list was generated before commencement of the study by the research manager and maintained by the ED pharmacy investigators, who prepared the medication and delivered it to the nurse or physician caring for the study participant in a blinded manner.

Enrollment of a convenience sample of patients occurred from May 2015 to November 2016. Screening and enrollment took place Monday through Friday 8 AM to 8 PM when an ED pharmacist was available for blinded medication preparation. Study investigators approached all potentially qualifying participants after they were evaluated by the treating pediatric emergency physician and determined to meet study inclusion criteria.

The study included patients aged 3 to 17 years, of weight less than 64 kg, presenting to the ED with acute moderate to severe pain, defined as at least 6 on a total 11-point (0–10) Numeric Rating Scale (NRS) or equivalent Wong-Baker Faces Pain Scale, and being of sufficient intensity to require opioid analgesia as
determined by the treating ED attending physician. Exclusion criteria included children with facial trauma or any abnormality of the nasal anatomy, circulatory insufficiency, developmental delay, head trauma/increased intracranial pressure/alteration of consciousness, known allergy to fentanyl or ketamine, inability to provide pain scale assessment, and receipt of opioid pain medication immediately before arrival to the ED.

Study Protocol
Each patient received written informed consent and each case complied with Health Insurance Portability and Accountability Act of 1996 authorization after being evaluated by the treating ED physician and determined to meet study eligibility criteria.

If English was not the participant’s primary language, professional interpreter services were used. For patients aged 8 to 17 years, an enrollment initial pain scale score was determined using an 11-point NRS (0–10) described to the patient as “no pain” being 0 and “the worst pain imaginable” being 10. For patients aged 3 to 7 years, initial pain scale score was determined using a Wong-Baker FACES Pain Scale, with 6 face options—labeled “no hurt” to “hurts worst,” corresponding to 0, 2, 4, 6, 8, and 10 on the NRS.11 A patient was eligible for enrollment when this initial pain scale score was 6 or higher on either scale.

Participants were allocated to 2 groups according to a predetermined randomization list that was generated using SPSS 19.0 by the research manager. The on-duty ED pharmacist prepared either 1 mg/kg of ketamine (100 mg/mL concentration) or 1.5 μg/kg of fentanyl (50 μg/mL concentration) in a 1-mL syringe. Ketamine containing syringes were prepared by dilution with normal saline to make an equivalent volume to a syringe containing fentanyl. There was no color, viscosity, or odor distinction between the medications. Volumes of each medication were calculated based on patients’ body weight rounded to the nearest kilogram. Syringe and nasal atomization devices were delivered to the treating nurse or physician in a blinded fashion.

The medication was administered in a protocolized manner, discharging approximately half the total dose in each naris. The medication-preparing pharmacist, research manager, and biostatistician (all offsite of the ED) were the only members of the team with knowledge of the study arm to which the participant was randomized, leaving the providers, participants, and study investigators blinded to the medication received. Blinding was strictly maintained by the on-duty ED pharmacist. Study investigators recorded pain scores, vital signs, adverse effects, and degree of sedation at the time of medication administration and at 10, 20, 30, and 60 minutes after medication administration. The requirement for rescue analgesia was assessed at each time point. If patients or parents requested additional pain relief, an IV catheter was placed and 1 mg/kg of parenterally administered morphine was given.

The degree of sedation was assessed by study investigators using the University of Michigan Sedation Scale, which has been validated in children.11 Scores were determined as follows: 0, awake and alert; 1, minimally sedated; 2, moderately sedated; 3, deeply sedated; and 4, unarousable.

Data including demographic profile, ED vital signs, preenrollment analgesic medication received, and sedation level were recorded for each patient and entered into SPSS 24.0 by the research manager (IBM SPSS Statistics for Windows, Version 24.0; IBM Corp, Armonk, NY).

Outcome Measures
The primary outcome measure was comparative reduction of NRS or Wong-Baker FACES pain scores between recipients of IN ketamine and fentanyl at 20 minutes after the administration of the respective analgesic medication. Secondary outcome measures included change in pain scale score at 10, 30, and 60 minutes. In addition, vital signs, adverse effects, and sedation scale score were analyzed. The treating physician was asked to guess as to which treatment had been given as a check on the blinding.

Data Analysis
The data were summarized by the use of descriptive statistics, using frequency (percentages) for all categorical variables, mean (SD) for all normally distributed variables, and median with lower and upper ranges for nonnormal continuous variables. Simple group comparisons were done using either the Student t test, Mann-Whitney test, or the χ² test, where appropriate. Pain ratings from the Wong-Baker FACES pain scale and NRS were combined and compared between groups using a generalized linear model to look at differences over time relative to baseline. A similar analysis plan was used to test for group differences for all other outcomes over time, with either a generalized linear model in the case of nonnormal outcomes (eg, feeling of unreality) or mixed-model regression in the case of normally distributed outcomes (eg, blood pressure). Levels of significance were tested at P ≤ 0.05. Analyses were conducted using SAS 9.4 (SAS Inc, Cary, NC) and IBM SPSS Statistics for Windows Version 24 (IBM Corp).

Sample size was calculated based on the premise that this was a noninferiority trial with change in pain scale score as the primary outcome; a 2-point difference was selected to define the margin of noninferiority based on established clinically significant change in acute pain in children.12 Assuming an SD of 3.0, a sample size of 58 (29 in each group) provided 80% power to detect a difference of 2 points on the pain scale with an α of 0.05.

RESULTS
A total of 22 patients were enrolled (11 received IN fentanyl and 11 received IN ketamine). The patient flow diagram is illustrated in Figure 1. Table 1 shows no significant differences in demographic or clinical characteristics between groups; In addition, median enrollment pain scale scores were virtually identical (median for both groups, 8; P = 0.95). Because of a manufacturer recall of the study atomizers in the beginning of November 2016 and an inability to order properly functioning atomizers for continuation of the study, a decision was made to terminate the trial and un-blind the data that had been collected.

Figure 2 shows the boxplots for the pain scores at each time point. At the primary time point of 20 minutes after analgesia, there was no significant difference relative to baseline in the in pain scale score between the fentanyl (median, 2; range, 0–8) and the ketamine group (median, 4; range, 0–7; P = 0.20). Eight patients in the fentanyl group (73%) reported a pain score of lower than 4 versus 5 (46%) in the ketamine group. The median difference was within the margin of noninferiority. Unfortunately, the comparison was insufficiently powered to make any conclusions with regard to noninferiority.

At 10 minutes after analgesia, median pain scores in the fentanyl group were found to be 3 points lower than in the ketamine group. Median pain scores for the fentanyl group had declined to 3 points (range, 0–6), whereas median pain for the ketamine group was 6 points (range, 0–8; P = 0.04 relative to baseline). Seven patients (64%) in the fentanyl groups had pain scores lower than 4 at 10 minutes versus 2 (18%) in the ketamine group. That the level of pain in the ketamine group at 10 minutes was substantially worse than that in the fentanyl group led us to conclude that the assumption of noninferiority for the ketamine group did not hold.
There were no further significant differences between the fentanyl and ketamine groups at 30 minutes (medians, 1 and 2, respectively; \( P = 0.18 \)) or at 60 minutes (both medians, 2; \( P = 0.50 \)). Again, because of insufficient power, no conclusions with regard to noninferiority were possible. Secondary analyses showed no significant interactions depending on whether the Wong-Baker FACES or an NRS was used to measure pain.

The ketamine group showed significantly higher levels of sedation on the Michigan University scale throughout the course of the study period (\( P = 0.007 \)). Seven patients (64%) in the ketamine

**TABLE 1.** Demographics and Clinical Characteristics of Patients at Time of Enrollment

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Fentanyl</th>
<th>Ketamine</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>9.58 (2.92)</td>
<td>9.77 (2.51)</td>
<td>0.87</td>
</tr>
<tr>
<td>Male sex</td>
<td>8 (73%)</td>
<td>10 (91%)</td>
<td>0.27</td>
</tr>
<tr>
<td>Baseline pain</td>
<td>8 (6–10)</td>
<td>8 (5–10)</td>
<td>0.95</td>
</tr>
<tr>
<td>Cause of pain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>8 (73%)</td>
<td>8 (73%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Abdominal</td>
<td>3 (27%)</td>
<td>3 (27%)</td>
<td></td>
</tr>
<tr>
<td>Pretreatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>2 (18%)</td>
<td>2 (18%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>2 (18%)</td>
<td>2 (18%)</td>
<td></td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>101.1 (20.1)</td>
<td>94.4 (10.4)</td>
<td>0.34</td>
</tr>
<tr>
<td>Respiratory rate, breaths/min</td>
<td>18.4 (1.80)</td>
<td>22.2 (5.5)</td>
<td>0.05</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic</td>
<td>63.8 (7.2)</td>
<td>69.9 (9.9)</td>
<td>0.14</td>
</tr>
<tr>
<td>Systolic</td>
<td>111.2 (10.4)</td>
<td>114.9 (9.9)</td>
<td>0.48</td>
</tr>
</tbody>
</table>

**FIGURE 1.** Patient flow diagram.
group showed at least 1 instance of sedation compared with 2 (18%) in the fentanyl group. The difference in sedation levels was especially marked at 20 minutes where 7 patients in the ketamine group (64%) group showed some degree of sedation versus no one in the fentanyl group (P = 0.004). Six patients in the ketamine group showed minimal sedation, and one showed moderate sedation. Similarly, the ketamine group showed a significantly greater rate of adverse effects: 73% versus 9% (P = 0.002). The most common adverse effect was dizziness, which was seen in 64% of the patients in the ketamine group and 9% of the patients in the fentanyl group (P = 0.02). Dizziness was most marked at 30 minutes where it affected 46% of the patients in the ketamine group versus 9% of patients in the fentanyl group.

No morphine (rescue medication) was needed for either group at any time point. In addition, there were no significant differences or changes in terms of vital signs in either group. Finally, there was no significant difference in the rate of correct guesses on behalf of treating physicians with respect to treatment group: 54% in the case of the fentanyl group versus 64% in the ketamine group (P = 0.67).

DISCUSSION

Ketamine is widely used for sedation in pediatric EDs and published literature has reported its efficacy when administered via the IN route for decades. In 1993, Weksler et al found that 6 mg/kg of IN ketamine for sedation for elective surgical procedures had similar sedative effects to standard pharmacologic means of achieving sedation. In 1997, Diaz found that IN ketamine at a dose of 3 mg/kg improved preoperative cooperation in children versus placebo.

Ketamine has recently been shown to be an important nonopioid option for adult pain management. In adults, a range of subdissociative doses have been shown to be effective, most recently 0.3 mg/kg IV. With a bioavailability of approximately 45% when administered IN, the optimal IN dose is not yet established. In a dose-discovery observational pilot study conducted in 2013, investigators found that IN ketamine (1 mg/kg) provided clinically significant analgesia in children with limb injuries. Adverse effects related to IN ketamine were transient and nonsevere, with dizziness (37%) and poor taste (27%) most commonly reported. A similar study in 2014 found that in 40 adult patients, the median dose of IN ketamine required to produce clinically significant pain relief was 0.98 mg/kg. The first reported clinical trial comparing IN fentanyl (1.5 μg/kg) to IN ketamine (1 mg/kg) for the treatment of pediatric pain caused by isolated musculoskeletal injury found no clinical or statistical difference between pain relief provided between medications.

In this prospective, randomized, double-blinded study, we compared analgesic efficacy of IN fentanyl with that of IN ketamine in a pediatric population. Two of the most common pediatric conditions requiring analgesia in an outpatient setting, musculoskeletal injury and abdominal pain, were exclusively represented in our study demographic. Based on analysis of the data from the 22 patients enrolled, our results suggest that IN ketamine was found to be as effective as IN fentanyl in relieving pain at 20 minutes after administration. In addition, there was no difference between treatment groups in rates of required administration of rescue analgesic medication.

Although no patient in either group experienced clinically concerning adverse effects or changes in vital signs, there were significantly more adverse effects and a higher level of sedation recorded in the ketamine group than in the fentanyl group. Prior studies of IN fentanyl report similar adverse effect profiles. The dose of ketamine may need to be investigated further to determine if there is a lower dose that will effectively treat pain while reducing the sedative effects. Future research may also benefit from assessment of IN ketamine as an adjunct to IN fentanyl or other analgesic medication.

CONCLUSIONS

Intranasal ketamine at a dose of 1 mg/kg provides similar analgesia to IN fentanyl at a dose of 1.5 μg/kg in children at 20 minutes after administration. However, IN ketamine administration was associated with significantly greater rates of sedation and dizziness. Further investigation is warranted to determine optimal dosing of ketamine to provide maximal analgesia while minimizing sedation.

LIMITATIONS

This is a single-center study in which patients were enrolled as a convenience sample based on availability of members of both the ED research and pharmacy teams. This may have led to selection bias or underrepresentation of patients who may present to the ED late at night. There was also potential for confounding of clinician blinding because some participants exhibited ketamine-specific reactions (eg, nystagmus). Sampling was skewed toward male sex, perhaps reflecting greater propensity toward accidental injury; it is unclear if sex-specific response to IN analgesia exists. Our stringent exclusion criteria and sample size of 22 subjects were inadequate to assess variance in safety of the 2 different administration routes of study medication. Furthermore, we were unable to reach our enrollment goal of 58 subjects partly due to manufacturer recall on the IN study atomizers. Lastly, our sample size was not powered to analyze differences between types of pain. It is possible that visceral pain, such as abdominal pain, responds differently to either or both medications, as compared with somatic pain.

ACKNOWLEDGMENTS

The authors thank John Marshall, MD, and Hector Vazquez, MD, for their support and guidance; Nechama Rothberger, PharmD, for medication administration to study patients; Rukhsana Hossain, MPH, and Mo Mai, MD, for assisting in data collection; Peter Homel, PhD, for statistical guidance; and all the volunteers for their assistance. They also acknowledge and thank all the ED nurses for their tireless help and support of this project.

REFERENCES


