Randomized Controlled Feasibility Trial of Intranasal Ketamine Compared to Intranasal Fentanyl for Analgesia in Children with Suspected Extremity Fractures

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Running Title: Intranasal Ketamine vs. Fentanyl for Pediatric Fractures

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acute pain into a randomized trial conducted under US regulations. All patients were monitored until 6 hours after their last dose of study drug, or until admission to the hospital ward or operating room.

**Results:** Of 629 patients screened, 87 received the study drug and 82 had complete data for the primary outcome (41 patients in each group). The median age (interquartile range) was 8 (3) years and 62% were male. Baseline pain scores were similar among patients randomized to receive ketamine (73 ± 26) and fentanyl (69 ± 26) [mean difference (95% CI): 4 (-7 to 15)]. The cumulative number of side effects was 2.2 times higher in the ketamine group, but there were no serious adverse events and no patients in either group required intervention. The most common side effects of ketamine were bad taste in the mouth (37; 90.2%), dizziness (30; 73.2%), and sleepiness (19; 46.3%). The most common side effects of fentanyl were sleepiness (15; 36.6%), bad taste in the mouth (9; 22%), and itchy nose (9; 22%). No patients experienced respiratory side effects. At 20 minutes, the mean pain scale score reduction was 44 ± 36 for ketamine and 35 ± 29 for fentanyl [mean difference: 9 (95% CI: -4 to 23)]. Procedural sedation with ketamine occurred in 28 ketamine patients (65%) and 25 fentanyl patients (57%) prior to completing the study.

**Conclusions:** Intranasal ketamine was associated with more minor side effects than intranasal fentanyl. Pain relief at 20 minutes was similar between groups. Our data support the feasibility of a larger, non-inferiority trial to more rigorously evaluate the safety, efficacy, and potential opioid sparing benefits of intranasal ketamine analgesia for children with acute pain.

**Trial Registration:** ClinicalTrials.gov (NCT02521415)
INTRODUCTION

Intranasal analgesia allows for rapid drug administration without the delay or discomfort associated with establishing intravenous (IV) access. Intranasal fentanyl is the most frequently used intranasal analgesic, though the supporting evidence originates from small prospective trials. Sub-dissociative ketamine, used for adults in the battlefield, post-operative, and emergency department settings, may offer a safe and efficacious non-opioid alternative for acute traumatic pain among children. Ketamine has been endorsed for its potential ability to offer multimodal analgesia rather than the targeted therapy, focused solely on the opioid receptors as offered by opioid medications. Ketamine is known to interact with multiple receptors, including the N-methyl-D-aspartate receptor. Ketamine is postulated to reduce central sensitization to pain, prevent opioid-induced hyperalgesia, and possibly decrease overall opioid utilization. However, the current evidence does not adequately support or refute the ability of ketamine to provide safe and effective analgesia or to spare opioid utilization in the treatment of children with acute pain.

It is also unclear from the current evidence if ketamine is an emerging first line analgesic or should be relegated to second line, or adjunctive, therapy behind intranasal fentanyl and intravenous morphine. Several prior studies have compared intranasal fentanyl to intravenous morphine and support the use of intranasal fentanyl in the pediatric emergency department (ED) setting and for fracture pain specifically. A retrospective study of 617 children in a tertiary pediatric ED compared the utilization trends between intranasal fentanyl and IV morphine and reported a reduction in IV morphine use and significantly reduced time to analgesia after intranasal fentanyl was introduced. A prospective, randomized, double-blind, placebo-controlled, clinical trial in a pediatric ED in 2007 concluded that intranasal fentanyl at a dose of

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1.7 μg/kg was as effective for analgesia as IV morphine at 0.1 mg/kg for fracture pain. Several other studies support the use of intranasal fentanyl as a first line agent for analgesia because it reduces time to analgesic administration and appears to be as effective as morphine.

The comparative efficacy of intranasal sub-dissociative ketamine to intranasal fentanyl for treatment of acute pain in children has been examined previously in only a single randomized controlled trial of 73 patients conducted in Australia. This trial was an important first step in introducing intranasal sub-dissociative ketamine to the pediatric emergency care setting. However, the trial was powered around a large effect size, and was stopped early before meeting the calculated sample size. While there was no observed difference in efficacy between ketamine and fentanyl, the trial was too small to support the stated conclusion that intranasal fentanyl and ketamine were associated with similar pain reduction in children with moderate to severe pain from limb injury. This study reported a substantial difference in rates of minor adverse events between ketamine (78%) and fentanyl (40%) and, therefore, raises the possibility that ketamine may be less well tolerated by patients despite its hypothesized, but unproven, advantages in mitigating the response to pain. The study was further underpowered to detect a difference in serious adverse events, though no serious adverse events were reported.

A multicenter, non-inferiority trial of intranasal ketamine compared with intranasal fentanyl will be required to a) draw a valid conclusion regarding the comparative efficacy of the agents; b) establish serious adverse event rates; and c) examine ketamine’s role in limiting downstream opioid utilization. Such a large trial may not be worth the investment if there is an unacceptably high difference in the tolerability of the two drugs. As such, the goals of this investigation were: 1) examine the feasibility of enrolling children presenting to the ED in acute pain into a randomized trial of intranasal ketamine vs. intranasal fentanyl conducted under US
regulations; 2) compare the tolerability of the study drugs; and 3) provide data necessary to calculate the required sample size for a non-inferiority trial investigating the outcomes of safety, efficacy, and differences in downstream opioid utilization between the two drugs.

METHODS

Study Design and Setting

This double-blind, randomized controlled trial compared intranasal sub-dissociative ketamine (1 mg/kg) to intranasal fentanyl (1.5 micrograms/kg) for analgesia in children presenting to the ED with acute pain from a suspected, single extremity fracture. These doses are based on prior trials and the bioavailability of the drugs.\(^2,5,16,21\) The trial was conducted at the Levine Children’s Hospital Emergency Department in Charlotte, North Carolina, USA, an urban, tertiary, pediatric level II trauma center, with more than 35,000 pediatric ED visits per year. The study protocol was reviewed and approved by the United States Food and Drug Administration (Investigational New Drug application #127351), the Carolinas HealthCare System Institutional Review Board (IRB), and the study-specific Data Safety Monitoring Board (DSMB). The study design met the criteria for waiver of assent and required the consent of only a single parent or guardian. The protocol was registered with clinicaltrials.gov prior to study initiation (NCT02521415). This work was supported by an internal grant from the Carolinas Trauma Network Research Center of Excellence at Carolinas Healthcare System. This project was also supported in part by the Health Resources and Services Administration, Maternal and Child Health Bureau, Emergency Medical Services for Children Targeted Issues grant program, Grant No. H34MC26201.
**Study Population**

Verbal children ages 4–17 years with a suspected, single extremity fracture requiring analgesia were screened for enrollment by ED triage nurses. A suspected fracture requiring analgesia was defined as deformity or pain to palpation in a single extremity in a patient with an initial Wong-Baker FACES Pain Scale Score of 4 or greater (for patients 4–10 years) or an Adult Pain Rating Scale score of at least 3 (for patients ages 11–17). These specific pain scales and thresholds are used at our institution to determine which patients qualify for analgesic administration in triage. The treating physician also had to agree that the patient’s presentation warranted narcotic pain medication.

We initially planned to enroll only children with suspected forearm fractures, but amended our protocol to include children with suspected fractures of any single extremity to increase patient accrual after enrolling only 12 patients in the first three months of the study. We excluded patients with any of the following: Glasgow Coma Scale < 15 at ED presentation, reported allergy or adverse reaction to ketamine or fentanyl, pregnancy, intoxication, age-adjusted hypotension at presentation (defined as systolic blood pressure less than 70 mmHg + 2x age for patients under 10 years old, or less than 90 mmHg for those greater than 10 years of age), weight > 70 kg, opioid analgesia administered prior to arrival, multiple injuries, non-verbal from developmental delay, or aberrant nasal anatomy that precluded intranasal medications.

**Study Protocol**

The complete study protocol has been published separately. Patients were randomized to receive either 1 mg/kg intranasal ketamine (Ketalar 50 mg/mL) or 1.5 micrograms/kg intranasal fentanyl (fentanyl citrate 50 µ/mL), administered per a standard dosing table. To avoid runoff and swallowing, we allowed a maximum volume of 1 mL of drug to be...
administered in each nostril. Both study drugs are odorless and similar in color and were administered in similar volumes with identical syringes attached to a mucosal atomizer device. As shown in Table 2, the drugs rarely displayed neuropsychological effects and both drugs caused dysphoria. No patient experienced dissociation as defined as nystagmus. At the discretion of the treating physician, patients could receive a second dose of study drug at least 20 minutes after the first dose (intranasal ketamine at 0.5 mg/kg or intranasal fentanyl at 0.75 µg/kg). After patients received two doses of study drug, additional analgesics were administered at the discretion of the treating physician. All patients also received un-blinded oral acetaminophen 15 mg/kg (maximum dose of 650 mg) or ibuprofen 10 mg/kg (maximum dose 600 mg).

Local pharmacy regulations required that the clinical nurse caring for the patient draw up and administer the study drug. As such, the clinical nurse was un-blinded. However, the physicians, patients, research associates, and investigators were all blinded to group allocation. A research nurse with an administrative role in the study was responsible for reviewing the clinical nursing documentation to ensure compliance with required regulations. The research nurse remained un-blinded throughout the study, and served as liaison to the investigational pharmacy and DSMB. All study measures and outcomes were assessed and recorded by a blinded research team member. Additional detail on measures taken to ensure allocation concealment and blinding is available in the published study protocol.

The study statistician generated the allocation list using permuted blocks of random size stratified by age (4–10 years and 11–17 years) with 1:1 allocation via the RANUNI function in SAS Enterprise Guide version 6.1 (SAS Institute Inc., Cary, NC, USA). Allocation was concealed in opaque, sequentially numbered study packets.
Measurements

All coordinators were trained on the study measures and procedures prior to study initiation and at monthly research staff meetings until enrollment was complete. Research coordinators used a standardized checklist to document adverse events and side effects every 5 minutes for the first 30 minutes following study drug administration, then every 30 minutes for the next two hours, and again at 6 hours or at the time of ED discharge. Six-hour measurements included adverse event reports from procedural sedation if performed in the ED prior to discharge. This endpoint was based on pilot data that demonstrated most fracture patients complete their ED stay in 6 hours. Vital signs and pain scores were recorded by the research coordinators at baseline and every 10 minutes for the first 30 minutes following study drug administration and then every 30 minutes for the next two hours. We assessed pain severity with two commonly used pediatric pain assessment tools: Faces Pain Scale - Revised (FPS-R) for children ages 4–10 years and the Visual Analog Scale (VAS) for children ages 11–17 years. These tools were selected due to their prior validation for pediatric research use. Study data were collected on a structured case report form and managed using Research Electronic Data Capture (REDCap) tools hosted at Carolinas HealthCare System.

Outcomes

We determined in advance that further study would not be feasible if enrollment targets could not be met within one year; if a difference in efficacy was observed; or if the cumulative side effect rate among those randomized to receive ketamine was more than three times that of those in the fentanyl group. This tolerability threshold was determined by investigator consensus based on the relative differences observed in the PICHFORK trial. Since most reported side effects were minor and did not result in study withdrawal, and given the hypothesized benefits of
ketamine analgesia, we believe this increase in minor effects to be acceptable. The primary outcome (rates of adverse events within 60 minutes after study drug delivery) was chosen as a measure of tolerability of the interventions. Adverse events were defined a priori. Dissociation was defined as the presence of nystagmus. The efficacy outcome was the reduction in pain scale scores at 20 minutes; however, additional time points were collected and analyzed for future trial planning. The comparative efficacy of the two drugs was an exploratory measure as the study was not powered to detect a difference in this outcome.

Additional secondary outcome measures were: 1) the proportion of patients in each group achieving a pain score reduction of at least 20/100 (the minimum clinically significant reduction in pain) at 20 minutes after study drug administration; 2) the proportion of patients in each group requiring a second dose of study drug; and 3) total dose of opioid pain medication in morphine equivalents/kg/hour (excluding study drug) required during the ED stay. The ED stay was defined as the time from ED presentation to a procedure requiring ketamine (sedation) or disposition out of the department. This time interval established the number of hours during which patients could require rescue analgesia. The FPS-R and VAS scales were merged for analysis as supported by a prior study and are reported as values from 0 to 100. The minimum clinically significant reduction in pain was defined as a decrease of 20, adapted from prior pediatric studies of the minimum clinically significant pediatric pain score reduction. Doses of rescue opioids administered in the ED were standardized for analysis by calculating the morphine equivalents/kg/hour to account for the specific medication, patient size, and the ED length of stay. Most procedural sedation for fractures at our institution utilizes ketamine; therefore, opioid administration between groups after this time should be equivalent. Details of opioid medications (names, doses, and routes of administration) given in the ED were abstracted.
from the electronic medical record and the morphine equivalents calculated using standard conversion tools.\textsuperscript{31-32} The results of radiographs and treatment interventions specific to fractures (defined as hematoma block, splinting/casting, and admission for operative intervention) were collected and compared between groups as in Table 1.

**Data Analysis**

Intention to treat principles were applied. With 40 children randomized to each group, we have greater than 90\% power to detect a difference in overall adverse events using a two-sided, two-sample test of proportions.\textsuperscript{22} We assumed an adverse rate of 40\% in the fentanyl group and 78\% in the ketamine group based on the rates in the PICHFORK trial.\textsuperscript{2} No formal power analyses were conducted for the outcome of pain reduction, but our data will provide sufficient numbers to estimate standard deviations for a larger trial.\textsuperscript{22} We did not initially adjust for attrition or loss to follow-up because of the short time patients were followed for cumulative effects, though we did subsequently increase enrollment due to missing data for our primary outcome.\textsuperscript{22}

The primary analysis compared the proportion of adverse events among children randomized to receive either intranasal sub-dissociative ketamine or intranasal fentanyl for pain control in the ED. Proportions and 95\% confidence intervals were calculated for each adverse event and compared using the chi-square test or Fisher’s exact test.

The FPR-S and VAS scores were merged for analysis and the differences in mean reduction were reported as raw scores. We estimated the mean difference in pain reduction between the two intervention groups and corresponding 95\% confidence intervals. Repeated measures analysis of variance (ANOVA) with a between-group factor of treatment group was performed to examine whether the magnitude of change in pain scores over time differed by
treatment group. Wilcoxon rank sum test was used to compare the median total dose of opioid pain medication in morphine equivalents/kg/hour required during the ED visit between groups. We hypothesized the ketamine group would have lower use of opioid pain medication. SAS® Enterprise Guide® 6.1 (SAS Institute Inc., Cary, NC, USA) was used for all analyses. A two-tailed p-value of less than 0.05 was considered statistically significant.

RESULTS

Characteristics of Study Subjects

Figure 1 summarizes the participant flow through the trial. We screened 629 patients for eligibility, enrolled 91, and 87 received the study drug, including 43 in the ketamine group and 44 in the fentanyl group. Table 1 displays baseline characteristics of the enrolled patients. The groups were similar in terms of age, gender, race, ethnicity, injury pattern, and baseline pain score. All patients received adjunctive analgesia with acetaminophen or ibuprofen. Fracture management, including rates of hematoma block, splinting/casting, and admission for operative intervention, was comparable between groups. The most common injuries were displaced forearm fractures. Five patients, including three in the ketamine group and two in the fentanyl group, had no fracture on x-ray, including one patient with a complex laceration requiring repair under sedation.

Main Results

The study met target enrollment in 11 months. Blinding was preserved in all subjects. Data for the primary outcome could not be obtained at the specified time point of 60 ± 10 minutes for two patients in the ketamine group and 3 patients in the fentanyl group due to competing clinical care priorities. The cumulative number of side effects was 2.2 times higher in
the ketamine group, which was below the a priori specified tolerability threshold of 3. No patient in either group experienced a serious adverse event, and none of the side effects required intervention. There was no observed difference in efficacy between the two drugs. Based on these findings, we believe a larger non-inferiority trial comparing these drugs is feasible.

Table 2 provides detail on the results for our primary (tolerability) outcome. All ketamine patients (41/41) and 61% (25/41) of the fentanyl patients reported adverse events [risk difference 39% (95% CI: 24% to 54%)]. Other than one episode of hypotension in the fentanyl group, which resolved without intervention, all adverse effects were minor. The cumulative number of side effects was 117 in the ketamine group compared with 53 in the fentanyl group. The most common side effects of ketamine were bad taste in the mouth (37; 90%), dizziness (30; 73%), and sleepiness (19; 46%). The most common side effects of fentanyl were sleepiness (15; 37%), bad taste in the mouth (9; 22%), itchy nose (9; 22%), and dizziness (6; 15%). An equal number of patients in each group experienced nausea (3; 7%). Dysphoria was rare and did not vary by treatment, occurring in one patient (2%) in the ketamine group and two patients (5%) in the fentanyl group [risk difference -2% (95% CI: -11% to 6%)]. One patient in the ketamine group reported a “funny dream” after awakening peacefully from a nap in the ED. No patient demonstrated nystagmus (the study definition of dissociation). Subsequent procedural sedation with ketamine occurred in 28 ketamine patients (65%) and 25 fentanyl patients (57%), prior to ED discharge. Additional rare minor events are reported in Supplemental Table 1.

As shown in Figure 2 and Supplemental Table 2, the mean pain scale score reduction at 20 minutes was 44 ± 36 for ketamine and 35 ± 29 for fentanyl [mean difference: 9 (95% CI: -5 to 23)]. Thirty subjects (77%) in the ketamine group and 35 (80%) in the fentanyl group achieved a clinically significant reduction in pain at 20 minutes [risk difference -3% (95% CI: -20% to 23%).
At 60 minutes after drug administration, the mean pain scale score reduction was 42 ± 32 for ketamine and 44 ± 28 for fentanyl [mean difference -2 (95% CI: -16 to 13); Supplemental Table 2]. There was no difference in the magnitude of change in pain score over time between the two treatment groups (p = 0.45). Likewise, there was no significant difference in pain scores between the two groups at any time point (Supplemental Table 3).

Twenty-four patients required a second dose of study drug, 10 (23%) in the ketamine group and 14 (32%) in the fentanyl group [risk difference -9 (95% CI: -27 to 10); data not shown].

Fifteen patients required additional opioid rescue analgesia during the ED stay, 7 patients in the ketamine group (16%) and 8 patients in the fentanyl group (18%) [risk difference -2% (95% CI: -18% to 14%)]. The median (interquartile range [IQR]) morphine equivalents/kg/hour of rescue analgesia received were 0.04 (0.02 to 0.11) and 0.05 (0.04 to 0.08) in the ketamine and fentanyl groups, respectively [median difference -0.01 (95% CI: -0.05 to 0.05); p = 0.6].

The median (IQR) time from ED presentation to sedation or ED discharge was 304 (259, 374) minutes for the ketamine group and 327 minutes (263, 408) for the fentanyl group [median difference -17 minutes (95% CI: -59 to 23)]. Only 14 ketamine subjects and 17 fentanyl subjects remained in the ED for a full 6 hours.

DISCUSSION

Sub-dissociative ketamine has been promoted for its analgesic effects and postulated ability to dampen the overall response to acute traumatic pain. However, the current literature comprises small, single center trials that fail to establish the non-inferiority of ketamine to opioid medication for acute pain. This double-blind, randomized controlled trial of intranasal ketamine compared to intranasal fentanyl among children with acute traumatic extremity pain establishes
the feasibility of conducting a larger non-inferiority trial under US regulations and provides important tolerability and efficacy data required to plan a larger trial.33

Opioid pain medications target a limited number of specific receptors that dampen the transmission of acute pain. However, repeated stimulation of the opioid pathway results in physiologic tolerance; places the patient at risk for the possible downstream effects of dependence, addiction, and opioid hyperalgesia; and may contribute to the development of chronic pain.34 Conversely, ketamine targets multiple pain pathways simultaneously and avoids hyperactivity in a single pain circuit. Ketamine is postulated to dampen the pain response, reduce wind-up pain and opioid hyperalgesia, and prevent central sensitization and chronic pain through its complex pharmacology.35-37 Wind-up pain refers to amplified nociceptive signals to the central nervous system from prolonged pain or repeated stimulation.36 Central sensitization refers to a loss of linkage between the presence, intensity, duration, and frequency of painful stimuli and the perceived pain intensity.18

Ketamine targets the N-methyl-D-aspartate receptors (NMDA-R), voltage gated sodium channels, large conductance potassium channels (BK channels), substance P receptors, and the mu and delta opioid receptors. Ketamine has the potential to block central and peripheral pain signaling, act as a local anesthetic,38 diminish neuropathic pain, and reduce pain reactivity.39 Most importantly, ketamine competitively antagonizes the NMDA-R, which act as a warning system, amplifying pain and forcing the body’s attention to the location of injury and inflammation. NMDA-R stimulation has been shown to increase wind-up pain, central sensitization, opioid mediated hyperalgesia, and the inflammatory response to pain.20 NMDA-R have a clear role in the amplification of acute pain and the development of chronic pain. Ketamine is one of only two FDA-approved NMDA-R antagonists.
While ketamine is postulated to have an opioid sparing effect by modulating the NMDA and other receptors,\textsuperscript{19,35,40} there is a paucity of compelling evidence for this effect in children with acute pain. A meta-analysis by Dahmani, et al. found that ketamine treatment was associated with a decrease in postoperative pain intensity in children, but failed to show an opioid sparing effect.\textsuperscript{41} In 2016, another meta-analysis of ketamine analgesia for postoperative pediatric patients reported no opioid sparing effect, but found the number of available studies insufficient to draw a definitive conclusion.\textsuperscript{42} Larger, adequately powered studies are required to answer this important clinical question.

Similarly, despite the renewed popularity of ketamine, there is a paucity of evidence for its efficacy as a stand-alone analgesic. A 2015 evidence-based review of the four existing randomized controlled trials evaluating sub-dissociative ketamine for acute analgesia in the emergency care setting failed to provide evidence to support or refute the use of ketamine.\textsuperscript{43} The only pediatric study included in this review used ketamine IV at 0.5 mg/kg every 3 minutes until patients were sedated.\textsuperscript{43} The PICHFORK trial, published after this review, concluded that intranasal fentanyl and intranasal ketamine were associated with similar pain reduction in children.\textsuperscript{2} While this trial provides important data from 73 children with acute fracture pain receiving intranasal fentanyl at 1.5 \(\mu\)g/kg or intranasal ketamine at 1 mg/kg, it was underpowered to detect all but a large efficacy difference between the drugs. Like the PICHFORK trial, we found no efficacy difference between the two drugs, but our study was also not adequately powered to detect a clinically important difference.

Lower rates of adverse events were reported in the PICHFORK trial than in our study.\textsuperscript{2} Although the drugs were administered in similar doses and routes, PICHFORK reported adverse effects for only 28/36 patients in the ketamine arm and 15/37 patients in the fentanyl arm.\textsuperscript{2} As
with our findings, there were no serious adverse events requiring intervention, and dizziness and bad taste in the mouth were the most common adverse effects reported. The higher overall adverse event rates for both drugs in our study likely reflects the methodology we used to measure adverse event rates. We collected adverse events and side effects by examining the vital signs, querying the patient through a checklist of potentially expected events, and then asking open-ended questions to identify novel events and recording the responses verbatim.

We did not expect to find a difference in efficacy between the two study drugs when we designed the trial. We anticipated a large, multicenter study would be required to examine the non-inferiority of ketamine compared with fentanyl. This question is worth answering because the current evidence for intranasal ketamine and intranasal fentanyl analgesia is sparse and significantly limited. Ketamine has many postulated benefits, but the evidence does not establish its role as a first or second line analgesic agent for acute pain. Other than PICHFORK and this trial, the pediatric literature to support intranasal ketamine analgesia comprises largely of case reports and case series that include both adult and pediatric patients. These small studies do not establish a scientific basis for safety or efficacy of either intranasal ketamine or fentanyl for analgesia in children.

LIMITATIONS

This study is limited by the relatively small number of patients enrolled at a single center and our results may not be generalizable to other centers or patient populations. To minimize selection bias, we planned to enroll consecutive patients with single extremity fractures. While we did not achieve this goal, for most of the study there was sufficient research coordinator coverage to facilitate enrollment 24 hours per day, 7 days per week. However, the data from our
screening log are insufficient to comment specifically on how the pain scores, injury patterns, and analgesic administration trends varied between enrolled patients and patients who were eligible but not enrolled. Despite sporadic gaps in coverage, we successfully screened over 600 patients and enrolled 87 patients in the trial over 11 months.

We converted the FPS-R to equivalent VAS scores prior to analysis. However, this means that our pain scales estimated the change in pain levels with less precision than the standard VAS scales. As such, we conservatively chose a difference in pain score of 20 mm as the minimal clinically significant difference, even though differences as small as 10 mm have been shown to be clinically significant in prior studies. A sub-analysis of subjects assessed with FPS-R vs. VAS scores was not possible given the small number of subjects in the trial.

The study protocol specified that all subjects receive initial analgesia with oral acetaminophen or ibuprofen in accordance with our local clinical practice. We did not attempt to standardize the specific drug or timing of administration, which may have biased our findings. There is evidence to support that ibuprofen is the superior agent compared to acetaminophen for fracture pain. In a future trial, we would recommend ibuprofen as the agent of choice in patients without a contraindication.

CONCLUSIONS

This study demonstrated the feasibility of a larger, multicenter trial comparing the safety and efficacy of intranasal sub-dissociative ketamine with intranasal fentanyl and the potential role for intranasal sub-dissociative ketamine in reducing opioid medication utilization. Minor adverse events, such as bad taste in the mouth and dizziness, occurred more frequently with
ketamine. Our exploratory analysis detected no difference in efficacy between the two drugs. A larger, multicenter, non-inferiority study comparing these drugs is recommended.

REFERENCES


Table 1. Baseline Characteristics

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<th>Ketamine (n = 43)</th>
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<tr>
<td>Displaced femur</td>
<td>2 (5%)</td>
<td>0</td>
</tr>
<tr>
<td>Displaced tibia/fibula</td>
<td>1 (2%)</td>
<td>0</td>
</tr>
<tr>
<td>Nondisplaced tibia/fibula</td>
<td>0</td>
<td>2 (5%)</td>
</tr>
<tr>
<td><strong>Anti-inflammatory meds</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>34 (79%)</td>
<td>35 (80%)</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>7 (16%)</td>
<td>5 (11%)</td>
</tr>
<tr>
<td>Both</td>
<td>1 (2%)</td>
<td>3 (7%)</td>
</tr>
<tr>
<td><strong>Treatment Interventions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Splinting/casting alone</td>
<td>13 (30%)</td>
<td>15 (34%)</td>
</tr>
</tbody>
</table>

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Splinting/casting with procedural sedation | 3 (7%) | 1 (2%)
---|---|---
Reduction with sedation | 24 (56%) | 24 (55%)
Inpatient reduction | 1 (2%) | 2 (5%)
Hematoma Block | 0 | 1 (2%)
No ED or IP procedure | 1 (2%) | 1 (2%)
ED wound exploration and repair with sedation | 1 (2%) | 0

| **Baseline Pain Scale Score, mean (standard deviation)** | 73 (26) | 69 (26) |

Table 2. Cumulative Adverse Events in First 60 Minutes Prior to Sedation/Operative Intervention*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ketamine (n = 41)</th>
<th>Fentanyl (n = 41)</th>
<th>Total (N = 82)</th>
<th>Risk Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bad Taste in Mouth/Throat</td>
<td>37 (90%)</td>
<td>9 (22%)</td>
<td>46 (56%)</td>
<td>68% (53% to 84%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>30 (73%)</td>
<td>6 (15%)</td>
<td>36 (44%)</td>
<td>59% (41% to 76%)</td>
</tr>
<tr>
<td>Sleepiness/Tired**</td>
<td>19 (46%)</td>
<td>15 (37%)</td>
<td>34 (42%)</td>
<td>10% (-11% to 31%)</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>6 (15%)</td>
<td>3 (7%)</td>
<td>9 (11%)</td>
<td>7% (-6% to 21%)</td>
</tr>
<tr>
<td>Itchy Nose</td>
<td>10 (24%)</td>
<td>9 (22%)</td>
<td>19 (23%)</td>
<td>2% (-16% to 21%)</td>
</tr>
<tr>
<td>Visual Disturbance***</td>
<td>4 (10%)</td>
<td>1 (2%)</td>
<td>5 (6%)</td>
<td>7% (-3% to 18%)</td>
</tr>
<tr>
<td>Mood change</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysphoria</td>
<td>1 (2%)</td>
<td>2 (5%)</td>
<td>3 (4%)</td>
<td>-2% (-11% to 6%)</td>
</tr>
<tr>
<td>Talkativeness</td>
<td>0</td>
<td>1 (2%)</td>
<td>1 (1%)</td>
<td>-2% (-7% to 2%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (7%)</td>
<td>3 (7%)</td>
<td>6 (7%)</td>
<td>0% (-11% to 11%)</td>
</tr>
<tr>
<td>Trouble Concentrating</td>
<td>1 (2%)</td>
<td>0</td>
<td>1 (1%)</td>
<td>2% (-2% to 7%)</td>
</tr>
<tr>
<td>Funny Dreams</td>
<td>1 (2%)</td>
<td>0</td>
<td>1 (1%)</td>
<td>2% (-2% to 7%)</td>
</tr>
<tr>
<td>Transient hypotension</td>
<td>0</td>
<td>1 (2%)</td>
<td>1 (1%)</td>
<td>-2% (-7% to 2%)</td>
</tr>
<tr>
<td>Other****</td>
<td>5 (12%)</td>
<td>3 (7%)</td>
<td>8 (10%)</td>
<td>5% (-8 to 18)</td>
</tr>
<tr>
<td>Any event</td>
<td>41 (100%)</td>
<td>25 (61%)</td>
<td>66 (80%)</td>
<td>39% (24 to 54)</td>
</tr>
</tbody>
</table>

*Complete data for every time point through 60 minutes were obtained in 82 patients as required to estimate sample sizes for a larger trial. Routine clinical care interfered with tolerability assessments in 5 patients with missing data.

**Sleepiness/Tired includes patient reports of sleepiness, tiredness, or increased sleepiness among patients who were observed to be wide awake and conversant.

***Visual disturbance includes patient reports of blurry vision, fuzzy vision, seeing a blue spot, and seeing multiples.

****Detail of additional rare minor adverse events are reported in Supplemental Table 1.
**Figure 1. Participant Flow Diagram**

- Assessed for eligibility (N=629)
  - Excluded (n=538)
    - Not meeting inclusion criteria (n=440)
      - No suspected fracture (n=115)
      - Narcotic prior to ED (n=110)
      - Less than 4 years (n=68)
      - No narcotic needed (n=64)
      - Weight > 70 kg (n=34)
      - Low triage pain scale (n=29)
      - Multiply injured (n=5)
      - Nonverbal (n=5)
      - Other (n=10)
    - Pre-Screen Fails (n=1)
    - Declined to participate (n=52)
    - Eligible but not enrolled (n=45)

- Randomized (N=91)
  - Allocated to INSD Ketamine (n=46)
    - Received allocated intervention (n=43)
    - Withdrew prior to intervention (n=3)
  - Allocated to IN Fentanyl (n=45)
    - Received allocated intervention (n=44)
    - Late recognition of a screen failure (n=1)

- Allocation

- Completed Study
  - Completed protocol to 60 min (n=43)
  - Completed protocol to 60 min (n=44)

- Analysis
  - Primary (tolerability) outcome (n=41)
  - Secondary (efficacy) outcome (n=43)
  - Primary (tolerability) outcome (N = 41)
  - Secondary (efficacy) outcome (N = 44)
Figure 2. Change in Mean Pain Scale Scores (N = 87)*

* + indicates the mean value

FIGURE LEGENDS

Figure 1. Participant Flow Diagram *

* INSD denotes intranasal sub-dissociative; IN denotes intranasal.

Figure 2. Change in Mean Pain Scale Scores (N = 87)*

* + indicates the mean value

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