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Study protocol of a randomised controlled trial of intranasal ketamine compared with intranasal fentanyl for analgesia in children with suspected, isolated extremity fractures in the paediatric emergency department

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ABSTRACT

Introduction: Fentanyl is the most widely studied intranasal (IN) analgesic in children. IN subdissociative (INSD) ketamine may offer a safe and efficacious alternative to IN fentanyl and may decrease overall opioid use during the emergency department (ED) stay. This study examines the feasibility of a larger, multicentre clinical trial comparing the safety and efficacy of INSD ketamine to IN fentanyl and the potential role for INSD ketamine in reducing total opioid medication usage.

Methods and analysis: This double-blind, randomised controlled, pilot trial will compare INSD ketamine (1 mg/kg) to IN fentanyl (1.5 μg/kg) for analgesia in 80 children aged 4–17 years with acute pain from a suspected, single extremity fracture. The primary safety outcome for this pilot trial will be the frequency of cumulative side effects and adverse events at 60 min after drug administration. The primary efficacy outcome will be exploratory and will be the mean reduction of pain scale scores at 20 min. The study is not powered to examine efficacy. Secondary outcome measures will include the total dose of opioid pain medication in morphine equivalents/kg/hour (excluding study drug) required during the ED stay, number and reason for screen failures, time to consent, and the number and type of protocol deviations. Patients may receive up to 2 doses of study drug.

Ethics and dissemination: This study was approved by the US Food and Drug Administration, the local institutional review board and the study data safety monitoring board. This study data will be submitted for publication regardless of results and will be used to establish feasibility for a multicentre, non-inferiority trial.

Trial registration number: NCT02521415.

Strengths and limitations of this study

- Tests a novel agent and route of administration for analgesia (intranasal subdissociative (INSD) ketamine) with potential for an opioid sparing effect.
- Double-blind, randomised controlled trial.
- Compliant with the SPIRIT guidelines.
- Trial examines feasibility of a protocol prior to multicentre implementation.
- Trial will not establish non-inferiority for INSD ketamine for analgesia compared with IN fentanyl, but will provide important safety and efficacy data required to design an adequately powered, multicentre, non-inferiority trial.

BACKGROUND AND RATIONALE

Children often do not receive adequate analgesia for traumatic injuries in the emergency department (ED) setting.[1–4] A study of 773 children 0–15 years of age with isolated long-bone fractures treated in the ED demonstrated that only 10% of injured children received adequate pain medicine.[4] Failure to recognise and treat pain adequately in children is associated with slower healing, emotional trauma and changes in how pain is processed.[5–10]

Intranasally (IN) administered analgesia provides safe and timely relief of pain without the time delay or discomfort associated with intravenous (IV) placement.[5 8] The pharmacokinetics of IN drug administration dampen the rapidity of drug absorption and minimise side effects, yet still achieve therapeutic drug levels and adequate analgesia.[11] IN fentanyl is the most frequently used and most widely studied IN analgesic with a reported bioavailability of 71%.[12 13] In one prospective, double-blind, placebo-controlled, randomised

clinical trial, IN fentanyl at 150 µg/kg demonstrated efficacy similar to IV morphine at 0.1 mg/kg.[8] IN fentanyl serves an ideal comparator in this study for its demonstrated benefit specific to children with orthopaedic injuries presenting to the ED.[8 14]

We believe intranasal, subdissociative (INSD) ketamine offers a safe and efficacious alternative to IN fentanyl with the potential added benefit of decreasing overall opioid use during the ED stay. Ketamine has a known bioavailability of 45–50% when administered through the IN route and standard 1 mg/kg doses provide absorbed drug levels in the subdissociative range.[15 16] Ketamine is used increasingly for acute and chronic pain in children and adults with sickle cell disease and cancer.[17–20] Ketamine has been found to be safe and effective for analgesia in the prehospital, battlefield, postoperative and ED settings.[11 21]

The largest double-blind, randomised, paediatric trial to date took place in Australia and examined the safety and the mean reduction in pain between INSD ketamine and IN fentanyl.[22] At 30 min, median pain scale score reductions on a 100 mm scale were 45 mm for ketamine and 40 mm for fentanyl (difference 5 mm; 95% CI −10 to 20) by combined results of the Faces Pain Scales-Revised (FPS-R; ages 3–6 years) and visual analogue scale (ages 7 and above).[22] For fentanyl, 15 patients reported adverse events (AEs) and for ketamine 28 patients reported AEs, including dizziness, drowsiness, bad taste in the mouth, nausea, itchy nose and dysphoria, and hallucinations.[22] The authors concluded that both agents were acceptable for the relief of pain, but ketamine was associated with more minor AEs.[22] This single study was underpowered to establish the non-inferiority of INSD ketamine. The study was also underpowered to examine the incidence of rare but important AEs such as laryngospasm (ketamine) or chest wall rigidity (fentanyl). The study did not examine the role of INSD ketamine in reducing the overall use of opioid analgesics in the treatment of acute fracture pain in children.

Animal studies have demonstrated that the NMDA receptor may play a role in opioid tolerance, and ketamine has been shown in rat models to prevent fentanyl-induced hyperalgesia by enhancing the antinociceptive activity of morphine.[20 23] It is unclear if IN ketamine reduces opioid consumption in the treatment of painful conditions in the acute ED setting. Three studies of IN ketamine in the ED setting reported the number of patients requiring additional opioids for rescue analgesia. An observational study of 40 patients aged 11–79 years with pain treated in the ED using doses of intranasal ketamine of 0.5–0.75 mg/kg reported that three patients failed to complete the protocol at 60 min because opioid rescue analgesia was required.[11] A pilot, observational study of 28 children aged 3–13 years with fracture pain examined the effectiveness of IN ketamine for analgesia and recommended a dose of 1 mg/kg to achieve pain control.[24] Eight patients or 33% required additional opioid analgesia.[24] In contrast, a randomised controlled, double-blind trial of adult patients treated for pain in the ED compared IV ketamine at 0.3 mg/kg to IV morphine at 0.1 mg/kg and found no difference in the incidence of rescue fentanyl analgesia at 30 or 60 min.[25] IN ketamine provides pain relief up to 1 hour and may reduce opioid usage during the ED stay on this basis alone.[22 24]

The current study examines the feasibility of a larger, multicentred clinical trial to compare the safety and efficacy of INSD ketamine to IN fentanyl and to examine a potential role for INSD ketamine in reducing total opioid medication usage during the ED stay.

AIMS AND HYPOTHESES

Primary hypotheses: We hypothesise that IN ketamine is comparable to IN fentanyl for efficacy and safety and represents a plausible alternative to IN fentanyl. We further hypothesise that IN ketamine will decrease the total opioid pain medication (in morphine equivalents/kg/hour excluding study drug) required to manage forearm fracture pain in the ED.

Primary aim: Examine the feasibility of a future multicentred ED, non-inferiority study by obtaining data required for trial planning, measuring the time to consent, and refining the processes to randomise patients and ensure blinded drug administration. We will conclude that such a study is NOT feasible if we observe a rate of side effects for ketamine that exceeds fentanyl threefold or a serious AE rate of 5% or more for ketamine.

Safety aim: Compare the frequency of cumulative AEs at 60 min after drug administration among children randomised to receive either INSD ketamine (IN ketamine) or IN fentanyl for pain control in the ED. To fully characterise novel side effects, AEs or additive effects of additional interventions such as sedation, we will collect data every 30 min for the first 2 hours and again at 6 hours unless the patient was already deemed safe for discharge by the treating physician.

Exploratory aim: Compare the efficacy of IN ketamine to IN fentanyl as measured by a reduction in age-appropriate pain scale scores at time points in the first 2 hours. The primary outcome measure will be the difference in the reduction of the pain scale scores at 20 min.

Secondary aim: Compare the total dose of opioid medication in morphine equivalents/kg/hour (excluding study drug) required during the ED stay of children with suspected, single extremity fractures after randomisation and treatment with IN ketamine or IN fentanyl.

TRIAL DESIGN

This double-blind, randomised controlled trial will compare INSD ketamine (1 mg/kg) to IN fentanyl (1.5 µg/kg) for analgesia in children presenting to the ED with acute pain from a suspected, single extremity fracture.

METHODS

Study setting

The trial will be conducted at the Levine Children's Hospital Emergency Department in Charlotte, North Carolina, USA, an urban, tertiary centre with 35 000 paediatric ED visits per year and a level II trauma centre. The department supports an emergency medicine residency programme and paediatric emergency medicine fellowship. There is in-house orthopaedic surgery coverage 24 hours per day and resident physicians are supervised by board-certified paediatric orthopaedic and emergency medicine specialists.

Eligibility criteria

Verbal children aged 4–17 years with a suspected, single extremity fracture requiring analgesia will be screened for enrolment. Suspected fractures will be defined as any deformity or pain to palpation that the triage nurse or treating physician deems as a potential fracture. Standard clinical practice at our hospital is for nurses to use the Wong-Baker FACES Pain Rating Scale (FPR-Scale) score (for children aged 4–10 years) or the Adult Pain Rating Scale score (for children aged 11–17 years) to quantify pain in triage. The triage nurses are asked to page a research associate for any patient with a suspected fracture and a Wong-Baker FPR-Scale score of ≥4 or an Adult Pain Rating Scale score of ≥3. These scales are suboptimal for research and are used solely to screen potentially eligible patients. The FPS-R (for children aged 4–10 years) and VAS scores (for children aged 11–17 years) are obtained after consent as baseline measures of pain and used thereafter as study measures.

Exclusion criteria

Patients with the following characteristics will be excluded:

1. Glasgow Coma Scale (GCS) <15 at ED presentation;
2. Reported allergy or adverse reaction to ketamine or fentanyl;
3. Reported pregnancy;
4. Intoxication;
5. Hypotension defined as <70 mm Hg+2× age or <90 mm Hg for patients >11 years of age;
6. Weight >70 kg;
7. Patients receiving opioid analgesia administered prior to arrival;
8. Multiply injured patients;
9. Aberrant nasal anatomy that precludes IN medications.

Recruitment and consent

Eligible patients will be identified at triage, via incoming medic radio calls, and via the patient tracking board (FirstNet, Cerner Corporation, Kansas City, Missouri, USA). The parents or legal guardians of eligible patients will be approached by a care team member. Research coordinators will use a standard Institutional Review Board (IRB)-approved script to review the merits and risks of the study. An abbreviated initial short form consent process, conducted in accordance with US21CFR50.27(b)(2), was adopted from our standard consent. This initial short form consent was required by our IRB to avoid any unethical delays in analgesic administration. After study drug administration, a standard long form consent will be completed that adds more detailed information about protections consistent with HIPAA laws. The study design meets the IRB criteria for waiver of assent and requires the consent of only a single parent or guardian.

Interventions and blinding

Arm 1 will receive 1 mg/kg IN ketamine (Ketalar 50 mg/mL) administered according to a standard dosing table (see online supplementary appendix A). Arm 2 will receive 1.5 µg/kg IN fentanyl (fentanyl citrate 100 µg/2 mL) administered according to a standard dosing table (see online supplementary appendix A). At the discretion of the treating physician, patients may receive a second dose of study drug (IN ketamine at 0.5 mg/kg for patients randomised to ketamine treatment or IN fentanyl at 0.75 µg/kg for patients randomised to fentanyl treatment) at least 20 min after administration of the first dose. The maximum dose of ketamine a patient may receive will be 70 mg (1 mg/kg) for the first dose and 35 mg (0.5 mg/kg) for the second dose or a total of 105 mg (1.5 mg/kg). The maximum dose of fentanyl a patient may receive will be 105 µg (1.5 µg/kg) for the first dose or 53 µg (0.75 µg/kg) for the second dose or a total of 158 µg (2.25 µg/kg).

The clinical nurse administering the study drug will be unblinded to the intervention. The physicians, patients, research associates and investigators will be blinded to the interventions. All study measurements will be made by a blinded research associate. One member of the research team will remain unblinded throughout the study to serve as the liaison with the investigational pharmacy and data safety monitoring board when needed, but will not enrol patients or participate in study data collection.

Concomitant medications

The patient will receive acetaminophen 15 mg/kg (maximum dose of 650 mg) by mouth or ibuprofen 10 mg/kg (maximum dose 600 mg) by mouth if one of these medications was not given prior to study enrolment. After the patient has received two doses of study drug, the patient may receive additional analgesics at the discretion of the treating physician. All medications administered during the 6-hour study period will be recorded.

Outcome measures

The primary safety outcome for this pilot trial will be the occurrence frequency of cumulative AEs and side effects at 60 min after drug delivery. These outcome

definitions are detailed in online supplementary appendix B. Patients were queried about these events and asked to report novel symptoms.

The secondary outcome measures will include the total dose of opioid pain medication in morphine equivalents/kg/hour (excluding study drug) required during the ED stay, number and reason for screen failures, time to consent, and the number and type of protocol deviations. Details of opioid medication administration (drug names, doses and routes) in the ED will be collected from the electronic medical record.

The primary efficacy outcome will be the difference in the reduction of the pain scale scores at 20 min. This will be treated as an exploratory outcome as we do not have adequate power to detect a difference in the drugs. The patient's pain level will be recorded on a validated, age-appropriate pain scale. The FPS-R will be used for patients aged 4–10 years and the VAS will be used for patients 11–17 years. The FPS-R and VAS scores will be used for the exploratory efficacy outcome measure as those scales are validated for research.[26–29] The Wong-Baker FPR-Scale (4–10 years of age) and the Adult Pain Rating Scale (11–17 years) are referenced under the eligibility criteria and are used in accordance with standard measures available at triage to establish eligibility for enrolment based on institutional practice. These scales are not used as study measures.

The patient will be directly asked if they require additional medication to control their pain at each pain reassessment. The study coordinator will prompt the treating physician to evaluate the patient for possible repeat dosing if the pain scale score remains unchanged or exceeds a FPR-Scale of 4 (ages 4–10 years) or a VAS score of 4 (ages 11–17 years) after 20 min. No more than two doses of study drug will be given.

Sample size

Owing to the preliminary nature of our study, we estimated the number of patients needed for our study based on our ability to detect a difference in the rate of any cumulative adverse effects at 60 min after drug delivery and the ability to detect occurrence of less common adverse effects. We used the rates of any adverse effect from a previous study (PICHFORK trial) where the ketamine group showed a rate of 78% and the fentanyl group had a rate of 40%.[22] With n=40 children randomised to each group, we would have over 90% power to detect this difference using a two-sided two-sample test of proportions. We would have extremely low power to detect differences in the occurrence of any one adverse effect. For more common effects such as bad taste in mouth or dizziness (rates 25–30%), with 40 children, the CI half-widths are ~13–14%. With n=40 children per group, we would expect to observe at least one case with 80% probability if the rate was as low as 4%. The tables in online supplementary appendix C provide more detail on the expected AE rates for the study drugs, the associated 95% CIs and the statistical power for demonstrating differences between the two groups. No formal power analyses were conducted for the outcome of pain but our data will provide sufficient numbers to estimate SDs for a larger trial.[30] We have not adjusted for attrition or loss to follow-up because we do not anticipate missing data for our primary outcome of cumulative AEs at 60 min after study drug administration.

Allocation and concealment

The study statistician will generate the allocation lists using a permuted block randomisation with random block sizes and stratification by age (4–10, 11–17 years) with 1:1 allocation. The lists will be generated using SAS Enterprise Guide V.6.1 and the RANUNI function. To maintain allocation concealment, assignments will be placed in consecutively numbered, sealed opaque study packets in the ED and only opened once a child is deemed eligible.

Blinded study labels in the study packets and prepared by the research pharmacy will be affixed to the study drug syringe and scanned into the electronic medication administration record without revealing the treatment arm. The randomisation assignment and dosing table will then be sealed in a separate envelope in the study packet and stored. The investigational pharmacy or treatment team may unblind a patient if needed. Randomisation tables, drug logs and all unblinded study documents will be maintained by the research pharmacy. The study pack will include a separate sealed opaque envelope with instructions for a second dose of the study medication.

The drugs will be administered in similar volumes with identical administration procedures. The drugs are similar in colour and odourless. The drug vial is not viewed at the bedside and both drugs are administered in similar syringes attached to a mucosal atomiser device. The participants, treating physicians and outcome assessors will remain blinded to the group allocation.

Data collection and management

Research coordinators will document AEs (using a standardised checklist) every 5 min for the first 15 min after medication administration and then every 30 min for the next 2 hours. Vital signs and pain scale assessments will be repeated every 10 min for the first 30 min and then every 30 min for the next 2 hours. Online supplementary appendix D details the schedule of study measures. All coordinators were trained on how to collect study measures prior to study initiation. Final assessments are made at 6 hours unless the patient was already discharged to home.

Study data will be collected on a structured case report form and managed using REDCap (Research Electronic Data Capture) electronic data capture tools.[31] REDCap is a secure, web-based application designed to support data capture for research studies, providing (1) an intuitive interface for validated data entry; (2) audit

trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages; and (4) procedures for importing data from external sources. Data discrepancies and missing data will be reviewed weekly with the principal investigator and research manager. Confidentiality of participant personal information (date of birth, age, birthdate, medical record number) will be protected via secured storage using REDCap.

Statistical methods

For assessing of feasibility of a multicentre trial, we will estimate the proportion of patients consented out of all potentially eligible patients, the time to consent, the proportion successfully randomised and the proportion with blinding maintained. For assessing safety profiles, the two treatment groups will be compared on demographic and baseline variables using Student's t-test for interval data, the Wilcoxon rank-sum test for ordinal data, and the χ^2 test or Fisher's exact test for categorical data. The primary safety analysis will compare the proportion of adverse events (AEs) among children randomised to receive either INSD ketamine or IN fentanyl for pain control in the ED. Proportions and 95% CIs will be calculated for each AE and compared using χ^2 test or Fisher's exact test where appropriate. Since we will stratify the randomisation by age (4–10 and 11–17 years), we will use multiple logistic regression to compare the rate of any AE between ketamine and fentanyl controlling for age. The Student's t-test or Wilcoxon rank-sum test will be used to compare the mean total dose of opioid pain medication in morphine equivalents/kg/hour required during ED evaluation. We hypothesise the ketamine group will have lower use of opioid pain medication. SAS Enterprise Guide V.6.1 will be used for all analyses. A two-tailed p value of <0.05 will be considered statistically significant. We will also use this study to gain preliminary estimates of SDs for pain scores since the larger trial for this study would have a non-inferiority hypothesis with respect to ketamine being as effective for pain management as fentanyl. As an exploratory analysis, we will estimate the mean pain scores and corresponding 95% CIs over time for the two groups. We will also estimate the correlation among measurements within the same child over time which will be needed for planning future studies.

Monitoring

A data and safety monitoring board (DSMB) will operate in accordance with the guidelines established by the Food and Drug Administration (FDA) in 'Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committee' jointly published by the Center for Biologics Evaluation and Research (CBER), Center for Drug Evaluation and Research (CDER), and Center for Devices and Radiological Health (CDRH) for the FDA, OMB Control No. 0910-0581, March 2006, expiration date 10/31/2015 (updated guidance will be used as available).

The DSMB will be chaired by the medical director of a paediatric ED and include several other clinicians including a paediatric intensivist and a biostatistician.

The study biostatistics team will provide a report to the DSMB after the first 5 patients, and then after every 10 patients (or in the event of a serious, unanticipated and related AE) to monitor the data for quality control and will review the occurrence of AEs.

Auditing

The study will undergo an independent audit conducted by the monitors/educators from the Institution's Office of Clinical and Translational Research at least once during the study. The Institution's audit programme is a systematic and independent examination of trial-related activities and regulatory documents and will be conducted according to institutional standard operational procedures.

Ethics and dissemination

This study will provide pilot data and establish feasibility for a multicentre, non-inferiority trial comparing IN ketamine and IN fentanyl and will add to the limited existing literature for IN ketamine in children. All protocol changes were reviewed by the DSMB, institutional review board, FDA and amended on clinical trials.gov.

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Contributors The principal investigator drafted and revised the protocol. JRS serves as the Research Director for the Mecklenburg County EMS Agency (Medic) and helped in the design of the study and the revisions of the protocol. MSR serves as the Research Director for the Department of Emergency Medicine and helped adapt the design of the study for implementation in the children's emergency department and assisted in revising the protocol. KB and JY are fellows in the Department of Emergency Medicine and revised the protocol and championed the nursing and physician education required for implementation. CGM is a biostatistician and assisted in the conception of the study and the analysis plan. KV, Department of Pediatric Orthopedics, and EG, Department of Surgery, assisted in revising the protocol. MH is the Research Manager in the Department of Emergency Medicine and participated in the design of the study, revision of the protocol and implementation of the study.

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Competing interests None declared.

Patient consent Obtained.

Ethics approval This study was approved by Carolinas Medical Center Institutional Review Board (IRB) and United States Food and Drug Administration. The trial will be conducted under the authority of the principal investigator based on a Food and Drug Administration Investigational New Drug (IND#127351) application. Trial oversight will be in accordance with the Code of Federal Regulations (21CFR312), Good Clinical Practice Guidelines, and International Conference on Harmonisation Guidelines.

Provenance and peer review Not commissioned; externally peer reviewed.

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