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Randomized Controlled Trial of Intranasal Ketamine Compared to Intranasal Fentanyl for Analgesia in Children with Suspected, Isolated Extremity Fractures in the Pediatric Emergency Department

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Regulatory Information: This trial will be conducted under the authority of the principal investigator based upon 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. This study was registered on clinicaltrials.gov prior to enrollment (NCT02521415).

Abstract

Introduction: Fentanyl is the most widely studied intranasal (IN) analgesic in children. Intranasal, sub-dissociative (INSD) ketamine may offer a safe and efficacious alternative to IN fentanyl with the potential benefit of decreasing overall opioid use during the emergency department (ED) stay. This study will examine the feasibility of a larger, multi-center 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 utilization.

Methods and Analysis: This double-blind, randomized controlled trial will compare INSD ketamine (1mg/kg) to IN fentanyl (1.5 micrograms/kg) for analgesia in 80 children ages 3-17 years with acute pain from a suspected, single extremity fracture. Patients will be excluded for Glasgow Coma Score < 15, allergy or adverse reaction to ketamine or fentanyl, pregnancy, intoxication, age-defined hypotension, weight > 70kg, receipt of opioids prior to enrollment, or aberrant nasal anatomy. The primary safety outcome for this pilot trial will be the occurrence and frequency of adverse events. The primary efficacy outcome will be the reduction of pain scale scores at 20 minutes. 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 will be followed for 6 hours and may receive up to two doses of study drug.

Ethics and Dissemination: This study was approved by the United States 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 multicenter, non-inferiority trial comparing INSD ketamine and IN fentanyl.

Trial Registration: Clinical trials NCT02521415

Protocol Strengths:

- Tests a novel agent and route of administration for analgesia (INSD ketamine) with potential for an opioid sparing effect
- Double, Blind, Randomized Controlled Trial
- Compliant with the SPIRIT guidelines
- Trial examines feasibility of a protocol prior to multicenter implementation

Protocol Weaknesses:

- Trial will not establish non-inferiority for INSD ketamine for analgesia compared to IN fentanyl but will provide important safety and efficacy data required to design an adequately powered, multi-center, non-inferiority trial.

Background and Rationale:

Children often do not receive adequate analgesia for traumatic injuries in the emergency department setting.[1-4] A study of 773 children 0-15 years of age with isolated long-bone fractures treated in the emergency department demonstrated that only 10% of injured children received adequate pain medicine.[4] Failure to recognize 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 IV placement.[5,8] The pharmacokinetics of intranasal drug administration dampen the rapidity of drug absorption and minimize side effects yet still achieve therapeutic drug levels and adequate analgesia.[11] IN fentanyl is the most frequently used and most widely studied intranasal analgesic.[12] In one prospective, double-blind, placebo-controlled, randomized clinical trial, intranasal fentanyl at 150 micrograms/kg demonstrated efficacy similar to intravenous morphine at 0.1 mg/kg.[8] IN fentanyl serves an ideal comparator in this study for its demonstrated benefit specific to children with orthopedic injuries presenting to the emergency department.[8,13]

We believe intranasal, sub-dissociative (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 intranasal route and standard 1mg/kg doses provide absorbed drug levels in the sub-dissociative range.[14,15]** Ketamine is used increasingly for acute and chronic pain in both children and adults with sickle cell disease and cancer.[16-19] Ketamine has been found to be safe and effective for analgesia in the pre-hospital, battlefield, post-operative, and emergency department settings.[11,20]

The largest double, blind, randomized, pediatric trial to date took place in Australia and examined the safety and the mean reduction in pain between INSD ketamine and IN fentanyl.[21] At 30 minutes, median pain scale score reductions on a 100 mm scale were 45 mm for ketamine and 40 mm for fentanyl (difference 5 mm; 95% confidence interval [CI] -10 to 20mm) by combined results of the Faces Pain Scales-Revised (ages 3-6 years) and VAS scales (ages 7 and up).[21] For fentanyl, 15 patients reported adverse events and for ketamine 28 patients reported adverse events, including dizziness, drowsiness, bad taste in the mouth, nausea, itchy nose and dysphoria, and hallucinations.[21] The authors concluded that both agents were acceptable for the relief of pain, but ketamine was associated with more minor adverse events.[21] 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 adverse events 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 anti-nociceptive activity of morphine.[19,20,22] IN ketamine provides pain relief up to one hour and may reduce opioid utilization during the ED stay on this basis alone.[21,23]

The current study examines the feasibility of a larger, multi-centered 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 utilization during the ED stay.

Aims and Hypotheses

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

Primary Aim: **Examine the feasibility of a future multi-centered emergency department, non-inferiority study by obtaining data required for trial planning, measuring the time to consent, and refining the processes to randomize 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 three-fold or a serious adverse event rate of 5% or more for ketamine.**

Safety Aim**: Compare the frequency of adverse events over 6-hours (2 hours of assessments and 6 hour follow up assessment) among children randomized to receive either intranasal sub-dissociative ketamine (IN ketamine) or intranasal fentanyl (IN fentanyl) for pain control in the emergency department.**

Exploratory Aim: **Compare the efficacy of intranasal ketamine to intranasal 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 minutes.**

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 randomization and treatment with IN ketamine or IN fentanyl.**

Trial Design

This double-blind, randomized controlled trial will compare intranasal, sub-dissociative ketamine (1mg/kg) to intranasal fentanyl (1.5 micrograms/kg) for analgesia in children presenting to the emergency department 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 center with 35,000 pediatric emergency department visits per year and a Level II trauma center. The department supports an emergency medicine residency program and pediatric emergency medicine fellowship. There is in-house orthopedic surgery coverage twenty-four hours per day and resident physicians are supervised by board-certified pediatric orthopedic and emergency medicine specialists.

Eligibility criteria

Verbal children ages 3-17 years with a suspected, single extremity fracture requiring analgesia will be screened for enrollment. Suspected fractures will be defined as any deformity or pain to palpation that the triage nurse or treating physician deems as a potential fracture. Injuries that require analgesia will be defined by a Wong-Baker FACES Pain Rating Scale score (for children ages 3-10 years) of at least 4 or an Adult Pain Rating Scale score (for children ages 11-17 years) of at least 3.

Exclusion criteria:

Patients with the following characteristics will be excluded:

1. GCS < 15 at ED presentation
2. Reported allergy or adverse reaction to ketamine or fentanyl
3. Reported pregnancy
4. Intoxication
5. Hypotension defined as less than 70 mmHg +2x age or less than 90 mm Hg for patients greater than 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, MO). The parents or legal guardians of eligible patients will be approached by a care team member. A standard script will be utilized to review the merits and risks of the study by a study coordinator. An abbreviated initial consent process will minimize unethical delays in analgesic administration. After study drug administration, a full-length consent form will be completed. The study design meets the IRB criteria for waiver of assent and requires the consent of only a single parent or guardian. The patient may withdraw at any time. Appendix D provides a copy of the short and full-length consent forms.

Interventions and Blinding

Arm one will receive 1 mg/kg intranasal ketamine (Ketalar 50mg/mL) administered according to a standard dosing table (Appendix C). Arm two will receive 1.5 micrograms/kg intranasal fentanyl (fentanyl citrate 100 micrograms/2 mL) administered according to a standard dosing table Appendix C. 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 randomized to ketamine treatment or IN fentanyl at 0.75 mcg/kg for patients randomized to fentanyl treatment) at least 20 minutes after administration of the first dose.

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 enrollment. 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 adverse events or side effects. These outcome definitions are shared below.

Side Effect Definitions

These are common events experienced by patients receiving ketamine or fentanyl that do not change outcomes for the patient but may affect the patient experience and willingness to receive the drug in the future. For the purposes of this study, we will screen patients for each of the following side effects, and report them as **anticipated adverse events**. Each individual event is defined below.

- **Bad taste in mouth** is defined as subjective agreement by the patient demonstrated by attempting to spit out the medicine, grimacing in response to a foul taste and/or when asked "did you experience a bad taste in your mouth after the medicine."
- **Drowsiness** is defined by subjective agreement by the patient or family that the patient appears drowsy. Drowsiness will be distinguished from altered mental status by awakening to voice.
- **Dizziness** is defined by subjective agreement by the patient or family that the patient feels or appears lightheaded or vertiginous. It may also be documented by unsteady gait.
- **Dysphoria** is defined by subjective agreement by the patient or family that the patient feels unpleasant or irritable.
- **Itchy nose** is defined by subjective agreement by the patient or family.
- **Myoclonus** is defined as muscle stiffening or jerking as noted on clinical examination.
- **Nausea** is defined by subjective agreement by the patient or family that the patient feels like he or she may vomit.
- **Vomiting** is defined as any emesis after administration of the drug.
- **Novel subjective negative experiences** are defined by asking the patient and family if the patient is experiencing any additional symptoms not already addressed.

Serious Adverse Events Definitions

A **serious adverse event** (SAE) includes any adverse event that begins after the short form consent has been completed or within 6-hours thereafter that causes a threat to life, threat to limb or an organ system, causes prolongation of hospitalization, or requires new medical or surgical treatment to correct. Events will be assessed by the PI. Events coded as possibly, probably or definitely related will be considered study-related. Specific SAEs previously reported in association with ketamine or fentanyl administration are listed below and will be considered **anticipated serious adverse events**. Anticipated SAE's will be addressed similarly to any SAE.

Apnea is defined as ceased respirations recognized by clinical examination, or end tidal C02 tracing, requiring bag valve mask ventilation.

Bradypnea is defined as a fall in respiratory rate and oxygen saturations requiring physical stimulation of the patient.

Chest wall rigidity is defined as ineffective ventilation requiring intervention, including bag valve mask ventilation or administration of naloxone.

Dissociative dosing is defined as development of nystagmus.

Emergence reaction is defined as any odd behavior or subjective report of an uncomfortable emotional experience or hallucinations during use of the drug during the study.

Hypotension is defined as blood pressure below 70 plus 2x the age in years, or less than 90 mm Hg for patients older than 10 years, requiring intervention.

Hypoxia is defined as oxygen saturations below 90% requiring bag valve mask ventilation.

Intubation is defined as an intubation or placement of a supraglottic airway secondary to loss of airway protective reflexes.

Laryngospasm is defined as an obstructive pattern by end tidal CO2 tracing OR clinical examination.

Nightmares will be defined as negative experiences during sleep during the study follow up period.

Seizure will be defined as generalized tonic and/or clonic movements in association with alteration of consciousness.

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 minutes. 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 FACES Pain-Revised Scale (FP-R) will be used for patients ages 3-10 years and the Visual Analog Scale (VAS) will be used for patients 11-17 years. These scales will be used for the exploratory efficacy outcome measure because that are validated for research.[24-27] The Wong-Baker FACES Pain Rating Scale will be used for patients ages 3-10 years of age and the Adult Pain Rating Scale score will be used for patients 11-17 years to establish eligibility for enrollment based on institutional practice. 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 3-10 years) or a VAS Scale score of 4 (ages 11-17 years) after 20 minutes. No more than two doses of study drug will be given.

Sample size

Due 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 adverse effect 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%.(21)With n=40 children randomized 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 confidence interval half-widths are approximately 13-14%. With n=40 children per group, we would expect to observe at least once case with 80% probability if the rate was as low as 4%. The tables in Appendix B provide more detailed information. No formal power analyses were conducted for the outcome of pain but our data will provide sufficient numbers to estimate standard deviations for a larger trial.[28] We have not adjusted for

attrition or loss to follow up because of the short time frame that patients will be followed (6 hours) for adverse events.

Allocation and Concealment

The study statistician will generate the allocation lists using a permuted block randomization with random block sizes and stratification by age (3-10 years, 11-17 years) with 1:1 allocation. The lists will be generated using SAS Enterprise Guide version 6.1 and the RANUNI function. To maintain allocation concealment, assignments will be placed in consecutively numbered, sealed opaque study packets in the emergency department and only opened once a child is deemed eligible.

To avoid unethical treatment delays, the nurse administering the drug will be unblinded. The unblinded nurse will open a separate sealed opaque envelope labeled, "first dose of study medication" containing the medication and detailed dosing instructions. Blinded study labels prepared by the research pharmacy will be affixed to the study drug syringe and scanned into the electronic medication administration record (MAR) without revealing the treatment arm. The randomization 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. Randomization tables, drug logs and all unblinded study documents will be maintained by the research pharmacy. The study pack, prepared by an unblinded research nurse that does not serve on the study team, 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 color and odorless. The drug vial is not viewed at the bedside and both drugs are administered in similar syringes attached to a mucosal atomizer device (MAD). The participants, treating physicians, and outcome assessors will remain blinded to the group allocation.

Data Collection and Management

Research coordinators will document adverse events (using a standardized checklist) every 5 minutes for the first fifteen minutes after medication administration and then every 30 minutes for the next two hours. Vital signs and pain scale assessments will be repeated every 10 minutes for the first 30 minutes and then every 30 minutes for the next two hours. Table 1 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 electronic data capture tools.[29] REDCap (Research Electronic Data Capture) 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 PI 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

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 chi-square test or Fisher's exact test for categorical data. The primary analysis will compare the proportion of adverse events among children randomized to receive either INSD ketamine or IN fentanyl for pain control in the emergency department. Proportions and 95% confidence intervals will be calculated for each adverse event and compared using chi-square test or Fisher's exact test where appropriate. Since we will stratify the randomization by age (3-10 years and 11-17 years), we will use multiple logistic regression to compare the rate of any adverse event between ketamine and fentanyl controlling for age. We will conduct stratified analyses by age if the number of children within each stratification level and treatment group is greater than 5. The Student 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 emergency department evaluation. We hypothesize the ketamine group will have lower use of opioid pain medication. We will use generalized linear models to compare total dose of opioid pain medication between the two groups controlling for age group. We anticipate these data will have a large number with 0 requiring a two-part model such as a zero-inflated Poisson or negative binomial distribution for better model fit. Secondary analysis for any adverse event and total dose of opioid pain medication will control for baseline pain to assess the impact on the treatment effect and its significance. SAS® Enterprise Guide® 6.1 will be used for all analyses. A two-tailed p-value of less than 0.05 will be considered statistically significant. We will also use this study to gain preliminary estimates of standard deviations 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% confidence intervals 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 safety monitoring board (DSMB) will operate in accordance with the guidelines established by the 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 pediatric emergency department and include several other clinicians including a pediatric intensivist and a biostatistician.

The study biostatistics team will provide a blinded analysis of outcomes and adverse events to the DSMB after the first five 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 adverse events.

The study will be stopped for harm if the rate of serious adverse events for ketamine exceeds 5% or if the side effects for intranasal ketamine exceeds that of intranasal fentanyl by three-fold. The DSMB can recommend the study be terminated for harm should an interim analysis show strong evidence that the

rate of related SAE is significantly higher a single treatment group. The DSMB can suspend the study, pending the completion of explicit recommendations with a majority vote, and can permanently close the study only with a unanimous vote.

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 program 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 multicenter, non-inferiority trial comparing intranasal ketamine and intranasal fentanyl and will add to the limited existing literature for intranasal ketamine in children. This study was approved by both the FDA and the local institutional review board. All protocol changes were reviewed by the DSMB, IRB, FDA and amended on clinical trials.gov.

Authors Contribution

The principal investigator drafted and revised the protocol. Dr. Jonathan Studnek 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. Dr. Michael Runyon 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. Dr. Kathleen Bryant and Dr. James Young are fellows in the Department of Emergency Medicine and revised the protocol and championed the nursing and physician education required for implementation. Dr. Charity Moore is a biostatistician and assisted in the conception of the study and the analysis plan. Dr. Kelly VanderHave, Department of Pediatric Orthopedics, and Dr. Eric Grossman, Department of Surgery, assisted in revising the protocol. Melanie Hogg 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 Statement

An annual conflict of interest disclosure form is completed by all faculty. No authors disclosed a relevant conflict of interest.

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Appendix A. Study Measures

Table 1. Example of Study Procedures for a Patient Receiving First Dose at Noon and Requiring a Second Dose

Dose 1			Dose 2	
Time	**Event**		**Time**	**Event**
11:50	Screening & Enrollment	Dose 2 Required		
11:53	Pre-medication and baseline measures			
12:00	Study Drug Dose 1		12:30	Study Drug Dose 2
12:05	5 minute time point: AEs		12:35	5 minute time point: AEs
12:10	10 minute time point: AEs, vitals, pain scale		12:40	10 minute time point: AEs, vitals, pain scale
12:15	15 minute time point: AEs		12:45	15 minute time point: AEs
12:20	20 minute time point: AEs, vitals, pain scale		12:50	20 minute time point: AEs, vitals, pain scale
12:30	30 minute time point: AEs, vitals, pain scale		13:00	30 minute time point: AEs, vitals, pain scale
13:00	60 minute time point: AEs, vitals, pain scale		13:30	60 minute time point: AEs, vitals, pain scale
13:30	90 minute time point: AEs, vitals, pain scale		14:00	90 minute time point: AEs, vitals, pain scale
14:00	2 hour time point: AEs, vitals, pain scale		14:30	2 hour time point: AEs, vitals, pain scale
18:00 (or d/c if earlier)	6 hour time point: end of study, AEs		18:30 (or d/c if earlier)	6 hour time point: end of study, AEs

Appendix B. Adverse Event Rates, Power, 95% CI Boundaries

Adverse Event	Fentanly (%)	Ketamine (%)	N per group	calculated power
Any adverse event	40	78	40	0.948
Bad taste in mouth	42	25	40	0.361
Drowsiness	21	16	40	0.088
Dizziness	17	30	40	0.276
Itchy nose	12	4	40	0.259
Nausea	4	6	40	0.069
Dysphoria	4	4	40	0.050
Hallucinations	0	6	40	
Other	0	7	40	

Intranasal sub-dissociative ketamine (IN ketamine)

Adverse Event	Fixed N	Proportion (%)	CI half-width	95% CI lower bound	95% CI upper bound
Any adverse event	40	78%	13%	65%	91%
Bad taste in mouth	40	25%	13%	12%	38%
Drowsiness	40	16%	11%	5%	27%
Dizziness	40	30%	14%	16%	44%
Itchy nose	40	4%	6%	0%	10%
Nausea	40	6%	7%	0%	13%
Dysphoria	40	4%	6%	0%	10%
Hallucinations	40	6%	7%	0%	13%
Other	40	7%	7%	0%	15%

Intranasal fentanyl (IN fentanyl)

Adverse Event	Fixed N	Proportion (%)	CI half-width	95% CI lower bound	95% CI upper bound
Any adverse event	40	40%	15%	25%	55%
Bad taste in mouth	40	42%	15%	27%	57%
Drowsiness	40	21%	13%	8%	34%
Dizziness	40	17%	12%	5%	29%
Itchy nose	40	12%	10%	2%	22%
Nausea	40	4%	6%	0%	10%
Dysphoria	40	4%	6%	0%	10%
Hallucinations	40	0%	0%	0%	0.00%
Other	40	0%	0%	0%	0.00%

Binomial (40, .05) ➔ Prob of 0 events is 0.13, so probably of observing at least one case is 87%.
Binomial (40, .04) ➔ Prob of 0 events is 0.20, so probably of observing at least one case is 80%.

Appendix C. Sample Dosing Tables

FIRST DOSE FENTANYL DOSING (50mcg / 1 mL) TARGET DOSE 1.5 mcg/kg (range 1-2 mcg/kg acceptable)					
Weight Range	**Fentanyl dose (mcg)**	**Fentanyl (mL) total**	**R nare (mL)**	**L nare (mL)**	**DOSE RANGE BY ESTIMATE**
10kg - 11.9kg	16.5 mcg	0.33 mL	0.17 mL	0.16 mL	1.39-1.65 mcg/kg
12kg - 13.9kg	19.5 mcg	0.39 mL	0.2 mL	0.19 mL	1.4-1.625 mcg/kg
14kg - 16.9kg	23 mcg	0.46 mL	0.23 mL	0.23 mL	1.36-1.64 mcg/kg
17kg - 19.9kg	27.5 mcg	0.55 mL	0.28 mL	0.27 mL	1.38-1.62 mcg/kg
20kg - 23.9kg	33 mcg	0.66 mL	0.33 mL	0.33 mL	1.38-1.65 mcg/kg
24kg - 27.9kg	39 mcg	0.78 mL	0.39 mL	0.39 mL	1.40-1.625 mcg/kg
28kg - 32.9kg	45.5 mcg	0.91 mL	0.46 mL	0.45 mL	1.38-1.625 mcg/kg
33kg - 37.9kg	53 mcg	1.06 mL	0.53 mL	0.53 mL	1.40-1.6 mcg/kg
38kg - 43.9kg	61.5 mcg	1.23 mL	0.62 mL	0.61 mL	1.4-1.62 mcg/kg
44kg - 49.9kg	70.5 mcg	1.41 mL	0.71 mL	0.7 mL	1.41-1.6 mcg/kg
50kg - 56.9kg	80 mcg	1.6 mL	0.8 mL	0.8 mL	1.41-1.6 mcg/kg
57kg - 63.9kg	90.5 mcg	1.81 mL	0.91 mL	0.9 mL	1.42-1.59 mcg/kg
64kg - 70kg	100 mcg	2 mL	1 mL	1mL	1.43-1.56 mcg/kg

SECOND DOSE FENTANYL DOSING (50mcg / 1 mL) TARGET DOSE 0.75 mcg/kg (range 0.5-1mcg/kg acceptable)					
Weight Range	**Fentanyl dose (mcg)**	**Fentanyl (mL) total**	**R nare (mL)**	**L nare (mL)**	**DOSE RANGE BY ESTIMATE**
10kg - 11.9kg	8 mcg	0.16 mL	0.08 mL	0.08 mL	0.67-0.8 mcg/kg
12kg - 13.9kg	9.5 mcg	0.19 mL	0.1 mL	0.09 mL	0.68-0.79 mcg/kg
14kg - 16.9kg	11.5 mcg	0.23 mL	0.12 mL	0.11 mL	0.68-0.82 mcg/kg
17kg - 19.9kg	14 mcg	0.28 mL	0.14 mL	0.14 mL	0.7-0.82 mcg/kg
20kg - 23.9kg	16.5 mcg	0.33 mL	0.17 mL	0.16 mL	0.69-0.825 mcg/kg
24kg - 27.9kg	19.5 mcg	0.39 mL	0.2 mL	0.19 mL	0.7-0.81 mcg/kg
28kg - 32.9kg	23 mcg	0.46 mL	0.23 mL	0.23 mL	0.7-0.82 mcg/kg
33kg - 37.9kg	26.5 mcg	0.53 mL	0.27 mL	0.26 mL	0.7-0.8 mcg/kg
38kg - 43.9kg	30.5 mcg	0.61 mL	0.31 mL	0.3 mL	0.69-0.8 mcg/kg
44kg - 49.9kg	35 mcg	0.7 mL	0.35 mL	0.35 mL	0.7-0.8 mcg/kg
50kg - 56.9kg	40 mcg	0.8 mL	0.4 mL	0.4 mL	0.7-0.8 mcg/kg
57kg - 63.9kg	45.5 mcg	0.91 mL	0.46 mL	0.45 mL	0.71-0.8 mcg/kg
64kg - 70kg	50 mcg	1 mL	0.5 mL	0.5 mL	0.71-0.78 mcg/kg

FIRST DOSE KETAMINE ESTIMATED INTRANASAL DOSING (50 mg/mL) Diluent = 0.9% NaCl to protect blinding between fentanyl and ketamine TARGET DOSE 1 mg/kg to achieve 0.4 mg/kg subdissociative dose (range 0.4-0.8 mg/kg)							
Weight Range	**Ketamine dose (mg)**	**Ketamine mL total**	**Diluent mL**	**Ketamine mL + diluent**	**R nare (mL)**	**L nare (mL)**	**Dose Range by Estimate**
10kg - 11.9kg	11 mg	0.22 mL	0.11 mL	0.33 mL	0.17 mL	0.16 mL	0.92-1.1 mg/kg
12kg - 13.9kg	13 mg	0.26 mL	0.13 mL	0.39 mL	0.2 mL	0.19 mL	0.94-1.08 mg/kg
14kg - 16.9kg	15.5 mg	0.31 mL	0.15 mL	0.46 mL	0.23 mL	0.23 mL	0.92-1.1 mg/kg
17kg - 19.9kg	18.5 mg	0.37 mL	0.18 mL	0.55 mL	0.28 mL	0.27 mL	0.93-1.09 mg/kg
20kg - 23.9kg	22 mg	0.44 mL	0.22 mL	0.66 mL	0.33 mL	0.33 mL	0.92-1.1 mg/kg
24kg - 27.9kg	26 mg	0.52 mL	0.26 mL	0.78 mL	0.39 mL	0.39 mL	0.93-1.08 mg/kg
28kg - 32.9kg	30.5 mg	0.61 mL	0.3 mL	0.91 mL	0.46 mL	0.45 mL	0.93-1.09 mg/kg
33kg - 37.9kg	35.5 mg	0.71 mL	0.35 mL	1.06 mL	0.53 mL	0.53 mL	0.94-1.08 mg/kg
38kg - 43.9kg	41 mg	0.82 mL	0.41 mL	1.23 mL	0.62 mL	0.61 mL	0.93-1.08 mg/kg
44kg - 49.9kg	47 mg	0.94 mL	0.47 mL	1.41 mL	0.71 mL	0.7 mL	0.94-1.07 mg/kg
50kg - 56.9kg	53.5 mg	1.07 mL	0.53 mL	1.6 mL	0.8 mL	0.8 mL	0.94-1.07 mg/kg
57kg - 63.9kg	60.5 mg	1.21 mL	0.6 mL	1.81 mL	0.91 mL	0.9 mL	0.95-1.06 mg/kg
64kg - 70kg	67 mg	1.34 mL	0.66 mL	2 mL	1 mL	1mL	0.96-1.05 mg/kg

SECOND DOSE KETAMINE ESTIMATED INTRANASAL DOSING (50 mg/mL) Diluent = 0.9% NaCl to protect blinding between fentanyl and ketamine TARGET DOSE 0.5 mg/kg to achieve 0.2 mg/kg subdissociative dose (range 0.2-0.4 mg/kg)							
Weight Range	**Ketamine dose (mg)**	**Ketamine mL total**	**Diluent mL**	**Ketamine mL + diluent**	**R nare (mL)**	**L nare (mL)**	**Dose Range by Estimate**
10kg - 11.9kg	5.5 mg	0.11 mL	0.05 mL	0.16 mL	0.08 mL	0.08 mL	0.46-0.55 mg/kg
12kg - 13.9kg	6.5 mg	0.13 mL	0.06 mL	0.19 mL	0.1 mL	0.09 mL	0.47-0.54 mg/kg
14kg - 16.9kg	7.5 mg	0.15 mL	0.08 mL	0.23 mL	0.12 mL	0.11 mL	0.44-0.54 mg/kg
17kg - 19.9kg	9 mg	0.18 mL	0.1 mL	0.28 mL	0.14 mL	0.14 mL	0.45-0.53 mg/kg
20kg - 23.9kg	11 mg	0.22 mL	0.11 mL	0.33 mL	0.17 mL	0.16 mL	0.46-0.55 mg/kg
24kg - 27.9kg	13 mg	0.26 mL	0.13 mL	0.39 mL	0.2 mL	0.19 mL	0.47-0.54 mg/kg
28kg - 32.9kg	15 mg	0.3 mL	0.16 mL	0.46 mL	0.23 mL	0.23 mL	0.46-0.54 mg/kg
33kg - 37.9kg	17.5 mg	0.35 mL	0.18 mL	0.53 mL	0.27 mL	0.26 mL	0.46-0.53 mg/kg
38kg - 43.9kg	20 mg	0.4 mL	0.21 mL	0.61 mL	0.31 mL	0.3 mL	0.46-0.53 mg/kg
44kg - 49.9kg	23.5 mg	0.47 mL	0.23 mL	0.7 mL	0.35 mL	0.35 mL	0.47-0.53 mg/kg
50kg - 56.9kg	26.5 mg	0.53 mL	0.27 mL	0.8 mL	0.4 mL	0.4 mL	0.47-0.53 mg/kg
57kg - 63.9kg	30 mg	0.6 mL	0.31 mL	0.91 mL	0.46 mL	0.45 mL	0.47-0.53 mg/kg
64kg - 70kg	33.5 mg	0.67 mL	0.33 mL	1 mL	0.5 mL	0.5 mL	0.48-0.52 mg/kg

Spirit Guideline 2013 Checklist: Randomized Controlled Trial of Intranasal Ketamine Compared to Intranasal Fentanyl for Analgesia in Children with Suspected Forearm Fractures in the Pediatric Emergency Department

This document details where the requirements of the spirit guideline are addressed in this submission. Thank you for considering the manuscript.

Administrative Information

Title: See title page 1.

Trial registration: See title page 1, under regulatory information.

Protocol version: See title page 1.

Funding: See page 10 under Funding Statement.

Roles and responsibilities: Names and contact information are given on the title page and the roles of the investigators are detailed under Author contributions on page 1. The study sponsors played no role in the administration of the trial as detailed on page 10 under Funding statement. The CHaMP node faculty collaborated in reviewing and revising the protocol. The PI is a faculty advisor for the CHaMP node (Charlotte site) and sought internal funding from Carolinas Healthcare System's Carolinas Trauma Network Research Center of Excellence to complete the trial.

Introduction

Background and rationale: The aims, hypotheses and rationale for the trial are provided on pages 2 and 3. The explanation for the comparator is detailed on page 2 in the second paragraph of the background and rationale.

Objectives: See aims on page 3.

Trial design: See trial design on page 3.

Methods: Participants, interventions, and outcomes

Study setting: This is listed on page 3.

Eligibility criteria: The criteria are given on pages 3 and 4.

Interventions: The interventions and drugs, concomitant drugs, and a detailed schedule of study measures are provided on pages 4 and 5 and Appendix A. Patients can withdraw from the study at any time as stated on page 4. The study utilizes a maximum of two doses of study drug and modifications of the intervention will not apply. Study drug is administered in the ED under the direct supervision of the unblinded nurse and adherence to the protocol is closely monitored as stated throughout the description of the interventions, blinding, and study measures Appendix A.

Outcomes: The primary, secondary and exploratory outcomes of the trial are detailed under Outcomes beginning on pages 4 and 5. Definitions of side effects and adverse events have been provided to improve transparency to other investigators.

Participant timeline: All interventions occur during a 6-hour period in the ED. A schematic of the study measures is provided on in Appendix A.

Sample size: The rationale for the estimated number of participants is provided on pages 6 and 7.

Recruitment: The recruitment strategies are detailed on page 4.

Methods: Assignment of interventions

Allocation and concealment: The mechanisms are described on page 7 under Allocation and Concealment.

Implementation: The randomization sequence was generated by the statistician prior to study initiation (page 7 under Allocation and Concealment). Study coordinators enroll the participants as detailed on page 4. The study packets were compiled by an unblinded study nurse who does not serve as a study coordinator prior to study initiation as listed on page 7 (Allocation and Concealment, paragraph 2). The packets contain necessary information to assign the participants to an intervention as detailed on page 7.

Blinding: The participants, study coordinators, and investigators are blinded to the study intervention. The nurse administering study drug is unblinded. A research nurse and the investigational pharmacist are unblinded to the study intervention. This is detailed on page 7 under Allocation and Concealment.

Methods: Data Collection, management, and analysis

Data collection methods: The data collection methods are detailed on page 7 under Data Collection and Management.

Data management: The last paragraph of page 7 details how data is stored using REDCap.

Statistical methods: The analysis of the primary, secondary and exploratory outcomes are detailed on page 8.

Sample size: A discussion of the sample size justification is detailed on pages 6 and 7.

Methods: Monitoring

Data monitoring: The composition of the data safety monitoring board and its role are detailed on page 8 and 9.

Harms: The types and definitions of side effects (adverse events) and serious adverse events are detailed under outcomes on page 5 and 6.

Auditing: See page 9.

Ethics and Dissemination

See page 9 for the research ethics approval and procedure for protocol modifications.

Consent and Assent: The consent procedures are described on page 4.

Confidentiality and access to data: See the bottom of the first paragraph on page 7 under Data Collection and Management.

Declaration of interests: See page 9 under Competing Interests Statement.

Dissemination policy: See page 9 which details how study data will be utilized.

BMJ Open

Study Protocol of a Randomized Controlled Trial of Intranasal Ketamine Compared to Intranasal Fentanyl for Analgesia in Children with Suspected, Isolated Extremity Fractures in the Pediatric Emergency Department

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Study Protocol of a Randomized Controlled Trial of Intranasal Ketamine Compared to Intranasal Fentanyl for Analgesia in Children with Suspected, Isolated Extremity Fractures in the Pediatric Emergency Department

Version 4.0

June 8, 2016

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Regulatory Information: This trial will be conducted under the authority of the principal investigator based upon 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. This study was registered on clinicaltrials.gov prior to enrollment (NCT02521415).

Abstract

Introduction: Fentanyl is the most widely studied intranasal (IN) analgesic in children. Intranasal, sub-dissociative (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, multi-center 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 utilization.

Methods and Analysis: This double-blind, randomized controlled, pilot trial will compare INSD ketamine (1mg/kg) to IN fentanyl (1.5 micrograms/kg) for analgesia in 80 children ages 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 minutes after drug administration. The primary efficacy outcome will be exploratory and will be the mean reduction of pain scale scores at 20 minutes. 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 two doses of study drug.

Ethics and Dissemination: This study was approved by the United States 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 multicenter, non-inferiority trial.

Trial Registration: Clinical trials NCT02521415

Protocol Strengths:

- Tests a novel agent and route of administration for analgesia (INSD ketamine) with potential for an opioid sparing effect
- Double, Blind, Randomized Controlled Trial
- Compliant with the SPIRIT guidelines
- Trial examines feasibility of a protocol prior to multicenter implementation

Protocol Weaknesses:

- Trial will not establish non-inferiority for INSD ketamine for analgesia compared to IN fentanyl, but will provide important safety and efficacy data required to design an adequately powered, multi-center, non-inferiority trial.

Background and Rationale:

Children often do not receive adequate analgesia for traumatic injuries in the emergency department setting.[1-4] A study of 773 children 0-15 years of age with isolated long-bone fractures treated in the emergency department demonstrated that only 10% of injured children received adequate pain medicine.[4] Failure to recognize 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 IV placement.[5,8] The pharmacokinetics of intranasal drug administration dampen the rapidity of drug absorption and minimize side effects yet still achieve therapeutic drug levels and adequate analgesia.[11] IN fentanyl is the most frequently used and most widely studied intranasal analgesic with a reported bioavailability of 71%.[12,13] In one prospective, double-blind, placebo-controlled, randomized clinical trial, intranasal fentanyl at 150 micrograms/kg demonstrated efficacy similar to intravenous morphine at 0.1 mg/kg.[8] IN fentanyl serves an ideal comparator in this study for its demonstrated benefit specific to children with orthopedic injuries presenting to the emergency department.[8,14]

We believe intranasal, sub-dissociative (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 intranasal route and standard 1mg/kg doses provide absorbed drug levels in the sub-dissociative range.[15,16]** Ketamine is used increasingly for acute and chronic pain in both children and adults with sickle cell disease and cancer.[17-20] Ketamine has been found to be safe and effective for analgesia in the pre-hospital, battlefield, post-operative, and emergency department settings.[11,21]

The largest double, blind, randomized, pediatric 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 minutes, median pain scale score reductions on a 100 mm scale were 45 mm for ketamine and 40 mm for fentanyl (difference 5 mm; 95% confidence interval [CI] -10 to 20mm) by combined results of the Faces Pain Scales-Revised (ages 3-6 years) and VAS scales (ages 7 and up).[22] For fentanyl, 15 patients reported adverse events and for ketamine 28 patients reported adverse events, 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 adverse events.[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 adverse events 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 anti-nociceptive activity of morphine.[20,21,23] 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 ages 11-79 years with pain treated in the ED using doses of IN ketamine of 0.5 mg/kg to 0.75 mg/kg reported that 3 patients failed to complete the protocol at 60 minutes because

opioid rescue analgesia was required.[11] A pilot, observational study of 28 children ages 3-13 years with fracture pain examined the effectiveness of intranasal 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 randomized controlled, double-blind trial of adult patients treated for pain in the ED compared intravenous ketamine at 0.3 mg/kg to intravenous morphine at 0.1 mg/kg and found no difference in the incidence of rescue fentanyl analgesia at 30 or 60 minutes.[25] IN ketamine provides pain relief up to one hour and may reduce opioid utilization during the ED stay on this basis alone.[22,24]

The current study examines the feasibility of a larger, multi-centered 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 utilization during the ED stay.

Aims and Hypotheses

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

Primary Aim: **Examine the feasibility of a future multi-centered emergency department, non-inferiority study by obtaining data required for trial planning, measuring the time to consent, and refining the processes to randomize 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 three-fold or a serious adverse event rate of 5% or more for ketamine.**

Safety Aim**: Compare the frequency of cumulative adverse events at 60 minutes after drug administration among children randomized to receive either intranasal sub-dissociative ketamine (IN ketamine) or intranasal fentanyl (IN fentanyl) for pain control in the emergency department. To fully characterize novel side effects, adverse events or additive effects of additional interventions such as sedation, we will collect data every 30 minutes 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 intranasal ketamine to intranasal 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 minutes.**

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 randomization and treatment with IN ketamine or IN fentanyl.**

Trial Design

This double-blind, randomized controlled trial will compare intranasal, sub-dissociative ketamine (1mg/kg) to intranasal fentanyl (1.5 micrograms/kg) for analgesia in children presenting to the emergency department 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 center with 35,000 pediatric emergency department visits per year and a Level II trauma center. The department supports an emergency medicine residency program and pediatric emergency medicine fellowship. There is in-house orthopedic surgery coverage twenty-four hours per day and resident physicians are supervised by board-certified pediatric orthopedic and emergency medicine specialists.

Eligibility criteria

Verbal children ages 4-17 years with a suspected, single extremity fracture requiring analgesia will be screened for enrollment. 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 score (for children ages 4-10 years) or the Adult Pain Rating Scale score (for children ages 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 FACES Pain Rating 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 FACES Pain-Revised Scale (for children ages 4-10 years) and Visual Analog Scale scores (for children ages 11-17) 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. GCS < 15 at ED presentation
2. Reported allergy or adverse reaction to ketamine or fentanyl
3. Reported pregnancy
4. Intoxication
5. Hypotension defined as less than 70 mmHg +2x age or less than 90 mm Hg for patients greater than 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, MO). The parents or legal guardians of eligible patients will be approached by a care team member. Research coordinators will utilize a standard 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 one will receive 1 mg/kg intranasal ketamine (Ketalar 50mg/mL) administered according to a standard dosing table (Appendix A). Arm two will receive 1.5 micrograms/kg intranasal fentanyl (fentanyl citrate 100 micrograms/2 mL) administered according to a standard dosing table (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 randomized to ketamine treatment or IN fentanyl at 0.75 mcg/kg for patients randomized to fentanyl treatment) at least 20 minutes after administration of the first dose. The maximum dose of ketamine a patient may receive will be 70 mg (1mg/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 micrograms (1.5 mcg/kg) for the first dose or 53 micrograms (0.75 mcg/kg) for the second dose or total of 158 micrograms (2.25 mcg/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 enroll 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 enrollment. 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 adverse events and side effects at 60 minutes after drug delivery. These outcome definitions are detailed in 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 minutes. 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 FACES Pain-Revised Scale (FPS-R) will be used for patients ages 4-10 years and the Visual Analog Scale (VAS) will be used for patients 11-17 years. The FPS-R and VAS scores will be used for the exploratory efficacy outcome measure because as those scales are validated for research.[26-29] The Wong-Baker FACES Pain Rating Scale (ages 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 enrollment 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 Scale score of 4 (ages 11-17 years) after 20 minutes. No more than two doses of study drug will be given.

Sample size

Due 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 minutes 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%.(21)With n=40 children randomized 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 confidence interval half-widths are approximately 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 Appendix C provide more detail on the expected adverse event rates for the study drugs, the associated 95% confidence intervals, 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 standard deviations 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 adverse events at 60 minutes after study drug administration.

Allocation and Concealment

The study statistician will generate the allocation lists using a permuted block randomization with random block sizes and stratification by age (4-10 years, 11-17 years) with 1:1 allocation. The lists will be generated using SAS Enterprise Guide version 6.1 and the RANUNI function. To maintain allocation concealment, assignments will be placed in consecutively numbered, sealed opaque study packets in the emergency department 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 (MAR) without revealing the treatment arm. The randomization 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. Randomization 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 color and odorless. The drug vial is not viewed at the bedside and both drugs are administered in similar syringes attached to a mucosal atomizer device (MAD). The participants, treating physicians, and outcome assessors will remain blinded to the group allocation.

Data Collection and Management

Research coordinators will document adverse events (using a standardized checklist) every 5 minutes for the first fifteen minutes after medication administration and then every 30 minutes for the next two hours. Vital signs and pain scale assessments will be repeated every 10 minutes for the first 30 minutes and then every 30 minutes for the next two hours. 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 electronic data capture tools.[31] REDCap (Research Electronic Data Capture) 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 PI 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 multicenter trial, we will estimate the proportion of patients consented out of all potentially eligible patients, the time to consent, the proportion successfully randomized, 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 chi-square test or Fisher's exact test for categorical data. The primary safety analysis will compare the proportion of adverse events among children randomized to receive either INSD ketamine or IN fentanyl for pain control in the emergency department. Proportions and 95% confidence intervals will be calculated for each adverse event and compared using chi-square test or Fisher's exact test where appropriate. Since we will stratify the randomization by age (4-10 years and 11-17 years), we will use multiple logistic regression to compare the rate of any adverse event between ketamine and fentanyl controlling for age. The Student 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 emergency department evaluation. We hypothesize the ketamine group will have lower use of opioid pain medication. SAS® Enterprise Guide® 6.1 will be used for all analyses. A two-tailed p-value of less than 0.05 will be considered statistically significant. We will also use this study to gain preliminary estimates of standard deviations 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% confidence intervals 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 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 pediatric emergency department and include several other clinicians including a pediatric intensivist and a biostatistician.

The study biostatistics team will provide a report to the DSMB after the first five 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 adverse events.

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 program 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 multicenter, non-inferiority trial comparing intranasal ketamine and intranasal fentanyl and will add to the limited existing literature for intranasal ketamine in children. This study was approved by both the FDA and the local institutional review board. All protocol changes were reviewed by the DSMB, IRB, FDA and amended on clinical trials.gov.

Authors Contribution

The principal investigator drafted and revised the protocol. Dr. Jonathan Studnek 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. Dr. Michael Runyon 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. Dr. Kathleen Bryant and Dr. James Young are fellows in the Department of Emergency Medicine and revised the protocol and championed the nursing and physician education required for implementation. Dr. Charity Moore is a biostatistician and assisted in the conception of the study and the analysis plan. Dr. Kelly VanderHave, Department of Pediatric Orthopedics, and Dr. Eric Grossman, Department of Surgery, assisted in revising the protocol. Melanie Hogg 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 Statement

An annual conflict of interest disclosure form is completed by all faculty. No authors disclosed a relevant conflict of interest.

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Appendix A. Sample Dosing Tables

FIRST DOSE FENTANYL DOSING (50mcg / 1 mL) TARGET DOSE 1.5 mcg/kg (range 1-2 mcg/kg acceptable)					
Weight Range	**Fentanyl dose (mcg)**	**Fentanyl (mL) total**	**R nare (mL)**	**L nare (mL)**	**DOSE RANGE BY ESTIMATE**
10kg - 11.9kg	16.5 mcg	0.33 mL	0.17 mL	0.16 mL	1.39-1.65 mcg/kg
12kg - 13.9kg	19.5 mcg	0.39 mL	0.2 mL	0.19 mL	1.4-1.625 mcg/kg
14kg - 16.9kg	23 mcg	0.46 mL	0.23 mL	0.23 mL	1.36-1.64 mcg/kg
17kg - 19.9kg	27.5 mcg	0.55 mL	0.28 mL	0.27 mL	1.38-1.62 mcg/kg
20kg - 23.9kg	33 mcg	0.66 mL	0.33 mL	0.33 mL	1.38-1.65 mcg/kg
24kg - 27.9kg	39 mcg	0.78 mL	0.39 mL	0.39 mL	1.40-1.625 mcg/kg
28kg - 32.9kg	45.5 mcg	0.91 mL	0.46 mL	0.45 mL	1.38-1.625 mcg/kg
33kg - 37.9kg	53 mcg	1.06 mL	0.53 mL	0.53 mL	1.40-1.6 mcg/kg
38kg - 43.9kg	61.5 mcg	1.23 mL	0.62 mL	0.61 mL	1.4-1.62 mcg/kg
44kg - 49.9kg	70.5 mcg	1.41 mL	0.71 mL	0.7 mL	1.41-1.6 mcg/kg
50kg - 56.9kg	80 mcg	1.6 mL	0.8 mL	0.8 mL	1.41-1.6 mcg/kg
57kg - 63.9kg	90.5 mcg	1.81 mL	0.91 mL	0.9 mL	1.42-1.59 mcg/kg
64kg - 70kg	100 mcg	2 mL	1 mL	1mL	1.43-1.56 mcg/kg

SECOND DOSE FENTANYL DOSING (50mcg / 1 mL) TARGET DOSE 0.75 mcg/kg (range 0.5-1mcg/kg acceptable)					
Weight Range	**Fentanyl dose (mcg)**	**Fentanyl (mL) total**	**R nare (mL)**	**L nare (mL)**	**DOSE RANGE BY ESTIMATE**
10kg - 11.9kg	8 mcg	0.16 mL	0.08 mL	0.08 mL	0.67-0.8 mcg/kg
12kg - 13.9kg	9.5 mcg	0.19 mL	0.1 mL	0.09 mL	0.68-0.79 mcg/kg
14kg - 16.9kg	11.5 mcg	0.23 mL	0.12 mL	0.11 mL	0.68-0.82 mcg/kg
17kg - 19.9kg	14 mcg	0.28 mL	0.14 mL	0.14 mL	0.7-0.82 mcg/kg
20kg - 23.9kg	16.5 mcg	0.33 mL	0.17 mL	0.16 mL	0.69-0.825 mcg/kg
24kg - 27.9kg	19.5 mcg	0.39 mL	0.2 mL	0.19 mL	0.7-0.81 mcg/kg
28kg - 32.9kg	23 mcg	0.46 mL	0.23 mL	0.23 mL	0.7-0.82 mcg/kg
33kg - 37.9kg	26.5 mcg	0.53 mL	0.27 mL	0.26 mL	0.7-0.8 mcg/kg
38kg - 43.9kg	30.5 mcg	0.61 mL	0.31 mL	0.3 mL	0.69-0.8 mcg/kg
44kg - 49.9kg	35 mcg	0.7 mL	0.35 mL	0.35 mL	0.7-0.8 mcg/kg
50kg - 56.9kg	40 mcg	0.8 mL	0.4 mL	0.4 mL	0.7-0.8 mcg/kg
57kg - 63.9kg	45.5 mcg	0.91 mL	0.46 mL	0.45 mL	0.71-0.8 mcg/kg
64kg - 70kg	50 mcg	1 mL	0.5 mL	0.5 mL	0.71-0.78 mcg/kg

Appendices Page **2** of **6** **IN Ketamine vs IN Fentanyl**

v 4.0 6/8/16

FIRST DOSE KETAMINE ESTIMATED INTRANASAL DOSING (50 mg/mL) Diluent = 0.9% NaCl to protect blinding between fentanyl and ketamine TARGET DOSE 1 mg/kg to achieve 0.4 mg/kg subdissociative dose (range 0.4-0.8 mg/kg)							
Weight Range	**Ketamine dose (mg)**	**Ketamine mL total**	**Diluent mL**	**Ketamine mL + diluent**	**R nare (mL)**	**L nare (mL)**	**Dose Range by Estimate**
10kg - 11.9kg	11 mg	0.22 mL	0.11 mL	0.33 mL	0.17 mL	0.16 mL	0.92-1.1 mg/kg
12kg - 13.9kg	13 mg	0.26 mL	0.13 mL	0.39 mL	0.2 mL	0.19 mL	0.94-1.08 mg/kg
14kg - 16.9kg	15.5 mg	0.31 mL	0.15 mL	0.46 mL	0.23 mL	0.23 mL	0.92-1.1 mg/kg
17kg - 19.9kg	18.5 mg	0.37 mL	0.18 mL	0.55 mL	0.28 mL	0.27 mL	0.93-1.09 mg/kg
20kg - 23.9kg	22 mg	0.44 mL	0.22 mL	0.66 mL	0.33 mL	0.33 mL	0.92-1.1 mg/kg
24kg - 27.9kg	26 mg	0.52 mL	0.26 mL	0.78 mL	0.39 mL	0.39 mL	0.93-1.08 mg/kg
28kg - 32.9kg	30.5 mg	0.61 mL	0.3 mL	0.91 mL	0.46 mL	0.45 mL	0.93-1.09 mg/kg
33kg - 37.9kg	35.5 mg	0.71 mL	0.35 mL	1.06 mL	0.53 mL	0.53 mL	0.94-1.08 mg/kg
38kg - 43.9kg	41 mg	0.82 mL	0.41 mL	1.23 mL	0.62 mL	0.61 mL	0.93-1.08 mg/kg
44kg - 49.9kg	47 mg	0.94 mL	0.47 mL	1.41 mL	0.71 mL	0.7 mL	0.94-1.07 mg/kg
50kg - 56.9kg	53.5 mg	1.07 mL	0.53 mL	1.6 mL	0.8 mL	0.8 mL	0.94-1.07 mg/kg
57kg - 63.9kg	60.5 mg	1.21 mL	0.6 mL	1.81 mL	0.91 mL	0.9 mL	0.95-1.06 mg/kg
64kg - 70kg	67 mg	1.34 mL	0.66 mL	2 mL	1 mL	1mL	0.96-1.05 mg/kg

SECOND DOSE KETAMINE ESTIMATED INTRANASAL DOSING (50 mg/mL) Diluent = 0.9% NaCl to protect blinding between fentanyl and ketamine TARGET DOSE 0.5 mg/kg to achieve 0.2 mg/kg subdissociative dose (range 0.2-0.4 mg/kg)							
Weight Range	**Ketamine dose (mg)**	**Ketamine mL total**	**Diluent mL**	**Ketamine mL + diluent**	**R nare (mL)**	**L nare (mL)**	**Dose Range by Estimate**
10kg - 11.9kg	5.5 mg	0.11 mL	0.05 mL	0.16 mL	0.08 mL	0.08 mL	0.46-0.55 mg/kg
12kg - 13.9kg	6.5 mg	0.13 mL	0.06 mL	0.19 mL	0.1 mL	0.09 mL	0.47-0.54 mg/kg
14kg - 16.9kg	7.5 mg	0.15 mL	0.08 mL	0.23 mL	0.12 mL	0.11 mL	0.44-0.54 mg/kg
17kg - 19.9kg	9 mg	0.18 mL	0.1 mL	0.28 mL	0.14 mL	0.14 mL	0.45-0.53 mg/kg
20kg - 23.9kg	11 mg	0.22 mL	0.11 mL	0.33 mL	0.17 mL	0.16 mL	0.46-0.55 mg/kg
24kg - 27.9kg	13 mg	0.26 mL	0.13 mL	0.39 mL	0.2 mL	0.19 mL	0.47-0.54 mg/kg
28kg - 32.9kg	15 mg	0.3 mL	0.16 mL	0.46 mL	0.23 mL	0.23 mL	0.46-0.54 mg/kg
33kg - 37.9kg	17.5 mg	0.35 mL	0.18 mL	0.53 mL	0.27 mL	0.26 mL	0.46-0.53 mg/kg
38kg - 43.9kg	20 mg	0.4 mL	0.21 mL	0.61 mL	0.31 mL	0.3 mL	0.46-0.53 mg/kg
44kg - 49.9kg	23.5 mg	0.47 mL	0.23 mL	0.7 mL	0.35 mL	0.35 mL	0.47-0.53 mg/kg
50kg - 56.9kg	26.5 mg	0.53 mL	0.27 mL	0.8 mL	0.4 mL	0.4 mL	0.47-0.53 mg/kg
57kg - 63.9kg	30 mg	0.6 mL	0.31 mL	0.91 mL	0.46 mL	0.45 mL	0.47-0.53 mg/kg
64kg - 70kg	33.5 mg	0.67 mL	0.33 mL	1 mL	0.5 mL	0.5 mL	0.48-0.52 mg/kg

Appendix B. Side Effects and Serious Adverse Events

Side Effect Definitions

These are common events experienced by patients receiving ketamine or fentanyl that do not change outcomes for the patient but may affect the patient experience and willingness to receive the drug in the future. For the purposes of this study, we will screen patients for each of the following side effects, and report them as **anticipated adverse events**. Each individual event is defined below.

- **Bad taste in mouth** is defined as subjective agreement by the patient demonstrated by attempting to spit out the medicine, grimacing in response to a foul taste and/or when asked "did you experience a bad taste in your mouth after the medicine."
- **Drowsiness** is defined by subjective agreement by the patient or family that the patient appears drowsy. Drowsiness will be distinguished from altered mental status by awakening to voice.
- **Dizziness** is defined by subjective agreement by the patient or family that the patient feels or appears lightheaded or vertiginous. It may also be documented by unsteady gait.
- **Dysphoria** is defined by subjective agreement by the patient or family that the patient feels unpleasant or irritable.
- **Itchy nose** is defined by subjective agreement by the patient or family.
- **Myoclonus** is defined as muscle stiffening or jerking as noted on clinical examination.
- **Nausea** is defined by subjective agreement by the patient or family that the patient feels like he or she may vomit.
- **Vomiting** is defined as any emesis after administration of the drug.
- **Novel subjective negative experiences** are defined by asking the patient and family if the patient is experiencing any additional symptoms not already addressed.

Serious Adverse Events Definitions

- A **serious adverse event** (SAE) includes any adverse event that begins after the short form consent has been completed or within 6-hours thereafter that causes a threat to life, threat to limb or an organ system, causes prolongation of hospitalization, or requires new medical or surgical treatment to correct. Events will be assessed by the PI. Events coded as possibly, probably or definitely related will be considered study-related. Specific SAEs previously reported in association with ketamine or fentanyl administration are listed below and will be considered **anticipated serious adverse events**. Anticipated SAE's will be addressed similarly to any SAE.
- **Apnea** is defined as ceased respirations recognized by clinical examination, or end tidal C02 tracing, requiring bag valve mask ventilation.
- **Bradypnea** is defined as a fall in respiratory rate and oxygen saturations requiring physical stimulation of the patient.
- **Chest wall rigidity** is defined as ineffective ventilation requiring intervention, including bag valve mask ventilation or administration of naloxone.
- **Dissociative dosing** is defined as development of nystagmus.
- **Emergence reaction** is defined as any odd behavior or subjective report of an uncomfortable emotional experience or hallucinations during use of the drug during the study.

- **Hypotension** is defined as blood pressure below 70 plus 2x the age in years, or less than 90 mm Hg for patients older than 10 years, requiring intervention.
- **Hypoxia** is defined as oxygen saturations below 90% requiring bag valve mask ventilation.
- **Intubation** is defined as an intubation or placement of a supraglottic airway secondary to loss of airway protective reflexes.
- **Laryngospasm** is defined as an obstructive pattern by end tidal CO2 tracing OR clinical examination.
- **Nightmares** will be defined as negative experiences during sleep during the study follow up period.

Seizure will be defined as generalized tonic and/or clonic movements in association with alteration of consciousness.

Appendix C. Adverse Event Rates, Power, 95% CI Boundaries

Adverse Event	Fentanly (%)	Ketamine (%)	N per group	calculated power
Any adverse event	40	78	40	0.948
Bad taste in mouth	42	25	40	0.361
Drowsiness	21	16	40	0.088
Dizziness	17	30	40	0.276
Itchy nose	12	4	40	0.259
Nausea	4	6	40	0.069
Dysphoria	4	4	40	0.050
Hallucinations	0	6	40	
Other	0	7	40	

Intranasal sub-dissociative ketamine (IN ketamine)

Adverse Event	Fixed N	Proportion (%)	CI half-width	95% CI lower bound	95% CI upper bound
Any adverse event	40	78%	13%	65%	91%
Bad taste in mouth	40	25%	13%	12%	38%
Drowsiness	40	16%	11%	5%	27%
Dizziness	40	30%	14%	16%	44%
Itchy nose	40	4%	6%	0%	10%
Nausea	40	6%	7%	0%	13%
Dysphoria	40	4%	6%	0%	10%
Hallucinations	40	6%	7%	0%	13%
Other	40	7%	7%	0%	15%

Intranasal fentanyl (IN fentanyl)

Adverse Event	Fixed N	Proportion (%)	CI half-width	95% CI lower bound	95% CI upper bound
Any adverse event	40	40%	15%	25%	55%
Bad taste in mouth	40	42%	15%	27%	57%
Drowsiness	40	21%	13%	8%	34%
Dizziness	40	17%	12%	5%	29%
Itchy nose	40	12%	10%	2%	22%
Nausea	40	4%	6%	0%	10%
Dysphoria	40	4%	6%	0%	10%
Hallucinations	40	0%	0%	0%	0.00%
Other	40	0%	0%	0%	0.00%

Binomial (40, .05) ➔ Prob of 0 events is 0.13, so probably of observing at least one case is 87%.
Binomial (40, .04) ➔ Prob of 0 events is 0.20, so probably of observing at least one case is 80%.

Appendix D. Study Measures: Example of Study Procedures for a Patient Receiving First Dose at Noon and Requiring a Second Dose

Dose 1			Dose 2	
Time	**Event**		**Time**	**Event**
11:50	Screening & Enrollment	Dose 2 Required		
11:53	Pre-medication and baseline measures			
12:00	Study Drug Dose 1		12:30	Study Drug Dose 2
12:05	5 minute time point: AEs		12:35	5 minute time point: AEs
12:10	10 minute time point: AEs, vitals, pain scale		12:40	10 minute time point: AEs, vitals, pain scale
12:15	15 minute time point: AEs		12:45	15 minute time point: AEs
12:20	20 minute time point: AEs, vitals, pain scale		12:50	20 minute time point: AEs, vitals, pain scale
12:30	30 minute time point: AEs, vitals, pain scale		13:00	30 minute time point: AEs, vitals, pain scale
13:00	60 minute time point: AEs, vitals, pain scale		13:30	60 minute time point: AEs, vitals, pain scale
13:30	90 minute time point: AEs, vitals, pain scale		14:00	90 minute time point: AEs, vitals, pain scale
14:00	2 hour time point: AEs, vitals, pain scale		14:30	2 hour time point: AEs, vitals, pain scale
18:00 (or d/c if earlier)	6 hour time point: end of study, AEs		18:30 (or d/c if earlier)	6 hour time point: end of study, AEs

Spirit Guideline 2013 Checklist: Study Protocol of a Randomized Controlled Trial of Intranasal Ketamine Compared to Intranasal Fentanyl for Analgesia in Children with Suspected, Isolated Extremity Fractures in the Pediatric Emergency Department

This document details where the requirements of the spirit guideline are addressed in this submission. Thank you for considering the manuscript.

Administrative Information

Title: See title page 1.

Trial registration: See title page 1, under regulatory information.

Protocol version: See title page 1.

Funding: See page 9 under Funding Statement.

Roles and responsibilities: Names and contact information are given on the title page and the roles of the investigators are detailed under Author contributions on page 9. The study sponsors played no role in the administration of the trial as detailed on page 9 under Funding statement. The CHaMP node faculty collaborated in reviewing and revising the protocol. The PI is a faculty advisor for the CHaMP node (Charlotte site) and sought internal funding from Carolinas Healthcare System's Carolinas Trauma Network Research Center of Excellence to complete the trial.

Introduction

Background and rationale: The aims, hypotheses and rationale for the trial are provided on pages 3 and 4. The explanation for the comparator is detailed on page 3 in the second paragraph of the background and rationale.

Objectives: See aims on page 4.

Trial design: See trial design on page 4.

Methods: Participants, interventions, and outcomes

Study setting: This is listed on page 5.

Eligibility criteria: The criteria are given on page 5.

Interventions: The interventions and drugs, concomitant drugs, and a detailed schedule of study measures are provided on page 6 and Appendix A. The study utilizes a maximum of two doses of study drug and modifications of the intervention will not apply. Study drug is administered in the ED under the direct supervision of the unblinded nurse and adherence to the protocol is closely monitored as stated throughout the description of the interventions, blinding, and study measures (pages 6 and 7 and Appendix D).

Outcomes: The primary, secondary and exploratory outcomes of the trial are detailed under Outcomes beginning on pages 6 and 7. Definitions of side effects and adverse events have been provided to improve transparency to other investigators (Appendix B).

Participant timeline: All interventions occur during a 6-hour period in the ED, or until the patient is discharged from the ED. A schematic of the study measures is provided on in Appendix D.

Sample size: The rationale for the estimated number of participants is provided on page 7.

Recruitment: The recruitment strategies are detailed on page 5.

Methods: Assignment of interventions

Allocation and concealment: The mechanisms are described on page 7 under Allocation and Concealment.

Implementation: The randomization sequence was generated by the statistician prior to study initiation (page 7 under Allocation and Concealment). Study coordinators enroll the participants as detailed on page 5. The study packets were compiled by an unblinded study nurse who does not serve as a study coordinator prior to study initiation as listed on page 7 (Allocation and Concealment, paragraph 2). The packets contain necessary information to assign the participants to an intervention as detailed on page 7.

Blinding: The participants, study coordinators, and investigators are blinded to the study intervention. The nurse administering study drug is unblinded. A research nurse and the investigational pharmacist are unblinded to the study intervention. This is detailed on page 7 under Allocation and Concealment.

Methods: Data Collection, management, and analysis

Data collection methods: The data collection methods are detailed on page 8 under Data Collection and Management.

Data management: The second paragraph of page 8 details how data is stored using REDCap.

Statistical methods: The analysis of the primary, secondary and exploratory outcomes are detailed on page 8.

Sample size: A discussion of the sample size justification is detailed on page 7.

Methods: Monitoring

Data monitoring: The composition of the data safety monitoring board and its role are detailed on page 8 and 9.

Harms: The types and definitions of side effects (adverse events) and serious adverse events are detailed in Appendix B.

Auditing: See page 9.

Ethics and Dissemination

See page 9 for the research ethics approval and procedure for protocol modifications.

Consent and Assent: The consent procedures are described on page 5.

Confidentiality and access to data: See the bottom of the second paragraph on page 8 under Data Collection and Management.

Declaration of interests: See page 10 under Competing Interests Statement.

Dissemination policy: See page 10 which details how study data will be utilized.