STUDY TITLE:
Pain Reduction with Intranasal Medication for Extremity Injuries (PRIME): A Randomized Clinical Noninferiority Trial of Intranasal Ketamine vs. Fentanyl

PROTOCOL TITLE:
Pain Reduction with Intranasal Medications for Extremity injuries (PRIME)

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PROTOCOL SYNOPSIS

STUDY TITLE:

A Randomized Controlled Trial of Intranasal Sub-dissociative Dosing of Ketamine Compared to Intranasal Fentanyl for Treatment of Pain Associated with Acute Extremity Injuries in Children

PROTOCOL TITLE

Pain Reduction with Intranasal Medications for Extremity injuries (PRIME)

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I. ABSTRACT

Introduction: Inadequate pain control in the emergency department, particularly in the pediatric population, is a major health concern. The intranasal route of medication administration is gaining popularity secondary to its rapid onset of action, minimal discomfort for the patient and relative simplicity. When pediatric patients present with moderate to severe pain from traumatic injuries, opioids are currently the most frequently used class of analgesia, but they may not always be the best option for numerous reasons. Sub-dissociative dosing of ketamine has been shown to be an effective alternative to opioids in providing adequate pain relief.

Objectives: The objectives of this study are to 1) determine if intranasal ketamine is non-inferior to intranasal fentanyl in reduction of pain in children presenting with extremity injuries and 2) define and compare the level of sedation and respiratory side effect profile associated with intranasal ketamine and fentanyl.

Methods: The proposed study is a double-blind, randomized clinical non-inferiority trial of intranasal sub-dissociative ketamine compared to intranasal fentanyl for children ages 8 through 17 years of age presenting to the emergency department with moderate or severe pain due to traumatic extremity injury.

Discussion: This study will determine whether intranasal ketamine is an effective alternative to intranasal fentanyl for analgesia in children. This would be particularly useful in children who experience adverse effects with opioids, have developed opioid tolerance as a result of chronic painful conditions, have poor opioid sensitivity due to their genetic predisposition, in pediatric trauma patients with hypotension or in patients requiring procedural sedation during their emergency department visit.

II. PURPOSE OF STUDY

The purpose of this study is to compare intranasal sub-dissociative dosing of ketamine with intranasal fentanyl for acute pain associated with traumatic limb injuries in children 8-17 years of age presenting to the emergency department.

Primary Objective (or Aim)

The primary objective of this study is to determine if intranasal sub-dissociative ketamine (1.5 mg/kg) is non-inferior to intranasal fentanyl (2 mcg/kg) in reduction of moderate and severe pain (VAS score greater than 35 mm [1]) associated with extremity injuries in children ages 8 years through 17 years of age.

> Hypothesis #1: Intranasal sub-dissociative ketamine (1.5 mg/kg) and intranasal fentanyl (2 mcg/kg) will both reduce pain by a mean VAS score of at least 15 mm. There will be no significant difference in the means for reduction in pain score between patients receiving intranasal ketamine and those receiving intranasal fentanyl.

Secondary Objective (or Aim)

The secondary objective is to define and compare the level of sedation associated with intranasal sub-dissociative ketamine (1.5 mg/kg) and intranasal fentanyl (2 mcg/kg) as measured by the University of Michigan Sedation Scale Score and capnometry values.

> Hypothesis #2a: There will be no significant difference in mean sedation scale scores between the intranasal ketamine group and the intranasal fentanyl group.
>
> Hypothesis #2b: There will be no significant difference in the mean capnometry values of the two groups. Patients in both groups will not experience hypopneic hypoventilation (decrease in capnometry value of ≥ 10 mm Hg).

III. BACKGROUND

A recent Institute of Medicine report illustrates that inadequate pain control is a major public health concern [2], especially in the emergency department [3]. Despite this increased awareness, pain continues to be underdiagnosed and undertreated, particularly in the pediatric population [4, 5]. In one study, less than half of 172 children presenting with acute limb fractures received an analgesic during their emergency department visit[6]. A more recent study in 2012 looking at 773 children with long bone fractures demonstrated that 10% received adequate pain medication, 31% received inadequate pain medication and 59% received no pain medication within the first hour of arriving in the emergency department [7]. In combined emergency departments where both adults and pediatric patients are treated, children are significantly less likely than adults to received pain medications [8, 9], with the youngest children being the most vulnerable population [7, 10]. Furthermore, when children do receive pain medication, they often encounter long delays in medication administration [11] possibly due to the time required to obtain intravenous access. More recently, the intranasal route has been shown to offer a more efficient alternative to allow for faster delivery of pain medication [12]. This route is gaining popularity secondary to its rapid onset of action, minimal discomfort for the patient and relative simplicity.

Opioids are the most commonly used class of analgesic pain medication for children presenting in severe pain due to traumatic injuries [7]. Their use during pediatric emergency department visits has increased significantly over the past decade [13]. However, multiple studies show the majority of children who present in severe pain do not receive opioids, receive doses that are below those recommended [4,

7-10, 14] or experience long delays in receiving opioids [11, 15]. The reasons for this are unclear, but we speculate that this may be due in part to fear of adverse effects of opioids, provider inexperience with opioid use in children or fear of contributing to opioid tolerance or abuse. Additionally, due to genetic variations that may affect opioid sensitivity, ideal dosing to adequately control severe pain in the majority of patients yet avoid adverse medication-related side effects is difficult to ascertain and may lead providers to seek out non-opioid alternatives for patients with acute severe pain [16-18].

In the adult population, low dose ketamine is well tolerated and has been used successfully as an adjuvant [19-25] and an alternative [26-30] to opioids to provide adequate, rapid pain relief in the emergency department. One study demonstrated that the majority of patients and physicians were satisfied with sub-dissociative dosing of ketamine and provided reasons why physicians opted to use ketamine, including opioid failure, concern for respiratory depression, concern for opioid allergy and concern for hypotension. In this study, 96% of emergency medicine physicians felt that low dose ketamine was underused [23]. Though most of these adult studies used the intravenous route, intranasal ketamine has also been used successfully in adults with acute pain in the emergency department, inpatient and outpatient settings [31-38].

As a dissociative anesthetic, ketamine is the most commonly used agent to facilitate painful procedures in the pediatric emergency department [39]. At lower doses, it has been used in children to provide analgesia in a variety of acute and chronic pain settings [40]. Low dose ketamine has been used effectively in children with terminal diagnoses [41-43], sickle cell disease [44], perioperative pain [45, 46], traumatic injuries [47, 48], extensive burns [49] and conditions where opioids are contraindicated [50]. As with the adult population, ketamine has been used via the intranasal route to provide adequate analgesia and sedation in children, specifically in the pre-hospital setting and in those undergoing various procedures [51-59].

To our knowledge, the PICHFORK trial was the first study to demonstrate the use of intranasal sub-dissociative dose ketamine as monotherapy for acute pain in children presenting to the emergency department with traumatic injuries [60, 61]. In this study, intranasal fentanyl and ketamine were associated with similar pain reduction and satisfaction scores. These study results have yet to be replicated. If the results are reproducible, intranasal ketamine would be particularly useful in children who experience adverse effects with opioids, have developed opioid tolerance as a result of chronic painful conditions, have poor opioid sensitivity due to their genetic predisposition or in pediatric trauma patients with hypotension. Additionally, for patients that require procedural sedation for fracture reduction, avoiding opioids early in the emergency department visit may help decrease sedation recovery time [62]. During the PICHFORK trial, adverse events were documented based on patient self-report. However, there have been no studies that document side effects, vital signs, and continuous end tidal CO_2 levels after administration of intranasal ketamine through direct observation via video monitoring. The objective of this study is to compare intranasal sub-dissociative ketamine with intranasal fentanyl for treatment of acute pain associated with traumatic limb injuries in children presenting to the emergency department and to document an objective respiratory side effect profile utilizing noninvasive capnometry. More specifically, we will compare analgesic effect, sedation level, vital signs, continuous end tidal CO2 monitoring and adverse events.

Findings from Clinical Studies

Clinical Studies of Sub-dissociative (Low-Dose) Dose Ketamine in Adults

Intravenous (IV) Administration

When used as monotherapy, subdissociative intravenous ketamine has been shown to provide effective analgesia and safety comparable to morphine for acute pain in the emergency department [27, 28]. Galinski, et al demonstrated that low doses of IV ketamine significantly lowered consumption of morphine by patients presenting to the emergency department with severe acute pain and resulted in minimal side effects (6 % with nausea/vomiting and 36% with neuropsychological effects, such as dizziness and dysphoria, in the ketamine group vs 6% with nausea/vomiting and 3% with neuropsychological effects in the placebo group) [25]. Ketamine combined with either morphine or hydromorphone has been shown to provide analgesia superior to that of morphine alone and resulted in only few minor side effects [19-22, 24]. In the pre-hospital setting, Tran et al found that ketamine had an analgesic effect similar to morphine and carried a lower risk of vomiting and airway problems than morphine. They also discovered that ketamine tended to improve blood pressure in hypotensive patients to a greater degree [63] (increase of 9.3 mm Hg with ketamine vs 4.8 mm Hg with morphine). In adult patients requiring procedural sedation and analgesia, Messenger et al found that patients receiving fentanyl and propofol were 5.1 times more likely to have a serious intrasedation event than patients receiving ketamine and propofol but the two groups had similar analgesic efficacy [29].

Intranasal (IN) Administration

More recently, the intranasal route has been a highly effective method of administering ketamine at sub-dissociative doses. One study revealed that intranasal ketamine was an effective analgesic agent in 56% of patients presenting to the emergency department with severe pain [32] while another demonstrated clinically significant reduction in pain scores in 88% of ED patients [31]. In both studies, IN ketamine resulted in very mild, transient side effects. Intranasal ketamine has been shown to be a safe, well-tolerated alternative to opioids for moderate to severe postoperative pain in adult patients [35, 38]. Furthermore, intranasal ketamine has provided rapid onset analgesia for breakthrough pain in adult patients with chronic pain conditions [33, 34]. One study showed that patients receiving ketamine achieved pain relief within 10 minutes of dosing which lasted up to 60 minutes and none of these patients required rescue medication to treat the pain episode [34]. **(See Appendix A for further details)**

TABLE 1: Sub-dissociative Dose Intranasal Ketamine for Analgesia in Adults

Study	N	Ages	Setting	Design	Doses	Route	Outcome	Adverse Effects
Yeaman, 2014	72	26-52 years (IQR)	Emergency Department, Australia	Prospective observational study: Ketamine, second dose if no improvement in 15 min	0.7-1 mg/kg, second dose (if necessary) 0.5 mg/kg, median total dose 0.98 mg/kg	IN	56% reported VAS reduction ≥20 mm at 30 minutes	Dizziness 32% Euphoria 24% Unpleasant taste 22% Drowsiness 19% Nausea 12% Numbness 8% Blurred vision 5% Nasal congestion 4% Throat irritation 3% Headache 3% None 21% No serious AEs
Andolfatto, 2013	40	36-57 years (IQR)	Emergency Department, Canada	Prospective observational study: Ketamine	0.5-0.75 mg/kg	IN	88% reported VAS reduction ≥13 mm at 30 minutes	(All transient and did not require treatment) Dizziness 38% Unreality feeling 25% Fatigue 10% Nausea 8% Mood change 8% Hearing change 3% *No headache, general discomfort or hallucination *No serious AEs
Carr, 2004	20	≥18 years	Outpatient, USA	Randomized double blind crossover trial: Ketamine vs placebo	Ketamine 10-50 mg	IN	Mean reduction in NPIS (10 point scale) score was 2.65 for ketamine vs 0.81 for placebo. IN ketamine is safe and effective for break through pain	Fatigue 45% Dizziness 20% Unreality feeling 20% Vision changes 10% Nausea 10% Hearing change 5% Mood change 5% *No serious AEs *No clinically significant change in vital signs
Christensen, 2007	40	≥16 years	Postoperative USA	Randomized double blind single dose parallel study: Ketamine #1 vs #2 vs #3 vs placebo	Ketamine 1 10 mg Ketamine 2 30 mg Ketamine 3 50 mg	IN	IN Ketamine at 50 mg dose demonstrated statistically significant pain relief (VAS score) compared to placebo. Largest difference in mean VAS scores relative to placebo was 46.5 mm at 30 minutes.	In all 4 groups: Hypertension 20% Poor concentration 8% Throat irritation 8% Tachycardia 8% Emesis 5% Placebo vs ketamine: Placebo-headache 50% Ketamine-dizzy 58%, fatigue 55%, nausea 25%, psychomimetic effects 27% No serious AEs

Afridi, 2013	18	18-57	Inpatient and Outpatient, London	Randomized double blind parallel controlled trial: Ketamine vs Midazolam	Ketamine 25 mg Midazolam 2 mg	IN	Ketamine reduced migraine severity but not the duration of aura, whereas midazolam as no effect	Ketamine: Euphoria/unreality 55% Midazolam: Sedation/giddy 44%

Clinical Studies of Sub-dissociative Dose Ketamine in Children

Intravenous (IV) Administration

Sub-dissociative intravenous dosing of ketamine has been used safely and effectively in a variety of acute and chronic pediatric conditions. One meta-analysis found that administration of ketamine was associated with decreased PACU postoperative pain intensity and analgesic requirement [45]. Two studies demonstrated that ketamine given prior to tonsillectomy resulted in significantly lower pain scores and less rescue analgesic consumption postoperatively with no difference in the incidence of vomiting or psychological sequelae [46, 64]. White et al described the use of ketamine as effective analgesia in children with toxic megacolon, a painful condition where morphine is contraindicated. None of these children reported adverse effects [50]. White et al also described the long-term (37 days), successful use of ketamine for a child with extensive burns. This patient tolerated the medication well, never developed signs of tolerance and was able to be weaned rapidly without adverse consequences [49]. Various hematologic and oncologic painful conditions that are insufficiently controlled with opioids have been effectively treated with low dose ketamine infusions. Two studies showed an opioid sparing effect of ketamine with no significant increase in adverse effects in children with cancer-related pain [41, 42], while another study described sickle cells patients with opioid-refractory pain who achieved clinically significant analgesia after the initiation of ketamine infusion [44]. Taylor et al describes the use of ketamine for end-of-life neuropathic pain in which all patients noted subjective pain relief and 79% of patients had no adverse effects [43]. Ketamine has been used effectively in the pre-hospital setting for pediatric trauma patients. None of these patients demonstrated a loss of airway, oxygen desaturation or clinically significant emergence reaction after ketamine [48]. One emergency department study demonstrated that ketamine combined with midazolam is more effective than fentanyl combined with midazolam when used for emergency pediatric orthopedic procedures and that respiratory complications occurred less frequently with ketamine than fentanyl [47].

Intranasal (IN) Administration

The intranasal route of administering ketamine to children has become more popular over the past few years. A study done in 2013 determined that 1 mg/kg intranasal ketamine provided adequate analgesia with only mild, transient side effects that did not require any treatment. None of these patients experienced dissociation or hallucination [61]. The PICHFORK trial followed in which intranasal ketamine and intranasal fentanyl were associated with similar pain reduction (82% and 79% respectively had VAS reductions > 20 mm) and satisfaction scores (83% and 72% respectively achieved satisfaction) in patients with pain from limb injuries. Again, these patients experienced no serious adverse events [60]. One case series and one case report describe the effective use of intranasal ketamine in patients where intravenous access could not be established. Patients encountered few, non-serious side effects [52, 53]. Tsze et al illustrates the use of various doses (3, 6, or 9 mg/kg) of intranasal ketamine for procedural sedation in pediatric laceration repair. The only adverse event documented was vomiting in 1 patient

[51]. Another study explored the use of ketamine in uncooperative pediatric dental patients. The overall sedation success rate was 89% with ketamine only, 84% with ketamine plus midazolam and 69% with midazolam only. There were no significant adverse effects in any of the three groups [55]. Intranasal ketamine was also found to be a safe and effective premedication in children undergoing MRI with nausea and vomiting as the only documented side effect [57]. Multiple studies have demonstrated the successful use of intranasal ketamine in combination with either intranasal midazolam or sufentanil as an analgesic or sedative for pediatric procedures [54, 56, 58, 59]. These studies demonstrated only few, mild adverse effects with intranasal ketamine. **(See Appendix B for further details)**

TABLE 2: Sub-dissociative and Dissociative Dose Intranasal Ketamine for Analgesia in Children

Study	N	Ages	Setting	Design	Doses	Route	Outcome	Adverse Effects
Graudins, 2015 Ketamine for analgesia (sub-dissociative low dose)	73	3-13 years	Emergency Department, Australia	Double blind, randomized controlled trial: Fentanyl vs Ketamine	Fentanyl 1.5 mcg/kg Ketamine 1 mg/kg	IN	Median reduction in VAS score at 30 minutes for ketamine was 45 mm and for fentanyl was 40 mm (no significant difference between groups), which was maintained to 60 minutes in both groups.	Fentanyl: Bad Taste 42% Drowsiness 21% Dizziness 17% Itchy nose 12% Nausea 4% Dysphoria 4% Hallucinations 0% Ketamine: Bad Taste 25% Drowsiness 16% Dizziness 30% Itchy nose 4% Nausea 6% Dysphoria 4% Hallucinations 6%
Yeaman, 2013 Ketamine for analgesia (sub-dissociative low dose)	28	3-13 years	Emergency Department, Australia	Observational study: Ketamine	Ketamine 0.8-1.48 mg/kg	IN	IN ketamine provided adequate analgesia by 30 minutes. Median VAS decreased from 74.5 mm to 30 mm.	Dizziness 36% Bad taste 29% Dysphoria 14% Nausea 11% Sore throat 7% Diplopia 7% Amnesia 4% Headache 4% Vomiting 4%
Johansson, 2013 Ketamine for analgesia (sub-dissociative low dose)	9	7-36 years	Prehospital trauma, Sweden	Case series: (S)-Ketamine	Ketamine 0.45 mg/kg-1.25 mg/kg	IN	IN S-ketamine provided adequate analgesia. Median pain score decreased from 10 to 3 (on a 10 point scale).	Vertigo Unpleasant taste
Tsze, 2012 Ketamine for sedation	12	1-7 years	Emergency Department, USA	Randomized, prospective double blind trial: Ketamine (3 doses)	Ketamine #1 3 mg/kg Ketamine #2 6 mg/kg Ketamine #3	IN	Significantly higher proportion of successful sedations with 9 mg/kg dose than	Vomiting 8%

(dissociative dosing)					9 mg/kg		the other two doses.	
Gyanesh, 2013 Ketamine for sedation (dissociative dosing)	150	1-10 years	Radiology (MRI), India	Randomized double blind trial: Dexmedetomidine (DXM) vs Ketamine vs Normal saline	DXM 1 mcg/kg Ketamine 5 mg/kg Normal saline	IN	DXM and ketamine were equally effective as pre-medication. In 90.4% of DXM patients and 82.7% of ketamine patients, satisfaction with conditions for IV insertion. Total dose of propofol used was less in DXM and ketamine groups.	DXM: Bradycardia 4% Nausea/Emesis 4% Ketamine: Nausea/Emesis 10% Saline: Nausea/Emesis 6%
Bahetwar, 2011 Ketamine for sedation (dissociative dosing)	45	2-6 years	Outpatient Dental Clinic, India	Triple blind randomized trial: Midazolam vs Ketamine vs Midazolam + Ketamine	Midazolam 0.3 mg/kg Ketamine 6 mg/kg Midazolam 0.2 mg/kg plus Ketamine 4 mg/kg	IN	Ketamine alone had the fastest onset of sedation. Sedation success rate with ketamine was 89%, midazolam was 69% and combination group was 84%.	No significant change in vital signs between groups. Ketamine alone: Vomiting 24% Ketamine + Midazolam: Vomiting 7%

TABLE 3. Current Unpublished Clinical Trials Involving Intranasal Ketamine

Principal Investigator	Location	Indication	Age	Dosing	Study Phase	FDA application IND required
Zavolkovskaya S	USA	Analgesia	3-17 years	1 mg/kg	Enrolling	NO
Linakis JG	USA	Sedation	1-7 years	Unknown	Completed	NO
Poonai N	Canada	Sedation	5-17 years	5 mg/kg	Active, not yet recruiting	N/A
Andolfatto G	Canada	Analgesia	≥ 6 years	0.5 mg/kg then 0.25 mg/kg if necessary	Completed	N/A
Henneberg SW Schmiegelow K	Denmark	Analgesia	1-19 years	0.5 mg/kg (plus sufentanil 0.5 mg/kg)	Completed	N/A
Christophe CM	France	Sedation	Up to 2 hours (newborn)	2 mg/kg	Active, not yet recruiting	N/A
Costa LR	Brazil	Sedation	2-6 years	4 mg/kg	Active, not yet recruiting	N/A

IV. STUDY DESIGN

The proposed study is a double-blind, randomized controlled non-inferiority trial of intranasal sub-dissociative ketamine compared to intranasal fentanyl for treatment of pain associated with extremity injuries.

Intervention drug:
Ketamine (50 mg/mL) injectable solution is a nonbarbiturate anesthetic chemically designated *dl* 2-(0-chlorophenyl)-2-(methylamino) cyclohexanone hydrochloride. It is formulated as a slightly acidic (pH 3.5-5.5) sterile solution for intravenous or intramuscular injection in concentrations containing the equivalent of 50 mg ketamine base per milliliter and contains not more than 0.1 mg/mL Phemerol® (benzethonium chloride) added as a preservative.

Comparator drug:
Fentanyl Citrate Injection, USP, CII (50 mcg/mL) is a sterile, nonpyrogenic solution of fentanyl citrate in water for injection. Fentanyl Citrate is a potent opioid agonist. Each milliliter contains fentanyl (as the citrate) 50 mcg (0.05 mg). It may contain sodium hydroxide and/or hydrochloric acid for pH adjustment. pH 4.7 (4.0 to 7.5). The solution contains no bacteriostat, antimicrobial agent or added buffer and is intended only for use as a single-dose injection.

For analgesic dose volumes equal to and less than 0.5 mL, the entire dose will be administered via mucosal atomizer in 1 of the nares. Doses greater than 0.5 mL will be divided equally to both nares. Medication will be given via the LMA MAD Nasal™ which enables a seal to be formed with the nostril and atomized particles of medication to be delivered to the nasal mucosa.

Should the guardian provide consent, the subject will be randomized to receive either the study medication of intranasal ketamine (1.5 mg/kg) or the comparator of intranasal fentanyl (2 mcg/kg). Patients of guardians who decline will receive standard Cincinnati Children's Hospital ED therapy for pain associated with extremity injuries. Enrolled subjects will be followed for a minimum of 120 minutes after receiving the study medication in the emergency department. Study data forms, electronic medical records, and continuous video monitoring of patients during the first 15 minutes will provide visual analog scale (VAS) pain scores, University of Michigan Sedation Scale scores, capnometry values, vital signs and detection of other adverse events. Study data beyond 15 minutes will be obtained from study data forms and electronic medical records.

Randomization and Blinding

Randomization will be allocated through permuted block randomization with randomly varied blocks of 6 and 8 using a 1:1 ratio within blocks. The randomization scheme will be generated by a computer random number generator. Subjects will be randomized to receive either intranasal ketamine (1.5 mg/kg) or intranasal fentanyl (2 mcg/kg) upon meeting inclusion criteria. Allocation will be concealed using pre-numbered syringes of study medication. The color and odor of the two medications in the syringes will be identical. The volumes will be slightly different due to the concentrations of the medications, but the syringes will be stored in a way that will not allow for comparison between the syringes. The syringes will be stored with sealed envelopes that contain instruction of how much volume of medication to administer. The instructions will not contain the name of the medication in the accompanying syringe. Investigational drug services (IDS) will prepare the study medication in a sterile fashion and place the pre-numbered syringes in the pyxis. Therefore, medications will be prepared prior to patient arrival in the

emergency department and IDS members will not engage in patient care. The nurses will obtain a pre-numbered syringe from the pyxis and administer the medication based on weight categories. Due to the nearly identical appearance of the syringes and the use of sealed envelopes with administration instructions, the nurses, physicians, PCAs, medics, staff, patient and family members will all be blinded to whether the subject is receiving ketamine or fentanyl.

The randomization list will be located in the office of investigational drug services. Should the need arise to unblind an investigator due to a subject experiencing a serious adverse event (SAE) or other serious circumstance, the investigator will contact investigational drug services for the particular subject in question. If there is a perceived immediate need for unblinding, the pharmacy may be contacted regarding which drug was given. A report detailing the need to unblind will be generated by the treating physician and forwarded to the IRB through the investigator. If unblinding occurs more than 60 minutes after the study medication is administered, this will not be considered a protocol violation.

V. DURATION

All study measures will occur during the emergency department visit, with the exception of the thirty day post treatment phone follow up call. The emergency department phase duration will last 120 minutes after study medication is administered while the patient remains in the emergency department. All pain scores, sedation scores, capnometry values, vital signs, adverse events, and rescue analgesia will be documented within the first 120 minutes of the visit.
Participants will receive a phone call 30 days after drug treatment to follow up on any adverse events that occur beyond 120 minutes after initial medication administration.

The anticipated duration of the enrollment phase of this study is nine months. Data analysis will occur over the following two months.

VI. SELECTION AND RECRUITMENT OF PARTICIPANTS

Inclusion Criteria:

1) Age 8 years to 17 years (up to the 18th birthday)
2) Presenting to emergency department with an extremity injury and triaged as an orthopedic evaluation. Extremity injuries may be single or multiple
3) VAS pain score 35 mm or greater
4) Patient with parent or legal guardian
5) Parent or legal guardian is willing to provide consent

Exclusion Criteria:

1) Received narcotic pain medication prior to arrival
2) Evidence of significant head, chest, abdominal, or spine injury
3) GCS < 15 or unable to self report pain score
4) Nasal trauma or aberrant nasal/airway anatomy per parent report
5) Active epistaxis

6) Allergy to ketamine, fentanyl or meperidine (Fentanyl and meperidine are both in the same class of medications—phenylpiperidines. An allergy to meperidine is an absolute contraindication to fentanyl use)
7) Non-English speaking parent and/or child
8) History of psychosis
9) Postmenarchal females without a urine or serum assay documenting the absence of pregnancy
10) Patient brought in by 20/20 juvenile detention in Cincinnati or in police custody (considered a vulnerable population)
11) Pregnancy

Subjects that do not meet all of the enrollment criteria may not be enrolled. If there is a question of whether a patient qualifies for enrollment, the principal investigators may be contacted. Any violations of these criteria must be reported in accordance with IRB Policies and Procedures.

Potential subjects will be identified during triage via the established orthopedic evaluation protocol as defined by a patient that has a "suspected acute deformity AND is experiencing pain and/or decreased pulses or sensation in the injured extremity." When a patient meets the orthopedic evaluation criteria, a page will go out to ED staff as is standard procedure. The patient will be brought to the designated location as directed by the orthopedic evaluation process. A member of the research study team trained in enrollment procedures for this trial will respond to the designated location. The study staff will screen potentially eligible subjects using the protocol inclusion and exclusion criteria. A urine or serum assay will be obtained on all postmenarchal females, if their pain level allows, to document negative pregnancy status. If a urine or serum assay cannot be obtained secondary to pain level, the subject will be excluded from the study as per the exclusion criteria.

Sample Size and Power Analysis

The sample size calculation is based on a non-inferiority test of the difference between two means. Group sample sizes of 39 and 39 achieve 80% power to detect non-inferiority using a one-sided, two-sample t-test. The margin of non-inferiority is 10. Literature has shown that the minimum clinically significant difference in VAS pain score in children is 10-12 [65, 66] which is why 10 was chosen as our non-inferiority margin. The true difference between the means is assumed to be 5 based on the PICHFORK trial, which found a median rating reduction of 40 mm (IQR 20 to 45) at 30 minutes for fentanyl and a median rating reduction of 45 mm (IQR 20-60) at 30 minutes for ketamine, and therefore, a difference in medians of 5 (-10 to 20, 95% CI) [60]. Using the IQR information from the PICHFORK trial and assuming normality for the pain scores, we estimate the standard deviations to be 29.63 and 22.22 for the rating reduction at 30 minutes for the fentanyl and ketamine groups, respectively. Therefore, with an α of 0.05 and a β of 0.2 (80% power), the sample size required to detect this difference was estimated to be 39 subjects in each group, for a total of 78 subjects. In order to achieve this number of evaluable subjects, we plan to enroll 90 subjects, anticipating that not all subjects enrolled will be fully evaluable. Over the last year, there were 634 patients who presented to the CCHMC ED and were triaged as orthopedic evaluations. Of these, 360 were in the age group specified in the inclusion criteria. Given this data, we expect to be able to successfully complete this study as planned.

VII. STUDY PROCEDURES

Table 4. Study Procedures

Visits	Visit 1						Visit 2
Study Procedure	Screening Phase	Enroll-ment	15 (±5) min	30 (±5) min	60 (±5) min	120 (+30) min	+30 (±5) days *
Informed Consent, Assent for subjects ages 12-17		X					
Review Inclusion/Exclusion Criteria	X						
Demographics/Medical History	X						
Physical Examination	X						
Vital signs (HR, RR, BP, O2 sat)		X	X	X	X	X	
Serum or urine pregnancy test for postmenarchal females	X						
Weight	X						
VAS pain score		X	X	X	X		
UMSS sedation score		X	X	X	X		
Nasal mucosal exam	X					X	
Smell test	X					X	
Capnometry value		X	X	X	X		
Randomization		X					
Dispense study drug		X					
Adverse event/Serious adverse event assessment		X	X	X	X	X	X

*Visit 2 window +/- 5 days.

(See Appendix C for study flow diagram, Appendix D for current orthopedic evaluation flow diagram, and Appendix E for duration of study procedures)

SCREENING

Potential subjects will be identified during triage via the established orthopedic evaluation protocol as defined by a patient that has a suspected acute deformity AND is experiencing pain and/or decreased pulses or sensation in the injured extremity. The patient will be brought to the shock trauma suite (STS) or designated area as directed via the orthopedic evaluation process where potential subjects will be rapidly screened using the protocol inclusion and exclusion criteria. An emergency medicine attending physician and/or fellow, resident, nurse, PCA, medic, and child life provider will respond to the STS or

designated area as per established protocol. Study staff trained in enrollment procedures for this trial will also respond to the STS or designated area. The nurse will obtain patient's pain score as per the standard of care. Physical exam, vital signs, weight and demographics will be collected as part of standard of care prior to consent.

VISIT 1

Process of Obtaining Informed Consent

Study staff will carry a pager and present to all orthopedic evaluations that are paged out to the ED staff. All patients who are triaged as an orthopedic evaluation will be screened for eligibility. Prior to approaching potential subjects, the eligibility criteria will be reviewed with the attending and/or fellow. Parents/guardians of subjects who meet eligibility criteria will be approached by trained study staff.

The study staff will briefly introduce the study and gauge the parent/guardian's interest. Study staff will initiate the consent process and review the consent document with parents/guardians who express interest. Parents/guardians will be given time to review the consent document independently and ask the study staff questions.

After the consent has been thoroughly reviewed and the parent/guardian has had all of their questions answered, the study staff will ask the parent/guardian if they would like for their child to participate in the research study. If the parent/guardian agrees to have their child participate in the study, then the study staff will obtain their signature on the consent document and initiate the start of study procedures. Parents/guardians will receive a copy of the signed consent form. Data collected as part of the routine standard of care interventions will be used as baseline study data.

We are requesting a waiver of assent for young children (defined as patients less than 12 years of age). Since we are enrolling patients with moderate to high pain scores, young patients may be limited in their capacity to provide assent prior to pain treatment. We will use parental permission in lieu of assent for these patients. However, patients 12-17 years of age will be required to assent to the study. The investigators will engage children 12-17 years in a thorough discussion of the study consent and seek their input/decision on participation. Their decision to participate will be documented in the informed consent process note. It is felt that the child is most served by maximizing focus on the actual discussion with the child; documentation of this assent is in the informed consent process note. Study staff will obtain and document assent prior to the initiation of study procedures.

Emergency Department Phase

After informed consent is obtained, the subject will be randomized to receive either intranasal ketamine (1.5 mg/kg) or intranasal fentanyl (2 mcg/kg). All data will be recorded on a standardized REDCap electronic case report form. Investigational drug services will independently prepare the study medications in pre-numbered sequential syringes. The volume, color and odor of the two medications in the syringes will be identical. Thus, the ED treatment team, patient and patient's family, and the research team will be blinded to which medication the patient will receive. The patient's physician will order plain radiographs as per standard of care, and the study drug through an EPIC order set. The study staff and nurse will ensure a full set of vital signs (including capnometry value) and urine or serum pregnancy test for all post menarchal female patients. A nasal mucosal exam and smell test will be performed prior to

drug treatment and at 120 minutes post treatment. Continuous pulse oximetry, which will be followed throughout the 120 minute duration of the study visit, will be applied prior to study drug administration. After randomization, the blinded study medication will be obtained from the designated pyxis by the nurse, who will prepare and administer a weight based amount of the study treatment under the observation of the study staff. Of note, the end tidal capnometry cannula will briefly be removed while drug is administered and then immediately replaced. The patient will be observed on monitors for 15 minutes in the STS or designated area. (Currently, the mean time from arrival in STS for an orthopedic evaluation to leaving for radiology is 24 minutes so enrollment in this study should not prolong time in the STS or designated area.) The study staff will document vital signs, capnometry value, a sedation score and obtain a pain score from the patient at 15 minutes after drug administration. The nurse will document vital signs and a capnometry value at 15 minutes after drug administration. The patient will be taken to radiology for plain radiographs of the injured extremity and then to an emergency department room where the orthopedic evaluation nurse will give report to the patient's primary nurse. The study staff will document a sedation score, obtain a pain score, document vital signs and a capnometry value from the patient at 30 and 60 minutes from drug administration. At 30 minutes, the study staff will also attempt to guess which medication the patient received and document this information in order to assess blinding of the study. At 120 minutes, a final set of vitals will be obtained and study staff will review all collected vitals and ask a study physician to record if vitals outside of the pre-determined normal ranges (see appendix G) are clinically significant or not clinically significant.

Additional data collected during the ED visit will include the need for rescue analgesia within 60 minutes of drug administration and adverse events within 120 minutes of drug administration. Enrolled subjects will be followed for a minimum of 120 minutes after receiving the study medication in the emergency department. Currently, the mean total time orthopedic evaluation patients spend in the emergency department is 260 minutes so we do not anticipate that enrollment in this study will prolong ED visits.

Rescue Medication Administration

At any time after receiving the study medication, the patient may request further analgesic medication which will be administered at the discretion of the treating PEM physician. Rescue analgesia does not require the patient to be withdrawn from the study.

Subjects may be withdrawn from the study for the events listed below. Should this be necessary, the subject may be removed from the study and receive further medications and therapies at the discretion of the treating PEM physician.

Subject Withdrawal

Subjects may withdraw from the study at any time without prejudice to their care. They may also be withdrawn from the study at the discretion of the investigator. The investigator or the sponsor may also withdraw subjects who violate the study plan, to protect the subject for reasons of safety or for administrative reasons. It will be documented whether or not each subject completes the clinical study.

VISIT 2

Visit 2 will conclude study participation and will consist of a phone follow up to the subject's parent or legal guardian to follow up on any ongoing adverse events from Visit 1 and to determine if any new

adverse events occurred. The study team will attempt to reach the subject's parent by phone at least five times within the follow up timeframe (30 +/- 5 days) before considering the subject lost to follow up. Adverse events will be followed until resolution or until no further change is expected.

Drugs, Devices, and Biologics: (see Appendix F for further details)

The intranasal route of administering medications had been reported for the past 20 years in the emergency care of pediatric patients. It has become a popular route of medication administration secondary to its rapid onset of action, minimal discomfort for the patient and relative simplicity. The nose contains a rich vascular supply with a relatively large surface area. Medications can be absorbed into vessels that lead to the superior vena cava bypassing first pass hepatic metabolism that limits bioavailability of oral medications.

Intervention drug:

Ketamine (50 mg/mL) injectable solution is a nonbarbiturate anesthetic chemically designated *dl* 2-(0-chlorophenyl)-2-(methylamino) cyclohexanone hydrochloride. It is formulated as a slightly acidic (pH 3.5-5.5) sterile solution for intravenous or intramuscular injection in concentrations containing the equivalent of 50 mg ketamine base per milliliter and contains not more than 0.1 mg/mL Phemerol® (benzethonium chloride) added as a preservative.

Human Pharmacokinetics:

Nielsen, et al in 2014 investigated a pediatric formulation of intranasal sufentanil 0.5 mcg/kg and ketamine 0.5 mg/kg for procedural pain and determined the bioavailability of ketamine was 35.8%. Maximum plasma concentration (Cmax) of ketamine was 0.102 mg/L (CV 10.8%) and Tmax was 8.5 min (CV 17.3%).

Malinovsky, et al in 1996 determined that after administration of intranasal ketamine in children 10-30 kg, 2-9 years of age, mean plasma concentrations after 3 mg/kg peaked at 496 ng/mL at 20 minutes and after 9 mg/kg peaked at 2104 ng/mL within 21 minutes. Plasma concentrations of norketamine (the predominate active metabolite), peaked at ~120 minutes after nasal ketamine. Calculated bioavailability from nasal administration was 50%. The authors concluded that nasal administration of low doses of ketamine produced plasma concentrations associated with analgesia (40-200 mg/mL), but using high doses produced high plasma concentrations similar to those that induce anesthesia (1100 to over 2000 ng/mL.

Packaging:

The study medication is prepackaged by the distributor in individual sterile vials of 10 mL each.

Labeling:

The product label reads "Ketamine HCL, Injection USP, Concentrate 500 mg/10 mL (50 mg/mL) for intramuscular or slow intravenous use, 10 x 10 mL multi-dose vials."

Manufacturer:

Mylan Institutional LLC, Rockford, IL

Dosing:

Ketamine is in individual sterile vials of 10 mL of solution. Investigational drug services will prepackage syringes with study medication using aseptic technique, cap the syringes and label each with a specific study number. Using weight based categories, patients who are randomized to receive ketamine will receive a dose of 1.5 mg/kg with a max dose of 100 mg.

Comparator drug:
Fentanyl Citrate Injection, USP, CII (50 mcg/mL) is a sterile, nonpyrogenic solution of fentanyl citrate in water for injection. Fentanyl Citrate is a potent opioid agonist. Each milliliter contains fentanyl (as the citrate) 50 mcg (0.05 mg). It may contain sodium hydroxide and/or hydrochloric acid for pH adjustment. pH 4.7 (4.0 to 7.5). The solution contains no bacteriostat, antimicrobial agent or added buffer and is intended only for use as a single-dose injection.

Intranasal fentanyl is currently the standard of care in the Cincinnati Children's Hospital Medical Center Emergency Department for the treatment of pain associated with acute extremity injuries prior to IV placement.

Human Pharmacokinetics
When fentanyl is administered by the intranasal route, the bioavailability is nearly 70%, with Tmax reached in 5–16 minutes.

Borland et al. conducted a study in 2002 looking at use of IN Fentanyl in pediatric patients (3-12 years of age) in the emergency department. With doses of 0.5-3.4 mcg/kg (median 1.5 mcg/kg), the authors found the drug achieved therapeutic levels and onset of analgesia within 10 minutes and had a half-life of 1 hour. The authors found it unlikely to cause respiratory compromise or hemodynamic instability based on no significant differences in HR, RR, BP, or oxygen saturations even with improvement in pain scores.

Packaging:
The study medication is packaged in 2 mL vials by the manufacturer.

Labeling:
The product label reads "Fentanyl Citrate, Injection USP, 100 mcg Fentanyl/2 mL (0.05 mg/mL) (50 mcg/mL) IV or IM use, 2 mL single dose vial."

Manufacturer:
West-Ward; Eatontown, NJ

Dosing:
Fentanyl is in individual sterile vials of 2 mL of solution. Investigational drug services will prepackage syringes of study medication using aseptic technique, cap the syringes and label each with a specific study number. Using weight based categories, patients who are randomized to receive Fentanyl will receive a dose of 2 mcg/kg with a max dose of 100 mcg.

Syringes with ketamine and fentanyl will look identical to maintain blinding. Syringes will expire after 9 days. Subjects will receive either intranasal ketamine (1.5 mg/kg) or fentanyl (2 mcg/kg) by blinded syringe in a standardized volume. For analgesic dose volumes equal to and less than 0.5 mL, the entire dose will be administered in 1 of the nares. Doses greater than 0.5 mL will be divided equally to both nares.

Medications will be given via a mucosal atomizer device. The LMA MAD Nasal (MAD300) intranasal mucosal atomization device (Wolfe-Tory, Medical, Inc, Salt Lake City, UT) will be attached to the Luer-Lok syringe just before study drug administration to the patient. 0.1 mL of drug solution will be used to prime the MAD nasal device.

These dosages and distribution of medication are similar to previous studies using intranasal ketamine and/or intranasal fentanyl in which there were no significant adverse effects observed [53, 60, 61, 67-69].

Adequate records of study drug administration and disposition will be maintained by the Cincinnati Children's Hospital Investigational Drug Services. The purpose of these records is to ensure regulatory authorities and the sponsor that the investigational drug will not be distributed to any person who is not a study subject under the terms and conditions set forth in this protocol. The study medication is to be prescribed by the members of this investigational team or designee and may not be used for any purpose other than that described in this protocol. At study completion, all drug supplies must be returned to the sponsor or designee.

VIII. DATA ANALYSIS/METHODS

Data Collection and Management

All data will be entered onto standardized electronic data reporting forms after initially being obtained on paper forms. The data reporting forms will contain the demographic, physical exam and treatment data outlined in this section. The forms will also contain the protected health information of subject name, visit date, contact information and medical record number. Data from the forms will be entered into a database. Protected health information will be entered into the database. The information will be de-identified after study completion.

Confidentiality will be maintained by using a locked cabinet in the research staff area and by maintaining password-protected databases and computers. The password for the database will only be known to the research study staff. Study files will be stored in a locked cabinet in the principal investigator's office which has limited public access. Entry to the office is protected by CCHMC ID card entry. Study files will be de-identified after publication and retained for 3 years after study closure.

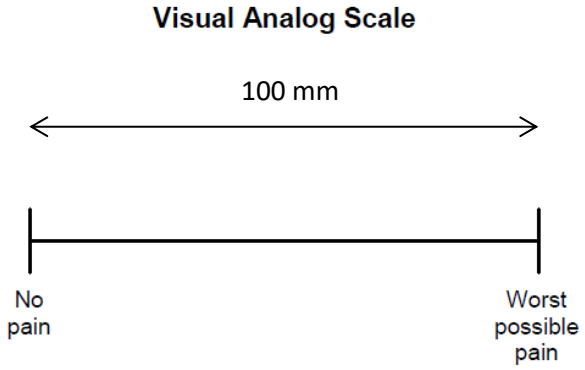
Additionally, data about missed eligible patients will be collected periodically through an EMR report and supplemented by chart review to assess screening hours, training needs or other issues that may inhibit staff's ability to enroll. We are requesting a HIPAA waiver to review the patient charts via the MRN and day/time of arrival and no information will be used for analysis in the research study. Consent would not otherwise be possible for these participants because of the nature of presentation to the ED; it is possible that these patients will have arrived when no study staff is available. Data collected on missed eligible patients will include MRN, encounter ID, date/time of ED arrival and discharge, means of arrival, date of birth, gender, whether or not they met study inclusion/exclusion criteria, disposition, discharge diagnosis, and provider name.

Primary Endpoint

The primary endpoint is the difference between the mean reduction in pain scores between the ketamine group and the fentanyl group as measured by the visual analog scale (VAS) at 30 minutes after study intervention.

The pain VAS is a unidimensional measure of pain intensity which has been widely used in diverse populations [66, 72, 73]. It is a continuous scale comprised of a horizontal or vertical line that is 10 cm (100 mm) in length anchored by two verbal descriptors representing pain extremes. The scale is most

commonly anchored by “no pain” (score of 0) and “pain as bad as it could be” or “worst imaginable pain” (score of 100). To avoid clustering of scores around a preferred numeric value, numbers or verbal descriptors at intermediate points are not present. The patient is asked to place a line perpendicular to the VAS line at the point that represents their current pain intensity. Using a ruler, the score is determined by measuring the distance (mm) on the 10-cm line between the “no pain” anchor and the patient's mark, providing a range of scores from 0–100. The visual analog scale has been shown to be valid and reliable in children 8 to 17 years of age suffering from acute pain and that a minimum clinically significant difference in VAS score ranges from 10 to 12 mm in children and adolescents [65, 66]. The optimal cut points for mild, moderate and severe pain on the VAS for children and adolescents have been determined to be 35 and 60 mm [1].



Secondary Endpoints

The secondary endpoints are to:

- Define and compare the level of sedation associated with intranasal sub-dissociative ketamine (1.5 mg/kg) and intranasal fentanyl (2 mcg/kg) as measured by the University of Michigan Sedation Scale Score and capnometry values.
- Compare adverse effects associated with intranasal sub-dissociative ketamine and intranasal fentanyl
- Compare vital sign changes associated with intranasal sub-dissociative ketamine and intranasal fentanyl

An additional secondary endpoint will be the difference between the ketamine group and the fentanyl group in pain score as measured by the visual analog scale at 15 and 60 minutes after study intervention.

Screening and Baseline Evaluation

Physical Examination

Baseline evaluation will include a physical examination and demographics as are routinely performed during the orthopedic evaluation process. Items recorded from physical examination will be weight and extremity injured. An exam of the nasal mucosa will be performed, and a nasal smell test will be administered prior to drug treatment and at 120 minutes post treatment. Demographic data recorded will include age, gender, ethnicity and race.
If there is a discrepancy between the information provided by the parent and information provided in the chart, the information provided by the parent will be used.

Vital signs

Vital sign data will be recorded at baseline, 15 minutes, 30 minutes, 60 minutes, and 120 minutes. It will include heart rate, respiratory rate, blood pressure, oxygen saturation and end tidal capnometry value. However, an end tidal capnometry value will not be obtained at the 120 minute assessment. Oxygen saturation levels and capnometry values will be obtained from the cardio-respiratory monitor once an appropriate waveform is obtained. Cardio-respiratory monitoring with pulse oximetry will be continuous for 120 minutes after the study medication is administered.

Table 5. Covariates

Age
Gender
Race
Insurance status
Weight
Time to medication from injury
Time to medication from arrival to ED
Injury Type
Extremity injured
Mechanism of injury

Other Evaluations/Measures

A urine or serum pregnancy test will be collected from all post menarchal females, and results must be negative before drug treatment may be initiated.

Visual analog scale pain scores will be obtained by study staff as described above.

University of Michigan Sedation Scale (UMSS) scores will also be obtained at baseline, 15, 30 and 60 minutes after study intervention. The University of Michigan Sedation Scale is a valid and reliable tool that allows for rapid assessment of the depth of sedation in children. It is a simple observational tool that assesses the level of alertness on a five-point scale [74]. It has been validated in children and has shown to have significant inter-rater reliability.

UMSS	Clinical Features
0	Awake and alert
1	Minimally sedated; tired/sleepy, appropriate response to verbal conversation and/or sound
2	Moderately sedated; somnolent/sleeping, easily aroused with light tactile stimulation or a simple verbal command
3	Deeply sedated; deep sleep, arousable only with significant physical stimulation
4	Unarousable

UMSS = University of Michigan Sedation Scale.

Efficacy Evaluations

Diagnostic Tests, Scales, Measures

A VAS score, UMSS sedation score and vital signs will be obtained at study entry and at 15 minutes, 30 minutes and 60 minutes after administration of study medication. Changes between these time points will be evaluated. The time from initial physician evaluation to study medication and to ED disposition will be recorded. Adjunct measures including additional analgesia or anti-emetics will be recorded.

Of note, pain scores, sedation scores, vital signs, capnometry values, and adverse effects will be obtained at specific windows of time such that the "15 minute" value will be obtained between 10 and 20 minutes after medication is given, "30 minute" value will be obtained between 25 and 35 minutes after medication is given, "60 minute" value will be obtained between 55 and 65 minutes after medication is given and "120 minute" value will be obtained between 120 and 150 minutes after medication is given.

Statistical Methods

Baseline Data

Baseline and demographic characteristics will be summarized by standard descriptive summary statistics. This will include means and standard deviations for continuous variables expected to be normally distributed, such as age, vital signs, capnometry values, weight and VAS pain scores; proportions for categorical variables such as gender, race and injury location; and medians with ranges for variables expected to not be normally distributed, such as UMSS sedation scores. All continuous variables will be assessed for normality; parametric statistics will be used for normally distributed variables and non-parametric statistics will be used for non-normally distributed variables.

Efficacy Analysis

The primary analysis will include all subjects randomized based on the principle of intention to treat. If necessary, a per-protocol analysis will also be performed to assess efficacy of the treatments actually received. The primary efficacy endpoint will be the difference in mean pain scores between the ketamine group and the fentanyl group at 30 minutes after study intervention. This difference will be evaluated using the t-test.

Demographic and historical baseline information of the 2 study groups will be compared using t-tests (means), Mann-Whitney U (medians), and chi-square (proportions) tests. If there are any significant differences, linear regression will be performed to adjust for significantly different covariates.

For secondary outcomes, t-tests, or Mann-Whitney U where appropriate, will be used to evaluate differences in continuous outcomes (e.g. heart rate, blood pressure). Chi-square tests will be used to evaluate proportions in dichotomous outcomes (e.g. proportion with presence of specific adverse effects). Risk differences with 95% confidence intervals will be used to compare dichotomous outcomes such as the use of rescue analgesia and adverse events.

Safety Analysis

All subjects entered into the study will be included in the safety analysis. The frequencies of adverse events, including type, body system, severity and relationship to the study drug, will be summarized. We do not anticipate any serious adverse events. However, if one were to occur, it would be described in detail.

Adverse event incidence will be summarized along with the corresponding exact binomial 95% two-sided confidence intervals.

Test of Non-Inferiority

A one-sided two-sample t-test will be used to test whether the pain reduction using ketamine is non-inferior to that of fentanyl. When the variances of the two groups are unequal, Welch's t-test will be used; if the data are not normally distributed, the Mann-Whitney (Wilcoxon signed rank) U test will be used [75, 76].

Interim Analysis

Due to the expected short duration of the study, no interim analysis will be performed. However, ongoing safety analysis of adverse events, serious adverse events and toxicities will be done.

IX. FACILITIES AND PERFORMANCE SITES

The study will be conducted at one investigative site in the United States. Cincinnati Children's Hospital Medical Center is an academic, freestanding, 523 bed children's hospital with 32,981 admissions and 125,130 Emergency Department visits annually. The population is diverse and includes 51% Caucasian, 40% African American, 2% Hispanic, and 7% other. Study enrollment will only be performed at the base campus.

X. POTENTIAL BENEFITS

Intranasal sub-dissociative dosing of ketamine has been shown in multiple studies to provide adequate analgesia to pediatric patients experiencing moderate to severe pain. Therefore, patients receiving the study medication may receive adequate analgesia and avoid the side effects associated with opioids and potentially the increased chance of adverse effects as a result of opioids in combination with ketamine procedural sedation later during their ED visit. Furthermore, patients who are genetically predisposed to have poor opioid sensitivity or those who have developed opioid tolerance due to other chronic painful conditions may find more benefit with the study medication.

XI. POTENTIAL RISKS, DISCOMFORTS, INCONVENIENCES and PRECAUTIONS

There are minimal risks associated with the administration of sub-dissociative ketamine via the intranasal route. All studies performed using intranasal ketamine at sub-dissociative dosing in children showed only minimal adverse events and no serious adverse events associated with the study medication. Examples of mild adverse events which could be expected to occur with both medications include drowsiness,

dizziness, pruritus, nausea, vomiting, dysphoria, unpleasant taste, vision changes, throat irritation, headache, and mild increase in heart rate and blood pressure.

Based on pharmacokinetic studies on intranasal ketamine use in children, the mean plasma concentrations peaked at about 20 minutes and the plasma concentrations of norketamine (the predominate active metabolite), peaked at about 120 minutes after administration of intranasal ketamine. Subjects will be observed in the emergency department for a minimum of 2 hours after study medication administration, thus providing resources and personnel for immediate, emergency care should the need arise. Those patients who are admitted and remain in the ED less than 2 hours will be monitored for the entirety of their ED stay. The admitting team will then be notified that they received a study medication. This length of observation is consistent with the amount of time that patients who are triaged as an orthopedic evaluation spend in the ED for standard therapy as most of these patients tend to remain in the ED for longer than two hours. This observation time does not pose any increased risk to the patient. Those patients discharged from the ED will be provided appropriate follow up instructions as per standard of care.

For these reasons, we expect enrollment in this trial to be of minimal risk to patients.

XII. RISK/BENEFIT ANALYSIS

Due to the prospect of direct benefit to patients and minimal risk to patients, the risk-benefit ratio seems favorable to patients, parents and providers.

XIII. DATA AND SAFETY MONITORING

Clinical Adverse Events

Clinical adverse events (AEs) will be monitored throughout the study. All adverse events will be followed until resolution.

Adverse Event Reporting

All on-site serious adverse events will be reported to the IRB in accordance with CCHMC IRB policies. Adverse Events will be reported to the IRB per CCHMC Research Policy R-18.

Definition of an Adverse Event

An adverse event is any untoward medical occurrence in a subject who has received an intervention (drug, biologic, or other intervention). The occurrence does not necessarily have to have a causal relationship with the treatment. An AE can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Adverse event monitoring for the emergency department phase would start at the time of randomization and end at two hours after initial medication administration. Any additional adverse events that occur beyond 120 minutes after initial medication administration will be obtained during the 30 day follow up phone call.

All AEs (including serious AEs) will be noted in the study records and on the case report form with a full description including the nature, date and time of onset, determination of non-serious versus serious, intensity (mild, moderate, severe), duration, causality, and outcome of the event. SAEs will be reported within 24 hours.

Definition of a Serious Adverse Event (SAE)

An SAE is any adverse drug experience occurring at any dose that results in any of the following outcomes:

- death
- a life-threatening event (at risk of death at the time of the event)
- requires inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant disability/incapacity
- results in a congenital anomaly or birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug event when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. The one exception to these criteria is hospitalization for repair and/or pain management associated with the injury. Since this can be expected as part of the standard treatment course for orthopedic injuries, admissions for this reason will not be reported as a serious adverse event. However, all admissions will be tracked and those related to adverse events or for reasons other than injury repair or pain management will be reported as an SAE.

Serious adverse event monitoring starts at the time of consent and ends at the time of discharge or admission. All SAEs will be followed until resolution, the event is considered to be medically stable, or for 30 days after the subject completes the study, whichever occurs first.

A distinction should be drawn between serious and severe AEs. A severe AE is a major event of its type. A severe AE does not necessarily need to be considered serious. For example, nausea which persists for several hours may be considered severe nausea, but would not be an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke, but would be an SAE.

Serious Adverse Events (SAEs) Specific to this Study

There has been documentation of a few significant adverse effects associated with the medications included in this study. These effects are exceedingly rare and are anticipated to be even rarer through an intranasal route of drug administration compared with an intravenous route and with sub-dissociative dosing of ketamine as compared with dissociative dosing.

Ketamine: cardiac arrhythmia, hypertensive emergency, prolonged emergence reaction, anaphylaxis, laryngospasm, apnea

Fentanyl: cardiac arrhythmia, cardiopulmonary arrest, chest wall rigidity, hypertensive emergency, hypotension, pulmonary embolism, anaphylaxis, apnea, bronchospasm, laryngospasm

In the exceedingly rare instance that one of these serious adverse effects was to occur, the patient would be treated for that particular emergency in a manner that is standard of care at CCHMC were the emergency to occur in any other setting.

Relationship of SAE to study drug or other intervention

The relationship of each SAE to the study intervention should be characterized using one of the following terms in accordance with CCHMC IRB Guidelines: definitely, probably, possibly, or unrelated.

Monitoring Plan

The medical monitor is the person responsible for the safety monitoring in this protocol and he will monitor all clinically significant adverse events (AEs) and provide consultation for any AEs that the investigators question the classification, severity or relatedness originally documented at the time of the ED visit. The medical monitor will be Scott Reeves, MD. He is a member of the Division of Emergency Medicine, who will not be involved with enrollment.

A risk-based monitoring plan will be developed for the conduct of study monitoring. On-site monitoring will occur throughout the duration of the study. A study initiation visit will be conducted by the study monitoring staff to ensure that the study staff have been completely trained in protocol procedures and Good Clinical Practices (GCP) and that facilities and personnel are adequate. Scheduled monitoring will occur at least once per year during the conduct of the trial, with the option of making a second visit if needed to address over-enrollment, under-enrollment, or protocol deviation issues. The Monitoring Plan will detail the frequency and level of intensity of on-site monitoring visits. In general, the study will be monitored for all subjects at a level of 100% of study data gathered for inclusion and exclusion criteria, informed consent procedures, and adverse events. At a minimum, at least 20% of the study subject's data will be monitored against the study's database.

During scheduled interim monitoring visits, the monitors will verify that the protocol is being followed and that data are being collected according to protocol requirements. The monitors will review the Study Regulatory File to determine that all required documentation is being collected and that the IRB approval for the study is current. They will then verify that each subject has signed the correct version of the informed consent document, and that this document is filed in the subject's file. Adverse event documentation is checked for completeness and accuracy. Drug and supplies accountability will also be monitored. At the study closeout, the monitors confirm that all data have been reviewed, all source documents have been verified, and all required documents are present in the Study Regulatory File. The table below describes the variables to be reviewed during monitoring visits.

Variable	% of Records Reviewed
Informed consents	100%
Eligibility criteria for all screened subjects	100%
Adverse events	100%
Drug accountability	20% of active subjects
Protocol adherence	20% of active subjects
Verification of eCRFs with source documents	20% of active subjects

Central study files-inclusion of all applicable documents	100%
Protocol deviations/violations	100%

AEs will be reported to the IRB as detailed below. Adverse events will be recorded on the study data form by the study team. Any serious adverse events (SAEs) will be reported to the investigator or designee immediately. Study forms and charts will be reviewed by the study coordinator and principal investigator for AEs after the ED visit. All identified AEs will be recorded. The investigator will determine the grade and attribution. If unblinding is required, the investigator will notify the IRB. The protocol and consent will be reviewed by the investigator to determine if any changes are required. SAE's that are related to the study and unexpected will be reported to the IRB and FDA. Any serious adverse events and/or adverse events that occur during the study will be followed to resolution.

For the purpose of this study, toxicity is defined using the Common Terminology Criteria for Adverse Events (CTCAE) v4.0 as defined by the National Cancer Institute (http://ctep.cancer.gov/reporting/ctc.html).

Grade level 4 or greater toxicity which are unexpected and related to the study will be reported to the IRB within 48 hours. Examples pertinent to this protocol include: life threatening respiratory compromise resulting in intubation, anaphylaxis, hypotension, hypertensive crisis, life-threatening cardiac arrhythmias requiring urgent intervention, nausea and emesis with life-threatening consequences, and change in mental status including states harmful to the subject.

Subjects will be withdrawn from study drug exposure if any of the following events occur during the patient's stay in the ED:

- The subject has a SAE possibly or definitely related to the study drug
- The subject experiences a level 4 toxicity as defined by CTCAE
- The subject experiences one or more level 3 toxicities as defined by CTCAE
- The subject has an adverse event experience that would, in the investigator's judgment, make continued participation in the study not in the subject's best medical interest.

The trial will stop enrollment for the following events:

- A SAE rate related to the study intervention of greater than or equal to 2 in 10 subjects is detected
- Subjects experiencing grade 3 toxicities occur more frequently than 3 in 10 subjects.

If the trial is stopped for the above events, a complete report of the events, AEs and SAEs will be provided to the IRB and FDA for review. The protocol and consent will be reviewed and any recommendations for revisions will be approved by the IRB before enrollment is reopened.

XIV. PRIVACY AND CONFIDENTIALITY

All data and records generated during this study will be kept confidential in accordance with institutional policies and HIPAA on subject privacy and that the investigator and other site personnel will not use such data and records for any purpose other than conducting the study. Safeguards to maintain confidentiality are discussed in Section VIII.

XV. COST OF PARTICIPATION

Third party payers and participants will not be billed for research procedures described.

XVI. PAYMENT FOR PARTICIPATION

Participants who complete the ED study procedures will be compensated with a $10 gift card for their time and effort towards the study.

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APPENDICES

APPENDIX A: Clinical Studies of Sub-dissociative (Intranasal and Intravenous) Dose Ketamine in Adults

Study	N	Ages	Setting	Design	Doses	Route	Outcome
Yeaman, 2014	72	26-52 years (IQR)	Emergency Department, Australia	Prospective observational study: Ketamine, second dose if no improvement in 15 min	0.7-1 mg/kg, second dose (if necessary) 0.5 mg/kg, median total dose 0.98 mg/kg	IN	56% reported VAS reduction ≥20 mm at 30 minutes
Andolfatto, 2013	40	36-57 years (IQR)	Emergency Department, Canada	Prospective observational study: Ketamine	0.5-0.75 mg/kg	IN	88% reported VAS reduction ≥13 mm at 30 minutes
Huge, 2010	16	54.5 ± 21.4 years	Outpatient, Germany	Double blind randomized trial: (S)-Ketamine at 2 different doses	Group 1: 0.2 mg/kg Group 2: 0.4 mg/kg	IN	Group 1: pain reduction to 70±10% of initial pain at 60 minutes Group 2: pain reduction to 61±13% of initial pain at 60 minutes
Carr, 2004	20	≥18 years	Outpatient, USA	Randomized double blind crossover trial: Ketamine vs placebo	Ketamine 10-50 mg	IN	Mean reduction in NPIS (10 point scale) score was 2.65 for ketamine vs 0.81 for placebo. IN ketamine is safe and effective for break through pain
Christensen, 2007	40	≥16 years	Postoperative USA	Randomized double blind single dose parallel study: Ketamine #1 vs #2 vs #3 vs placebo	Ketamine 1 10 mg Ketamine 2 30 mg Ketamine 3 50 mg	IN	IN Ketamine at 50 mg dose demonstrated statistically significant pain relief (VAS score) compared to placebo. Largest difference in mean VAS scores relative to placebo was 46.5 mm at 30 minutes.
Abdel-Ghaffar, 2012	60	18-65 years	Pre-operative Egypt	Randomized double blind placebo controlled trial: Ketamine vs Fentanyl vs Saline	Ketamine 1.5 mg/kg Fentanyl 1.5 mcg/kg	IN	Ketamine and fentanyl significantly prolonged time to first analgesic request. VAS scores were significantly lower with ketamine and fentanyl compared to saline in first 4h postop
Afridi, 2013	18	18-57	Inpatient and Outpatient, London	Randomized double blind parallel controlled trial: Ketamine vs Midazolam	Ketamine 25 mg Midazolam 2 mg	IN	Ketamine reduced the severity but not the duration of aura, whereas midazolam as no effect

Riediger, 2015	22	≥18 years	Postoperative Switzerland	Randomized double blind noninferiority trial: S-Ketamine+Midazolam Vs Morphine	S-ketamine 6 mg alternating with Midazolam 0.75 mg (lockout interval of 20 min between meds) Morphine 2 mg (lockout interval of 12 min)	IN	Similar NRS scores in morphine and S-ketamine groups as 1, 2, 4, 24, 48 and 72 hours after surgery. No difference in bolus demands and deliveries of medications.
Messenger, 2008	63	14-65 years	Emergency Department, Canada	Randomized double blind controlled triai: ketamine vs fentanyl (followed by propofol)	Ketamine 0.3 mg/kg Fentanyl 1.5 mcg/kg	IV	Ketamine and fentanyl have similar efficacy. Sub-dissociative ketamine is safer than fentanyl for ED procedural sedation and analgesia with propofol.
Galinski, 2007	65	18-70 years	Emergency Department, France	Multicenter, randomized double blind trial: Ketamine + morphine vs Normal saline + morphine	Ketamine 0.2 mg/kg Morphine 0.1 mg/kg	IV	Morphine consumption significantly lower in ketamine group than placebo (0.149 mg/kg vs 0.202 mg/kg). No significant difference in VAS score at 30 minutes
Gurnani, 1996	40	Adult	Emergency Department, India	Randomized double blind pilot trial: Ketamine dose followed by infusion vs Morphine dose followed by q4 hour dosing	Ketamine 0.25 mg/kg initial dose, infusion at 0.1 mg/kg/hr Morphine 0.1 mg/kg initial dose, 0.1 mg/kg q4	IV	VAS scores significantly lower in ketamine group. Patients in ketamine group significantly less drowsy. No ketamine patients required supplemental analgesia vs 90% of morphine patients required supplemental analgesia
Motov, 2015	90	18-55 years	Emergency Department, USA	Randomized double blind trial: Ketamine vs Morphine	Ketamine 0.3 mg/kg Morphine 0.1 mg/kg	IV	Ketamine is as effective as morphine for analgesia at 15 and 30 minutes (8.6 vs 8.5 at baseline, 3.2 vs 4.2 at 30 minutes)
Miller, 2015	45	18-59 years	Emergency Department, USA	Randomized controlled double blind superiority trial: Ketamine vs Morphine	Ketamine 0.3 mg/kg Morphine 0.1 mg/kg	IV	Ketamine did not produce a greater reduction in NRS scores compared with morphine. Time to achieve maximum reduction in NRS was 5

							min for ketamine and 100 min for morphine
Tran, 2014	308	>30 months	Prehospital trauma, Vietnam	Prospective, cluster randomized study: Ketamine vs Morphine	Ketamine 0.2-0.3 mg/kg Morphine 10 mg (adults) 5 mg (children)	IV IM	Ketamine provided an analgesic effect equal to that of morphine, no significant differences between the two groups.
Beaudoin, 2014	60	18-65 years	Emergency Department, USA	Randomized controlled double blind trial: Morphine/NS Vs Morphine/Ketamine 1 Vs Morphine/Ketamine 2	Morphine 0.5 mg/kg Ketamine 1 0.15 mg/kg Ketamine 2 0.3 mg/kg	IV	SPIDs (summed pain intensity difference) were higher for the ketamine groups. Patients in morphine group required rescue analgesia sooner than the ketamine groups. Patients with the higher ketamine dose sustained analgesic effect longer.
Lester, 2010	35	21-57 years	Emergency Department, USA	Retrospective chart review: low dose ketamine as adjunct to opioids	0.1-0.6 mg/kg (5-35 mg)	IV (30) IM (5)	Improvement in pain in 54% of cases
Johansson, 2009	27	Adults	Prehospital trauma, Sweden	Prospective cohort study: Morphine vs Morphine+Ketamine	Morphine 0.2 mg/kg Morphine (0.1 mg/kg) + Ketamine (0.2 mg/kg)	IV	Ketamine/morphine group had significant lower NRS scores than morphine alone (5.4±1.9 vs 3.1±1.4)
Ahern, 2013	30	23-62 years	Emergency Department, USA	Prospective observational study: Hydromorphone + Ketamine	Hydromorphone (0.5 mg) Ketamine (15 mg)	IV	Mean reduction in NRS score at 5 min was 6 and at 15 min was 5. SPID at 30 min was 25 and at 60 min was 41. (This protocol provided profound, rapid pain relief)
Jennings, 2012	135	≥18 years	Prehospital trauma, Australia	Prospective, randomized controlled multicenter study: Morphine alone vs Morphine+Ketamine	Morphine 5 mg every 5 min until pain free Morphine 5 mg + Ketamine 10 or 20 mg then 10 mg every 3 min until pain free	IV	Morphine plus ketamine provides analgesia superior to that of morphine alone. (mean NRS reduction of 5.6 vs 3.2). Ketamine had a quicker reduction of pain intensity.

APPENDIX B: Clinical Studies of Sub-dissociative (Intranasal and Intravenous) and Dissociative (Intranasal) Dose Ketamine in Children

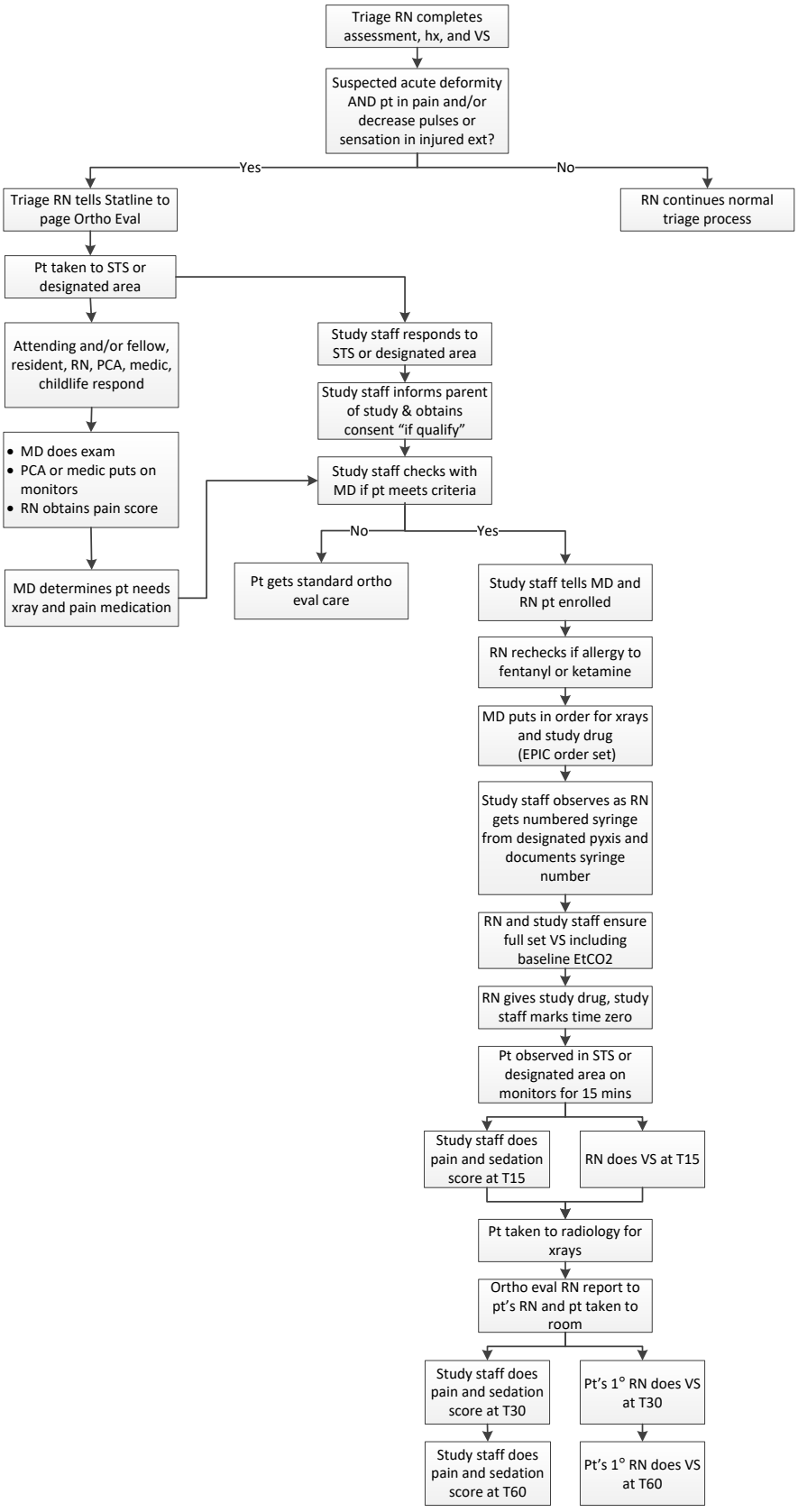
Study	N	Ages	Setting	Design	Doses	Route	Outcome
Graudins, 2015 Ketamine for analgesia (sub-dissociative low dose)	73	3-13 years	Emergency Department, Australia	Double blind, randomized controlled trial: Fentanyl vs Ketamine	Fentanyl 1.5 mcg/kg Ketamine 1 mg/kg	IN	Median reduction in VAS score at 30 minutes for ketamine was 45 mm and for fentanyl was 40 mm (no significant difference between groups), which was maintained to 60 minutes in both groups.
Yeaman, 2013 Ketamine for analgesia (sub-dissociative low dose)	28	3-13 years	Emergency Department, Australia	Observational study: Ketamine	Ketamine 0.8-1.48 mg/kg	IN	IN ketamine provided adequate analgesia by 30 minutes. Median VAS decreased from 74.5 mm to 30 mm.
Johansson, 2013 Ketamine for analgesia (sub-dissociative low dose)	9	7-36 years	Prehospital trauma, Sweden	Case series: (S)-Ketamine	Ketamine 0.45 mg/kg-1.25 mg/kg	IN	IN S-ketamine provided adequate analgesia. Median pain score decreased from 10 to 3 (on a 10 point scale).
Nielsen, 2013 Ketamine for analgesia (sub-dissociative low dose)	50	0.8-17 years	Inpatient, Denmark	Prospective nonrandomized trial: Sufentanil + Ketamine	Sufentanil 0.5 mcg.kg PLUS Ketamine 0.5 mg/kg	IN	Provided rapid analgesia in 78% of patients (decreased pain score to ≤5 on 10 pt scale).
Tsze, 2012 Ketamine for sedation (dissociative dosing)	12	1-7 years	Emergency Department, USA	Randomized, prospective double blind trial: Ketamine (3 doses)	Ketamine #1 3 mg/kg Ketamine #2 6 mg/kg Ketamine #3 9 mg/kg	IN	Significantly higher proportion of successful sedations with 9 mg/kg dose than the other two doses.
Reid, 2011 Ketamine for analgesia (sub-dissociative low dose)	1	9 years	Prehospital, Australia	Case Report: Ketamine	Ketamine 0.5 mg/kg	IN	Provided rapid resolution of pain and effective anxiolysis
Roelofse, 2004 Ketamine for sedation	50	5-7 years	Operating room (Dental), New Zealand	Randomized double blind trial: Sufentanil/Midazolam Vs Ketamine/Midazolam	Sufentanil 20 mcg + Midazolam 0.3 mg/kg	IN	No significant difference in sedation and anxiety levels pre-operatively or in

(dissociative dosing)					Ketamine 5 mg/kg + Midazolam 0.3 mg/kg		postoperative recovery between the 2 groups. Sufentanil group experienced less pain but not statistically significant (P > 0.05).
Bahetwar, 2011 Ketamine for sedation (dissociative dosing)	45	2-6 years	Outpatient Dental Clinic, India	Triple blind randomized trial: Midazolam vs Ketamine vs Midazolam+Ketamine	Midazolam 0.3 mg/kg Ketamine 6 mg/kg Midazolam 0.2 mg/kg plus Ketamine 4 mg/kg	IN	Ketamine alone had the fastest onset of sedation. Sedation success rate with ketamine was 89%, midazolam was 69% and combination group was 84%.
Khatavkar, 2014 Ketamine for sedation (dissociative dosing)	60	1-12 years	Pre-operative, India	Randomized single blind trial: Midazolam vs Midazolam+Ketamine	Midazolam 0.2 mg/kg Midazolam 0.15 mg/kg + Ketamine 1 mg/kg	IN	Sedation score, anxiolysis, reaction to IV insertion, face mask acceptance and emotional reaction were significantly better in Midazolam+Ketamine group
Gyanesh, 2013 Ketamine for sedation (dissociative dosing)	150	1-10 years	Radiology (MRI), India	Randomized double blind trial: Dexmedetomidine vs Ketamine vs Normal saline	Dexmedetomidine 1 mcg/kg Ketamine 5 mg/kg Normal saline	IN	Dexmedetomidine and ketamine were equally effective as premedication. In 90.4% of DXM patients and 82.7% of ketamine patients, anesthesiologists were satisfied with conditions for IV insertion. Total dose of propofol used was less in DXM and ketamine groups.
Buonsenso, 2014 Ketamine for sedation (dissociative dosing)	36	< 14 years	Inpatient, Italy	Randomized double blind placebo controlled trial: Midazolam+Ketamine Vs Normal saline	Midazolam 0.5 mg/kg + Ketamine 2 mg/kg	IN	Significantly better MOPS (Modified Objective Pain Score) reduction in treatment group. Mean MOPS in treatment group was 3.5 vs mean MOPS in placebo group was 7.2
Kennedy, 1998 Ketamine for sedation	260	5-15 years	Emergency Department, USA	Randomized nonblinded trial: Fentanyl+midazolam vs Ketamine+midazolam	Midazolam 0.5 mg/kg Fentanyl 0.5 mcg/kg Ketamine	IV	Patients receiving ketamine had significant reduction in mean OSBD-R scores compared to those

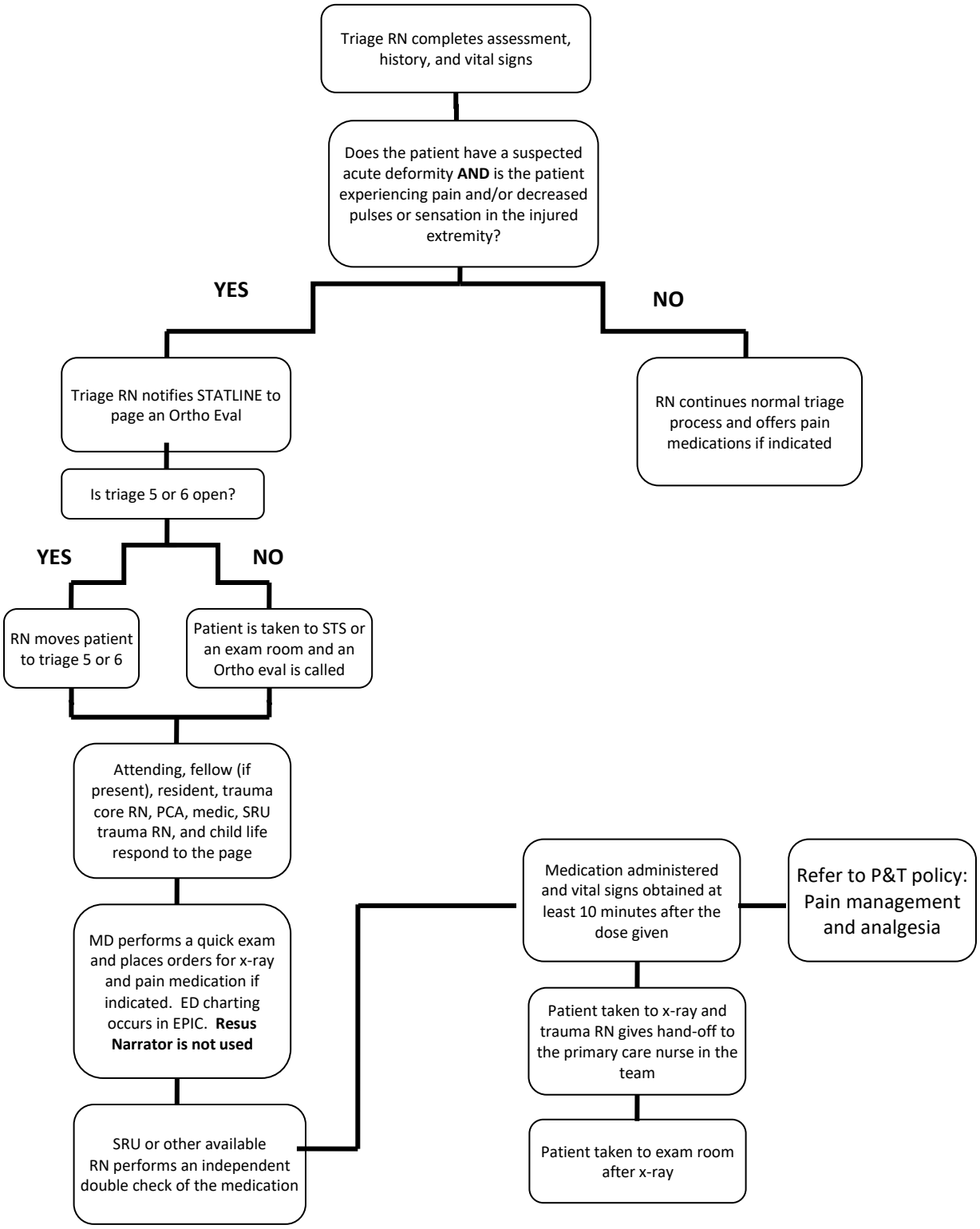
(dissociative dosing)					0.5 mg/kg		receiving fentanyl during fracture reduction
Elhakim, 2003 Ketamine for analgesia (sub-dissociative low dose)	50	5-12 years	Preoperative, Egypt	Randomized double blind placebo controlled trial: Ketamine + diclofenac + fentanyl Vs Placebo + diclofenac + fentanyl	Ketamine 0.1 mg/kg Normal saline (same volume) Diclofenac 2 mg/kg Fentanyl 1 mcg/kg	IM	Ketamine group had significantly lower pain scores at rest and on swallowing postoperatively. Ketamine group required less postoperative analgesia.
Finkel, 2007 Ketamine for analgesia (sub-dissociative low dose)	11	3-17 years	Inpatient, USA	Retrospective review: Ketamine infusion in addition to opioid analgesia	Ketamine 0.1-1 mg/kg/hr	IV	73% of patients experienced significant decrease in opioid requirements after ketamine initiated
White, 2011 Ketamine for analgesia (sub-dissociative low dose)	100	3-14 years	Inpatient, United Kingdom	Retrospective review: Morphine PCA Vs Morphine+Ketamine PCA	Morphine PCA 1 mg/kg made up to 50 mL with saline Morphine 1 mg/kg PLUS Ketamine 1 mg/kg PCA made up to 50 mL with saline (bolus 20-40 mcg/kg, infusion 0-40 mcg/kg/hr, max 4h dose of 400 mcg/kg)	IV	Addition of ketamine to the morphine PCA is associated with reduced morphine consumption and improved pain scores.
Taylor, 2014 Ketamine for analgesia (sub-dissociative low dose)	14	1 month-23 years	Inpatient and Outpatient, USA	Retrospective case review: Ketamine PCA in addition to prolonged opioid use	Ketamine 0.014-0.308 mg/kg/hr with demand dose of 0.03/0.5 mg/kg every 10-60 min	IV	All patients with opioid refractory neuropathic pain had improved pain with the addition of ketamine to pain regimen
White, 2006 Ketamine for analgesia (sub-dissociative low dose)	3	12 years	Inpatient, United Kingdom	Case series of patients with toxic megacolon: Ketamine PCA	Ketamine PCA 2 mg/kg made up to 50 mL with 5% dextrose (infusion 0-40 mcg/kg/hr, bolus 20-40 mcg/kg, lockout period 10-30 min	IV	Improved pain scores in all patients. Safe and effective use of ketamine infusion
White, 2007	1	9 years	Inpatient, Canada	Case report:	Morphine 40 mcg/kg/hr	IV	Long term ketamine infusion (37 days)

Ketamine for analgesia (sub-dissociative low dose)				Ketamine infusion in addition to Morphine infusion	Ketamine 80-200 mcg/kg/hr		provided safe and effective analgesia
Dal, 2007 Ketamine for analgesia (sub-dissociative low dose)	90	2-12 years	Perioperative, Turkey	Randomized placebo controlled trial: Saline vs IV Ketamine bolus vs Peritonsillar ketamine infiltration	Saline 2 mL Ketamine bolus 0.5 mg/kg Ketamine infiltration 0.5 mg/kg	IV	Ketamine groups had significant lower observational pain scores in hospital and at home than saline group. No significant difference in pain score between ketamine groups. Saline group had significantly shorter time to first rescue analgesia.
Bredmose, 2009 Ketamine for analgesia and sedation	164	< 16 years	Prehospital trauma, United Kingdom	Retrospective database review: Ketamine use (68% of these patients also received Midazolam)	Ketamine 0.1-5.8 mg/kg (mean=1.0 mg/kg) Midazolam 0.1-0.5 mg/kg (mean=0.1 mg/kg)	IV/IM	Ketamine provided adequate analgesia and appropriate sedation without major side effects
Zempsky, 2010 Ketamine for analgesia (sub-dissociative low dose)	5	12-18 years	Inpatient, USA	Case series of sickle cell disease patients: Ketamine infusion	Ketamine 0.1-0.2 mg/kg/hr	IV	2 of 5 patients achieved adequate pain control. 1 patient used significantly less opioids.

APPENDIX C: Study Flow Diagram



APPENDIX D: Current Orthopedic Evaluation Flow Diagram



APPENDIX E: Study Procedures

Study Procedure	Who?	How much time?
Screening for eligibility	Research Study Staff	5 minutes
Obtain baseline measurements (vital signs, EtCO2, weight, VAS, UMSS)	Nursing/Research study staff	3 minutes
Order, dispense and administer study medication	Patient's physician/Nursing	5 minutes
Obtain measurements at 15 minutes after medication	Nursing/Research study staff	1 minute
Obtain measurements at 30 minutes after medication	Nursing/Research study staff	1 minute
Obtain measurements at 60 minutes after medication	Nursing/Research study staff	1 minute
Document adverse events	Research study staff	Throughout ED visit
Phone Follow up call	Research study staff	10 minutes

APPENDIX F: Drug Information and Package Inserts

Ketamine Human Pharmacokinetics

- Nielsen, et al in 2014 investigated a pediatric formulation of intranasal sufentanil 0.5 mcg/kg and ketamine 0.5 mg/kg for procedural pain and determined the bioavailability of ketamine was 35.8%. Maximum plasma concentration (Cmax) of ketamine was 0.102 mg/L (CV 10.8%) and Tmax was 8.5 min (CV 17.3%).

- Malinovsky, et al in 1996 determined that after intranasal ketamine in children 10-30 kg, 2-9 years of age, mean plasma concentrations after 3 mg/kg peaked at 496 ng/mL at 20 minutes and after 9 mg/kg peaked at 2104 ng/mL within 21 minutes. Plasma concentrations of norketamine (the predominate metabolite), peaked at ~120 minutes after nasal ketamine. Calculated bioavailability from nasal administration was 0.5. The authors concluded that nasal administration of low doses of ketamine produced plasma concentrations associated with analgesia, but using high doses produced high plasma concentrations similar to those that induce anesthesia.

Dosing:

Children:

IM: 3 to 7 mg/kg

IV: Range: 0.5 to 2 mg/kg, use smaller doses (0.5 to 1 mg/kg) for sedation for minor procedures; usual induction dosage: 1 to 2 mg/kg

Adults:

IM: 3 to 8 mg/kg

IV: Range: 1 to 4.5 mg/kg; usual induction dosage: 1 to 2 mg/kg

Fentanyl Human Pharmacokinetics

- Onset of action: Analgesia: Intranasal: Children 3-12 years: 5-10 minutes (Borland, 2002)
- Half-life: Nasal spray: 15-25 hours (based on a multiple-dose pharmacokinetic study when doses are administered in the same nostril and separated by a 1-, 2-, or 4-hour time lapse)
- Time to peak serum concentration: Nasal spray: Median: 15-21 minutes

Dosing:

Infants and Children:

Acute pain: IV: Opioid-naive:

Infants: Limited data available: Initial: 1-2 mcg/kg/dose; may repeat at 2-4 hour intervals; in opioid-tolerant or younger infants, titration to higher doses may be required (up to 4 mcg/kg/dose) (Hegenbarth, 2008; Nelson, 1996; WHO, 2012)

Children: Limited data available in children <2 years: Initial: 1-2 mcg/kg/dose; may repeat at 30- to 60-minute intervals; in opioid-tolerant children, titration to higher doses may be required (Hegenbarth, 2008; Nelson, 1996; WHO, 2012)

Analgesia for minor procedures/sedation: Limited data available in children <2 years:

IM, IV: 1-2 mcg/kg/dose; administer 3 minutes before the procedure; maximum dose: 50 mcg; may repeat $^1/_2$ original dose every 3-5 minutes if necessary; titrate to effect (Cramton, 2012; Krauss, 2006; Zeltzer, 1990)

Intranasal (using parenteral preparation): Limited data available: Infants and Children ≥10 kg: 1.5 mcg/kg once (maximum: 100 mcg/dose); reported range: 1-2 mcg/kg; some studies that used an initial dose of 1.5 mcg/kg allowed for additional incremental doses of 0.3-0.5 mcg/kg to be administered every 5 minutes, not to exceed a total dose of 3 mcg/kg depending on pain type and severity (Borland, 2002; Borland, 2005; Borland, 2007; Chung, 2010; Cole, 2009; Crellin, 2010; Herd, 2009; Manjushree, 2002; Saunders, 2010)

Adolescents and Adults:

Analgesia for minor procedures/sedation:

IV: 0.5-1 mcg/kg/dose; may repeat after 30-60 minutes; or 25-50 mcg, repeat full dose in 5 minutes if needed, may repeat 4-5 times with 25 mcg at 5-minute intervals if needed.

Manufacturer Information

Ketamine Hydrochloride Injection, USP, CII (50 mg/mL): Mylan Institutional LLC, Rockford, IL

Fentanyl Citrate Injection, USP, CII (50 mcg/mL): West-Ward Pharmaceuticals, Eatontown, New Jersey

LMA MAD Nasal Intranasal Mucosal Atomization Device: Wolfe-Tory Medical, Inc. Salt Lake City, Utah 84107

Note: Please see Ketamine and Fentanyl package inserts for further information.

APPENDIX G: Normal Ranges for Study Vital Signs

NORMAL VALUES (notify MD if outside range)

HEART RATE (per minute)

Age	Awake Rate
8-10 years	60 to 150
> 10 years	45 to 140

RESPIRATORY RATE (breaths/minute)

Age	Rate
8-10 years	10 to 30
> 10 years	10 to 30

BLOOD PRESSURE

Age	Systolic Pressure (top)	Diastolic Pressure (bottom)
8-9 years	80-160	40-80
10-11 years	80-160	50-80
> 11 years	90-160	50-80

OXYGEN SATURATION should always be greater than 90 %
END TIDAL should not decrease by more than 10 from baseline
VAS should not increase by more than 15 from previous assessment
UMSS should be 2 or less