TITLE: Comparison of Sedation, Pain, and Care Provider Satisfaction between the Use of Intranasal

Ketamine Versus Intranasal Midazolam and Fentanyl during Laceration Repair

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## 1. Study Overview

Children frequently present to pediatric emergency center (PEC) with lacerations. Often, laceration repair proves to be traumatic for the children and the parents alike. Ideally, laceration repair should be as painless and free from anxiety as possible. To work towards this goal, different analgesic and sedative management strategies use intravenous, intramuscular and, more recently, intranasal routes.

Unfortunately, intravenous access is hard to establish and may be painful for the child. The intramuscular route is often similarly painful. Due to the rich blood supply and large surface area of the nasal vestibule, intranasally (IN) administered medications are highly absorbed. IN approaches for procedural pain reduction, such as during dental work, have been demonstrated to make drug administration painless and well tolerated, making it an attractive potential alternative to commonly used intravenous and intramuscular approaches.

In several small research studies, high doses of intranasal ketamine (9 mg/kg) produce adequate sedation during laceration repair with minimal side effects. A recent study compared IN ketamine, midazolam, fentanyl or combination of these drugs for pain management and urgent analgesia sedation, and demonstrated that they are effective and safe, reporting that ~60% of study participants sustained mild to moderate sedation.

Unfortunately, there are not enough studies done to evaluate the sedation effect of IN ketamine for laceration repair. Small studies (Tsze, DS and Nemeth, M) showed that IN ketamine is an effective alternative but no studies are done to compare combination IN midazolam and fentanyl to IN ketamine. Our null hypothesis is that there is no difference in sedation scores during laceration repair when comparing use of IN ketamine to IN midazolam and IN fentanyl.

We will recruit a total of 30 pediatric patients (6 months – 10 y age) in a randomized double-blinded pilot study of IN ketamine alone or combined IN midazolam and IN fentanyl for laceration repair, comparing levels of pain and sedation scores using validated pediatric metrics as the primary outcomes. In addition, we will assess comparative nurse and physician satisfaction in each of these two groups. Understanding the relative effectiveness of these two approaches will help us identify a safe, effective, and easily administrable method to manage pain and anxiety, thereby, improving patient experience and outcomes during the often traumatic laceration repair procedure.

## 2. Study Objectives

**Primary objectives:**

1. The primary outcome variable is the maximum sedation score as measured by the University of Michigan Sedation Scale. This scale consists of an ordinal scale from 0 to 4.

2. The proportion of children who receive a maximum sedation score of either 1 or 2 (without distinguishing between those values) between the two sedation groups (IN ketamine versus IN midazolam + IN fentanyl) will be compared.

**Secondary (or specific) objectives:**

The effect of IN ketamine vs IN midazolam + IN fentanyl on pain scores during laceration repair will be compared between the two groups

Nurse and physician satisfaction will be compared between the two groups

Any adverse events will be compared between the two groups.

Rates of failure to repair laceration due to agitation or intolerable pain with switch to intravenous medications will be compared between two groups

Any significant change in vitals during analgosedation (any desaturation - spO2 < 90, and hypotension per age-related norms) will be compared between the two groups.

## 3. Methodology

**Study Design:**

We will conduct a pilot study as a randomized double blinded clinical fashion between March 2018 - March 2019 in the Pediatric Emergency Center at Beaumont Children's Hospital, a tertiary pediatric hospital in Royal Oak, MI. Parents of children who meet study inclusion criteria and none of the exclusion criteria will be approached and consented by the physician prior to randomization (consent form attached). Verbal assent will be obtained for children 7-10 years of age.

**Randomization:**

A randomization list created by an online randomization tool* will be used to assign participants to a treatment arm (in random blocks of 4, 6, and 8). As participants are enrolled into the study, they will be assigned to the next available sequential treatment arm.

* Sealed Envelope Ltd. 2017. Create a blocked randomization list. [Online] Available from: https://www.sealedenvelope.com/simple-randomiser/v1/lists [Accessed 10 Jan 2018].

Once the treatment arm has been determined, two syringes of medication will be prepared. One syringe will contain either midazolam (for those assigned to the midazolam + fentanyl arm) or ketamine (for those assigned to the ketamine arm). The other syringe will contain either fentanyl (for those assigned to the midazolam + fentanyl arm) or 0.9% sodium chloride (for those assigned to the ketamine arm).

Syringes for each treatment assignment will be visually identical in appearance. The volume of each syringe will depend on weight-based dosing of the study medication. Each treatment arm

will have the same volumes of medications so it will be indistinguishable between treatment arms.

For example, if a participant weighs 30 kg and is assigned to the midazolam + fentanyl arm, one syringe will contain midazolam (9 mg/1.8 mL) and the other syringe will contain fentanyl (45 mcg/0.9 mL). If the same participant was assigned to the ketamine arm, one syringe will contain ketamine (90 mg/1.8 mL) and the other syringe will contain 0.9% sodium chloride (0.9 mL).

**Medication Concentrations:**
Midazolam 5mg/mL
Fentanyl 50 mcg/mL
Ketamine 50 mg/mL
Sodium chloride 9mg/mL

**Explanation of Activities:**

Eligibility criteria screening will be done by the fellow or attending physician during the shift.
Participants who met inclusion criteria and none of the exclusion criteria will be approached and consented by the physician prior to randomization (consent form attached).
Verbal assent will be obtained for children 7-10 years of age.
XAP (topical anesthetic - lidocaine-epinephrine-tetracaine topical solution) will be applied to all lacerations for 20 minutes duration before giving the intranasal medications

Participants will be randomized to one of two groups:

**Group 1:** Intranasal ketamine 3mg/kg (max 100 mg) + saline 0.03 ml/kg (max 2ml)

**Group 2:** Intranasal midazolam 0.3 mg/kg (max 10 mg) + fentanyl 1.5mcg/kg (max 100 mcg)

The EC pharmacist will prepare syringes dependent on group assignment by consecutively numbered envelopes, and will be provided to a nurse who will be blinded by these assignments. These drugs will be delivered to the participant via two MAD (mucosal atomization) devices for intranasal application of medications prior to laceration repair.

**Intranasal Administration of Study Medications:**

For this study, intranasal medications will be administered via an intranasal MAD device to maximize the surface area for absorption.

The participant will be positioned sitting at 45 degrees, or lying supine with head turned to one side, and the atomizer (MAD device) will be applied to the nostril (pointing slightly up and outward)
If the syringe fluid volume is larger than 1ml, then ½ of the volume will be delivered to each nostril. The same process will occur for the second medication.
After the intranasal application of the medications, the physician will wait for 10 min before starting the laceration repair.

**Laceration Repair:**

Laceration will be repaired by the resident, fellow or attending working in PEC.
Vitals (heart rate, respiratory rate, oxygen saturation and blood pressure) and baseline pain score will be recorded prior to intranasal medication administration.
When the nurse records the first set of vitals before giving the medications they will also complete a form which includes vital signs, sedation score, pain score and will repeat every 5 minutes until 10 minutes after the laceration repair or until the patient is awake.
The nurse will fill out a form that includes vitals (heart rate, respiratory rate, oxygen saturation and blood pressure), sedation score, pain score immediately prior to applying IN medications and repeat every 5 minutes until the end of the laceration repair, and five minutes after the end of the procedure or until the patient is able to follow commands.
Any adverse events (e.g. nausea, vomiting, epistaxis, dizziness) will be recorded on the nurse's form.

Once the procedure has been completed, the satisfaction questionnaire will be filled out by the nurse and physician who were at bedside during the procedure. (Questionnaire attached below)
All process will be videotaped and two consistent scorers who are blinded to the medications, will watch all the videos in the end of the study and will fill the questionnaire to prevent interrater reliability as a limitation to the study.

**Pain Scores:**

6 months of age to < 4 years of age, FLACC pain scale will be used for pain evaluation.
≥ 4 to 10 years of age FACES pain scale will be used for pain evaluation.

FLACC pain scale;

Medscape® www.medscape.com

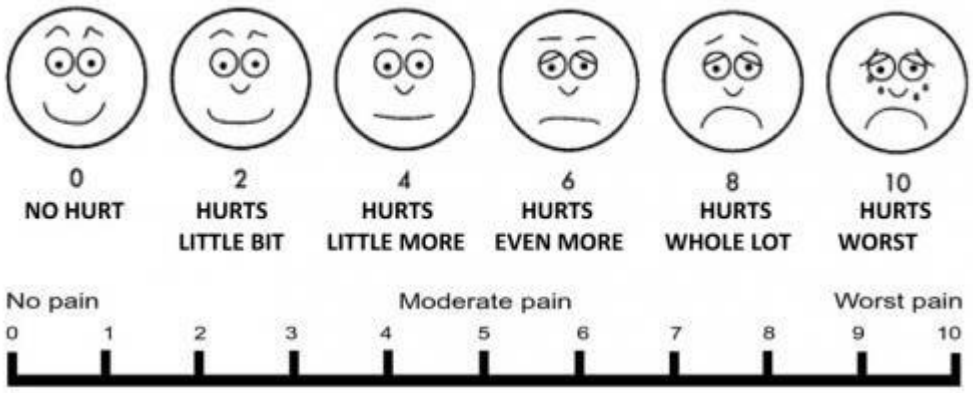
| | Scoring | | |
|---|---|---|---|
| **Categories** | **0** | **1** | **2** |
| Face | No particular expression or smile | Occasional grimace or frown, withdrawn, disinterested | Frequent to constant frown, quivering chin, clenched jaw |
| Legs | Normal position or relaxed | Uneasy, restless, tense | Kicking or legs drawn up |
| Activity | Lying quietly, normal position, moves easily | Squirming, shifting back and forth, tense | Arched, rigid, or jerking |
| Cry | No cry (awake or asleep) | Moans or whimpers; occasional complaint | Crying steadily, screams or sobs, frequent complaints |
| Consolability | Content, relaxed | Reassured by occasional touching, hugging, or being talked to; distractible | Difficult to console or comfort |

**Note:** Each of the five categories Face (F), Legs (L), Activity (A), Cry (C), and Consolability (C) is scored from 0-2, which results in a total score between 0 and 10.

From Merkel, Voepel-Lewis, Shayevitz, & Malviya (1997). The FLACC: A behavioral scale for scoring postoperative pain in young children. *Pediatric Nursing, 23*(3) 293-297.

Source: Pediatr Nurs © 2003 Jannetti Publications, Inc.

## FACES pain scale



**Sedation Score:**

University of Michigan Sedation Scale (UMSS)

| | |
|---|---|
| 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 |

**Hypotension (age-related criteria):**
Infants, 6 months to 12 months: Systolic Blood Pressure <70 mmHg
Children 1 to 10 years: Systolic Blood Pressure <70 + (age in years x 2) mmHg
Children >10 years: Systolic Blood Pressure <90 mmHg

**4. Data collection:**

Age, Sex, Weight
The site of the laceration and number of sutures placed
Past medical history – e.g. history of autism or behavior issues (if documented)
Baseline pain scores and mean pain score during the laceration repair, and scale used
Mean sedation score during the laceration repair, also sedation scores at every 5 minutes interval before, during and after the procedure
Nurse, physician satisfaction questionnaire
Adverse events (nausea, vomiting, epistaxis, dizziness, etc) and significant change in vitals (desaturation, hypotension)
Total length of stay in the PEC, and length of stay from the intranasal medication administration to the discharge from the PEC.

**5. Risks and Benefits**

**Risk assessment:**

Patients will be monitored continuously starting immediately before administration of the drugs until the patient is awake, able to follow instructions and can drink. Respiratory rate, heart rate and oxygen saturation will be monitored continuously and blood pressure will be monitored every 5 minutes.

**Study Risks:**

**Intranasal midazolam:**

Most frequent (>10%)

- Burning sensation in the nose while drug administration
- Unpleasant taste
- Salivation
- Nausea

Less frequent (1-10%)

- Vomiting

Rare (<1%)

- Low Blood Pressure
- Allergic Reaction

**Intranasal fentanyl:**

Most frequent (>10%)

- Burning sensation in the nose while drug administration
- Unpleasant taste

Rare (<1%)

- Nose bleeding
- Allergic Reaction

**Intranasal ketamine:**

Most frequent (>10%)

- Nausea
- Salivation

Less frequent (1-10%)

- Vomiting
- Dizziness

Rare (<1%)

- Difficulty breathing
- Brief low oxygen saturation

**Benefits:**
The patient will be more comfortable and experience less pain during the procedure with minimal recall of the procedure afterwards, but this cannot be guaranteed. Information gained from the results of this study may be of benefit to other children in the future who undergo similar procedures.

**6. Eligibility Criteria:**
**Inclusion Criteria**

- Pediatric patients 6 months to 10 years who required laceration repair in the pediatric emergency center.
- Laceration should be less than 5 cm long, require 2 or more sutures and no consult supspeciality consult for repair.
- XAP (topical anesthetic - lidocaine-epinephrine-tetracaine topical solution) will be applied to all lacerations for 20 minutes duration before giving the intranasal medications.

**Exclusion Criteria**

- Age < 6 months
- Documented allergy or adverse effect to ketamine, midazolam or fentanyl
- Epistaxis
- Partial upper airway obstruction
- Oxygen requirement via nasal cannula
- Acute mental status changes (e.g. obtunded or somnolent)
- Documented increased intracranial pressure or increased ocular pressure
- Documented porphyria
- Previously involved in the study
- Parent or patient refusal
- Acutely compromised vitals (hypotension, desaturations, respiratory distress)
- Any known heart disease
- If any previous opioid use for analgesia during the visit
- Need for staples
- Scalp wounds
- General trauma requiring additional sedation
- Patients who received pain medications before laceration repair (acetaminophen or ibuprofen use)

**7. Data Analysis:**
Our primary goal with the pilot study is to determine if there is any difference between IN ketamine versus IN midazolam and IN fentanyl on sedation scores during laceration repair. Mean sedation scores during laceration repair will be filled by the nurse, physician and 2 consistent scorers in the questionnaire. Two consistent scorers will be chosen from EC or pediatric attendings who are not enrolled any patient to the study. In the end of the study, they

will be asked to watch the videos and fill the questionnaire. Kappa coefficient ($\kappa$) will be measured which measures the inter-rater agreement for qualitative items.
The analysis strategy for the primary outcome will be a test of equal probabilities of maximum sedation scores of 1 or 2 for the two schemes, along with a 95% confidence interval for the odds ratio relating the proportion of 1's or 2's for the two medication schemes. After our pilot study, we will evaluate the effect of IN ketamine in comparison to IN midazolam and IN fentanyl, as well as, evaluate potential adverse effects. If results are significant, we will conduct a randomized double blinded controlled trial with the goal of 162 patients in total with calculated study power of 0.8.

**8. Data Safety Monitoring Plan:**
IN ketamine, midazolam and fentanyl are safe medications that are FDA approved for use in pediatric emergencies. Dr. Graham Krasan will participate as the Medical Monitor and will review the study every quarter for eligibility criteria of enrolled participants, serious adverse events, drop outs, and potential difficulties in recruiting children to the study. He will oversee the progress of the trial and to ensure that the study is conducted and data are handled in accordance with the protocol, Good Clinical Practice, and applicable ethical and regulatory requirements. He will be responsible for controlling adherence to the protocol, ensuring that data are correctly and completely recorded and reported, and confirming that informed consent is being obtained and recorded for all subjects prior to their participation in the trial.

**9. Existing Study Data**

**Nemeth, M** developed a protocol for INA (intranasal analgesia) for acute pain therapy and urgent analgesia and/or sedation and assess the level of pain, sedation and reactivity score. The study team found that fentanyl was the most frequently used drug for acute pain therapy. S-ketamine/midazolam was the most frequent combination for urgent analgesia and/or sedation. They showed that intranasal fentanyl, s-ketamine, and midazolam was effective and safe for a broad range of indications in pediatric acute care and failure rate was low with only 5% of the pediatric patients needing conversion to IV. It was a non-blinded and non randomised study and drug choice made by attending pediatric anesthesiologist. In our population sedation is applied mostly by pediatric emergency attendings and randomised comparison of different intranasal administration can guide us to use most efficient medication. Nemeth,M used fentanyl 2 ug/kg of fentanyl, 4mg/kg of s-ketamine and 0.5mg/kg of midazolam in the study.

**Weber, F** conducted a prospective randomized double-blind clinical trial to evaluate the effect of intranasal s-ketamine and midazolam for induction of anesthesia to preschool children. They found that intranasal administration of s-ketamine and midazolam provides good conditions for induction of anesthesia without evidence of serious adverse effects. Compares midazolam 0.2 mg/kg with s-ketamine 1 mg/kg, midazolam 0.2mg/kg with s-ketamine 2mg/kg and midazolam 0/2mg/kg alone. Sedation scores improve significantly with both ketamine groups. This study is done to evaluate induction and parental separation and there was no painful procedures, so the

effects evaluated mostly for anxiolysis. Dose for ketamine is low for analgosedation which usually suggested 3 - 6mg/kg.

**Del Pizzo, J** wrote a review of intranasal medications for sedation. Del Pizzo,J cited study of **Theroux et al** that intranasal midazolam at 0.4 mg/kg reduced cry and struggle scores of preschool children requiring laceration repair. Adverse effects of intranasal midazolam reported as nasal irritation, unpleasant taste, salivation, nausea and vomiting, change in vision, and gait difficulties.

Fentanyl is an ideal intranasal medication because of its high lipophilicity and relatively low molecular weight. Peak plasma concentration is reached in 10 to 15 minutes and Del Pizzo cited study of Borland et al that 1.7 mcg/kg of intranasal fentanyl had comparable analgesia to 0.1 mg/kg of intravenous morphine for long-bone fractures in children. Adverse effects are rare and include epistaxis, unpleasant taste, and nasal irritation.

Ketamine is often used in the pediatric population as a potent analgesic and sedative. It has recently been the focus of study for intranasal administration and Del Pizzo cited a trial by Roelofse and colleagues that compares the intranasal administration of 20 mcg sufentanil and 0.3 mg/kg midazolam to 5 mg/kg ketamine and 0.3 mg/kg midazolam in healthy children undergoing dental surgery and found that both groups were equally sedated and received the general anesthesia mask well. All three medications were effective for procedural sedation.

**Tsze DS** conducted a randomized, prospective, double-blind trial of children who required sedation for laceration repair. Participants with simple lacerations were randomized by age to receive 3, 6, or 9 mg/kg intranasal ketamine. Of the 12 participants enrolled, 3 children achieved adequate sedation, all at the 9 mg/kg dose. Both the 3 mg/kg and 6 mg/kg doses were not evaluated further due to their lack of efficacy. The only adverse event documented in this study was vomiting in 1 patient. Of note, this study compared different doses of intranasal ketamine. Due to the low number of participants enrolled the study was suspended early and data is not reliable. Our goal is to use ketamine 3 mg/kg intranasally, which in other pediatric studies was sufficient to produce mild sedation.

**Lane RD** studied the effect of atomized intranasal midazolam for minor procedures in the pediatric emergency department. Lane, RD performed a retrospective chart review of children who received intranasal midazolam sedation. Initial IN midazolam dose was 0.4 mg/kg (range, 0.3-0.8 mg/kg). Laceration repair was the most common procedure necessitating sedation (89%). Showed that median degree-of-sedation was anxiolysis without any adverse events. This study shows that 0.4mg/kg of midazolam is effective for anxiolysis. In our study we will use 0.5 mg/kg as mentioned by Nemeth,M. We will compare the known effect of midazolam to ketamine for non-inferiority.

**Andolfatto G** assessed the analgesic effect of intranasal ketamine in the emergency department with doses of 0.5 to 0.75 mg/kg of intranasal ketamine. No serious adverse effects occurred. Minor adverse effects included dizziness, feeling of unreality, nausea, mood change and changes in hearing. All adverse effects were transient and none required intervention.

There were no changes in vital signs requiring clinical intervention. Intranasal ketamine reduced pain scores to a clinically significant degree in 88% of ED patients in this study. We will study high dose of intranasal ketamine for analgosedation in our study.

**Graudins A** conducted the PICHFORK (Pain in Children Fentanyl or Ketamine) trial: a randomized controlled trial comparing intranasal ketamine and fentanyl for the relief of moderate to severe pain in children with limb injuries.
Graudins conducted a double-blind, randomized, controlled trial comparing fentanyl at 1.5 mg/kg with ketamine at 1 mg/kg in children aged 3 to 13 years with isolated limb injury and pain of more than 6 of 10 at triage. In the study it was found that intranasal fentanyl and ketamine were associated with similar pain reduction and ketamine with more minor adverse events. This study is another study only done for the purpose of pain reduction with no procedures.

**Louon A** checked the effect of nasal midazolam and ketamine for pediatric sedation during CT. In this study, a mixture of midazolam (0.56 mg/kg) and ketamine (5 mg/kg) administered nasally Louon A observed that the combination was effective in 83% of the cases and there was no complications. There was no respiratory depression and oxygen desaturation, suggestive that this combination is safe and efficient in the CT room. (30 children). We will use the similar doses in our study and it is good to see that there was no complications.

**Abrams R** evaluated the safety and effectiveness of intranasal administration of sedative medications (ketamine, midazolam, or sufentanil) for urgent brief pediatric dental procedures. In this study they used ketamine 3 mg/kg; midazolam 0.4 mg/kg; or sufentanil 1.5 or 1.0 mcg/kg-intranasally in a randomized, double-blinded protocol. The sedation scores for midazolam and ketamine were both 4. 2 children in ketamine group had brief desaturations.

They also compared the effect of Sufentanil 1.5 mcg/kg and 1.0 mcg/kg. The 1.5 mcg/kg dose caused significant desaturations and 1 mcg/kg dose no desaturations. In their conclusion, the investigators mentioned that midazolam and ketamine are acceptable and ideal for urgent brief pediatric dental procedures.
Our study will be similar to the Abrams study with the difference of using ketamine, and midazolam with fentanyl om combination. Our study will employ these medications for laceration repair.

**Green SM, Roback MG, Kennedy RM, Krauss B** wrote an updated guideline for emergency department ketamine dissociative sedation in 2011.
They mentioned that ketamine dissociation appears at a dosing of approximately 1.0 to 1.5 mg/kg intravenously (IV) or 3 to 4 mg/kg intramuscularly (IM).

Once the dissociative threshold is reached, administration of additional ketamine does not enhance or deepen sedation, as would be the case with opioids, sedative-hypnotics, or inhalational agent, American College of Emergency Physicians: “A trancelike cataleptic state characterized by profound analgesia and amnesia, with retention of protective airway reflexes, spontaneous respirations, and cardiopulmonary stability,” ie, dissociative sedation.

The literature is strongly supportive of the safety and efficacy of ED dissociative sedation for a variety of brief painful or emotionally disturbing procedures in both children and adults. In their update, they mention that it is safe to use ketamine in infants younger than 12 months, but not in infants younger than 3 months of age due to reported cases of airway complications including airway obstruction, laryngospasm, and apnea. Ketamine has been shown to exacerbate schizophrenia. They also recommend that ketamine should be avoided in children with known or possible coronary artery disease, congestive heart failure, or hypertension due to inhibition of the reuptake of catecholamines, and the resulting sympathomimetic effect.

In our study, we will exclude infants younger than 3 months and children with known heart disease. We will also exclude children older than 10 years of age because they mostly tolerate laceration repair with only local anesthesia and usually does not require sedation.

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Attached documents:
**Satisfaction Questionnaire**
**Nursing Sheet**
**Screening and Eligibility Criteria**
**Data collection tool**
**Schedule of events**
**Budget Estimate**
**Consent Form**

**Nurse/Doctor Questionnaire:**

1- Any difficulties administering the intranasal medications? (only nurse)
Yes, please explain
No

In your opinion, please rate.

2- Patient had tolerable pain during the procedure.
1-Strongly disagree
2-Disagree
3-Neutral
4-Agree
5-Strongly agree

3- Patient was adequately sedated/ calm for the procedure?
1-Strongly disagree
2-Disagree
3-Neutral
4-Agree

5-Strongly agree

4- Patient tolerated the procedure well?

1-Strongly disagree
2-Disagree
3-Neutral
4-Agree
5-Strongly agree

5- Would you recommend this process if there was a need to repeat the same procedure?

Yes
No

6- How do you rate overall experience for this procedural sedation ?

Poor
Fair
Good
Very good
Excellent

7. Physician Name

## Nursing Sheet

MRN:
Age:
Sex:
Race:
Time of IN administration:
Time of starting laceration repair:
Time of ending the procedure:
Time of discharge:
If procedure is longer than 30 min, please continue recording the vitals, sedation and pain score

| **Vital signs** | **Prior to IN medication** | **5 min** | **10 min** | **15 min** | **20 min** | **25 min** | **30 min** | | |
|---|---|---|---|---|---|---|---|---|---|
| **Time** | | | | | | | | | |
| **HR** | | | | | | | | | |
| **BP** | | | | | | | | | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **RR** | | | | | | | | | |
| **pO2** | | | | | | | | | |
| **Sedation score** | | | | | | | | | |
| **Pain Score** | | | | | | | | | |

**Adverse events:**

| | | |
|---|---|---|
| Nausea | Yes | No |
| Vomiting | Yes | No |
| Epistaxis | Yes | No |
| Irritation during IN administration | Yes | No |
| Desaturations | Yes | No |

If patient required any intervention, please specify

- Tactile stimulation
- Oxygen support
- Bag-valve mask
- Intubation
- Other _____

| | | |
|---|---|---|
| Hypotension that required intravenous fluid | Yes | No |
| Stridor, difficulty breathing, laryngospasm | Yes | No |
| Allergic reaction (Rash, difficulty breathing, tongue swelling) | Yes | No |
| Procedure failure requiring other meds | Yes | No |

- Other _____

**Screening and Eligibility Criteria:**

**Inclusion Criteria**

- Pediatric patients 6 months to 10 years who required laceration repair in the pediatric emergency center.
- Laceration less than 5 cm long, require more than 2 sutures, and no consult for repair.
- XAP (topical anesthetic - lidocaine-epinephrine-tetracaine topical solution) needs to be applied for all lacerations for 20 minutes duration before giving intranasal medications.

**Exclusion Criteria**

- Age < 6 months

- Documented allergy or adverse effect to ketamine, midazolam, or fentanyl
- Epistaxis
- Partial upper airway obstruction
- Oxygen requirement via nasal cannula
- Acute mental status changes (e.g. obtunded or somnolent)
- Increased intracranial pressure or increased ocular pressure
- Porphyria
- Previously involved in the study
- Parent or patient refusal
- Acutely compromised vitals (hypotension, low saturations, respiratory distress)
- Any known heart disease
- If any previous opioid use for analgesia during the visit
- Need for staples
- Scalp wounds
- General trauma requiring additional sedation
- Patients who received pain medications before laceration repair

**Data Collection Tool**

Patient Number
MRN
Age
Sex
Race
Time between IN administration to start laceration repair
Time between IN administration to end of the procedure
Time between IN administration to discharge
Any Bradycardia (HR<60)
Any Hypotension
Any apnea
Any significant change in pO2 (<90%)
Max sedation score during the procedure
Mean pain score during the procedure
Nause
Vomiting
Epistaxis
Nasal irritation
Desaturations
Hypotension
Intervention for desaturation
Stridor, difficulty breathing, laryngospasm
Allergic reaction
Failure

Other adverse events
Survey Nurse Q1
Survey Nurse Q2
Survey Nurse Q3
Survey Nurse Q4
Survey Nurse Q5
Survey Nurse Q6
Survey Nurse Q6
Survey MD Q1
Survey MD Q2
Survey MD Q3
Survey MD Q4
Survey MD Q5
Survey MD Q6
Survey 1st Scorer Q1
Survey 1st Scorer Q2
Survey 1st Scorer Q3
Survey 1st Scorer Q4
Survey 1st Scorer Q5
Survey 1st Scorer Q6
Survey 2nd Scorer Q1
Survey 2nd Scorer Q2
Survey 2nd Scorer Q3
Survey 2nd Scorer Q4
Survey 2nd Scorer Q5
Survey 2nd Scorer Q6

**Schedule of Events**
Screening for eligibility criteria will be done by the fellow or attending physician during the shift. Patients who met inclusion criteria will be approached and consented by the physician prior to randomization (consent form attached).
Verbal assent will be obtained for the children 7-12 years of age.

The treatment groups are:
First group will receive ketamine 3mg/kg (50mg/ml) (max 100mg) plus saline 0.03ml/kg (max 2ml) through the nose with an applicator.
Second group will receive midazolam 0.3mg/kg (5mg/ml) (max 10mg) plus fentanyl 1.5mcg/kg (50mcg/ml) (max 100mcg) through the nose with an applicator.
The following activities will occur at the specified study visits:

**Screening and Study Activities:**
Medical history obtained

Physical exam
Vital signs (blood pressure, heart rate, breathing rate, oxygen saturation)
A numbing cream (lido-epitetracaine topical solution,5ml) will be applied onto the cut for all the children in both treatment group as standard of care and we will wait for 20 minutes for the cream to show the effect.

20 minutes after the numbing cream:

The nurse will record a full set of vitals and connect the patient to the cardiac and respiratory monitor.
Patient will receive the drug that is assigned through the nose with an applicator.
The nurse will complete the form

We will wait for 10 minutes after medication is administered before performing the procedure Laceration repair will be performed.

Patient's respiratory rate, blood pressure, heart rate and oxygen saturation will be continuously monitored starting before administration of the medications and will be monitored until the patient is awake and able to follow commands.
Patient will be discharged when able to follow commands and drink fluids.

All the process will be videotaped for the two consistent scorers. They will be chosen from Emergency Medicine Physicians or Pediatricians. In the end of the study, they will watch the videos and evaluate the sedation effects of these medications. The videos will be recorded in a memory disc which will be kept in a safe place and will be deleted and discarded in the end of the study. This process will be HIPAA compliant, no patient information will be shared with the scorers.

**Budget Estimate**

1. Personnel :
Emergency Center Research Staff and Biostatistician- $5,303.
Mara Branoff, RN BSN is the Emergency Medicine Clinical Research Manager who will be provided study oversight and regulatory support. $1,125 inclusive of salary, FICA and fringe is requested in support of her effort on the study.
Clinical research coordinator (TBD) who will recruit study participants and collect data. We request $3,144 inclusive of salary, FICA and fringe in support of the research coordinator's time on this study. Effort on project 5%.
Biostatistical support to provide assistance with randomization, development of the study data files, and statistical analysis will cost $1,034. Effort on project 1%.
2. Research Pharmacy. A total of $3,697 is requested. This request includes costs for research pharmacy setup, record administration and study drug management. Medication costs are dependent on medication type, doses per patient, patient enrollment, and extra preparation

requirements. Calculation assumed all the patients will require maximum dose of the medications.
Preparation of intranasal medication $10/dose $20 x 30 = 600
Midazolam 5mg/mL, 1 mL vial $0.77/vial $1.54 x 15 = 23.1
Fentanyl 50mcg/mL, 2 mL vial $0.59/vial $0.59 x 15 = 8.85
Ketamine 100mg/mL, 5 mL vial $7.64/ vial $7.64 x 15 = 114.6
3. Equipment: Video camera with tripod: $500

**Total Budget: $5,303 + $3,697 + $500 = $9,500**

**Funding:**
**$5000 from Beaumont Emergency Center Research Fund**
**2018 Society for Pediatric Sedation Scholarly Grant Application is done, awaiting results for $10,000.**