

# Comparison of Two Methods Using Lidocaine to Alleviate Discomfort Associated with Administration of Intranasal Midazolam in Children: Standalone Protocol

## Study Purpose and Rationale

Intranasal (IN) midazolam is a common medication administered to children requiring anxiolysis to facilitate distressing medical procedures in the pediatric emergency department (Klein 2011, Yealy 1992, Theroux 1993). IN midazolam is safe and effective, but it causes a significant amount of nasal pain and burning when administered by the IN route (Lugo 1993, Chiaretti 2011, Smith 2016). One way of ameliorating the nasal pain associated with IN midazolam is to use IN lidocaine.

Prior studies have described the successful use of IN lidocaine to decrease the pain associated with acidic IN medications, such as midazolam. One method is to premedicate using IN lidocaine (PREMED), meaning that lidocaine is sprayed into the nares prior to a subsequent administration of IN midazolam (Chiaretti 2011, Lugo 1993, Smith 2016). The second method is to mix the lidocaine with the midazolam (PREMIX), and to administer both medications at the same time as a mixed solution (Antonio 2011).

Both methods have been shown to effectively decrease the pain associated with acidic IN medications, such as midazolam (Chiaretti 2011, Smith 2016, Antonio 2011). However, it is unclear whether one method is more effective than the other when used in children. A method, such as PREMIX, which requires administering only one solution, rather than two as required by the PREMED method, would be more convenient and potentially less distressing to children if it worked as well as the PREMED method. Therefore, we aim to determine whether using intranasal lidocaine via the PREMIX method is non-inferior to the PREMED method for reducing pain associated with IN midazolam.

## REFERENCES:

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## **Study Design**

We will conduct a prospective, randomized, investigator blinded, non-inferiority clinical trial of 55 children comparing the PREMED (premedicating with IN lidocaine before IN midazolam administration) versus the PREMIX (mixing lidocaine with midazolam and administering the combined mixture) methods of administering IN lidocaine to decrease the pain associated with IN midazolam. Eligible patients will be block randomized to receive IN midazolam and lidocaine by either the PREMED or PREMIX method. Both techniques are currently considered standard of care at NYPH (please see attached hospital protocol).

## **Statistical Procedures**

We will enroll 55 children to determine whether the PREMED method is non-inferior to the PREMIX method. We based our sample size on the outcome of pain and distress associated with the administration of IN midazolam, which will be measured using our primary outcome measure of the Observational Scale of Behavioral Distress-Revised (OSBD-R). The OSBD-R is an observational measure of distress that has been well validated in the pediatric population for evaluating painful and distressing procedures, and has been used in children as young as 1 year of age (Tsze 2013, Tsze 2016).

The sample size of 50 patients was determined based on a pre-stated margin of non-inferiority (delta) of 1.8 (SD 2.25). This value was based on the minimum clinically significant differences used in prior studies of painful procedures in children in the emergency department (Fenster 2016, Godambe 2003, Lee-Jayaram 2010). To determine non-inferiority using a delta of 1.80 (SD 2.25), with a 1-tailed alpha of 0.025 and power of 80%, we would require 25 patients in each arm, for a total of 50 patients.

OSBD-R scores will be determined independently by two blinded trained assessors who will review the videotapes of the study procedures. Interrater reliability of the OSBD-R between the two assessors will be evaluated by determining the intraclass correlation coefficient. The period of administration of the midazolam alone in the PREMED group and the period of administration of the midazolam/lidocaine mixture in the PREMIX group are the two phases which will be compared to each other to determine our primary outcome (See Figure 2; phases to be compared highlighted by red boxes).

Secondary outcome measures of pain and distress associated with IN midazolam administration will include the Children's Hospital of Eastern Ontario Pain Scale (CHEOPS); the Faces-Legs-Activity-Crying-Consolability (FLACC) scale; and cry duration. These are all continuous measures that will be analyzed using the independent samples t-test.

We will also evaluate parental and provider satisfaction across various domains using a 5-point Likert scale (see attached document for questions to be asked). Responses will be dichotomized into "agree" (i.e. if respondent answers "agree" or "strongly agree") or "disagree" (i.e. if respondent responds "undecided", "disagree", or "strongly disagree") and analyzed using the chi square test.

## **Procedures**

Patients between the ages of 6 months to 7 years who require a laceration repair will be screened for possible enrolment. If the patient requires IN midazolam to facilitate the laceration repair, as determined by their treating physician, and the patient fulfills inclusion criteria (age of  $\geq 6$  months or  $\leq 7$  years old, undergoing a laceration repair, and identified by physician as needing IN Midazolam) and exclusion criteria (weight  $< 5$  kg, known allergy to Lidocaine or Midazolam, inability to speak English or Spanish, nasal injury precluding IN medication delivery, presence of intranasal obstruction (mucous/blood) not easily cleared with suction or nose blowing, baseline motor neurological abnormality (e.g. motor deficit, cerebral palsy), developmental delay, autism, or autism spectrum disorder). The treating physician will ask the family if they would be interested in hearing about the study. If the family agrees, the study will be introduced and discussed with the family, and written informed consent obtained, by a member of the study team.

Enrolled patients will be block randomized using an online randomization program to either the PREMED or PREMIX study arm. Study arm assignment will be concealed until the patient is enrolled and the online randomization program is accessed.

We will collect patient demographics and relevant historical information. These data elements include the patient's age (years); sex (female/male); weight (kilograms); race (Black/African American, White, Asian, Native American/Other Pacific Islander, American Indian/Alaskan Native, more than one race, non-specific ) and ethnicity (Hispanic or Latino, Non-Hispanic or Latino, or non-specific); whether the patient has ever received IN midazolam before (yes/no); and whether the patient has received any type of intranasal medication before (yes/no). The dose of IN midazolam administered (milligrams) will be recorded.

All IN medications will be administered in a standardized fashion using a mucosal atomization device (MAD), as per NYPH Medication Use Manual Policy "Intranasal Administration of Analgesics and Sedatives Using a Mucosal Atomization Device (see attached documents). All patients will receive the standard dose of IN midazolam (0.05 mg/kg, maximum total dose 20 mg), and the standard dose of IN lidocaine (4% lidocaine, 20 mg = 0.5 mL total; 0.25 mL per nare), as per NYPH policy.

All patients will have a baseline assessment of pain and distress prior to administration of any medications. A study team member will videotape the child for 1 minute.

\*For patients randomized to the PREMED study arm:

1. Patients will receive 0.25 mL of IN lidocaine in each nare (0.5 mL total)
2. IN lidocaine administration will be videotaped, starting from time of administration of the first aliquot of lidocaine.
3. Wait at least 5 minutes after time of IN lidocaine administration (patient will still be videotaped during this time).
4. Patients will receive 0.5 mg/kg of IN midazolam. The total volume will be divided into aliquots of 0.5 mL, and administered into alternating nares until the total volume is dispensed. There will be at least a 10-second pause before re-administering to the same nare a subsequent time.
5. The administration of IN midazolam administration will also be videotaped, continuing from the prior steps; it will continue until at least 1 minute after completion of administration of IN midazolam, or until at least 30 seconds after cessation of crying (if crying occurs).
6. The administration of all medications must be completed by a pediatric emergency medicine attending or pediatric emergency medicine fellow.

\*For patients randomized to the PREMIX study arm:

1. 0.5 mg/kg of midazolam will be mixed with 20 mg (0.5 mL) of 4% lidocaine.
2. The total volume will be administered to the patient in aliquots of 0.5 mL, and administered into alternating nares until the total volume is dispensed. There will be at least a 10-second pause before re-administering to the same nare a subsequent time.
3. Administration of the midazolam/lidocaine mixture will be videotaped, starting from the time of administration of the first aliquot of the mixture, until at least 1 minute later, or until at least 30 seconds after cessation of crying (if crying occurs).

A flowchart illustrating the study procedure has been attached (see Figure 1 in attached documents).

After the videotaping has been completed, all caregivers/providers who administered the IN medications will be asked to complete a brief questionnaire regarding their satisfaction with the administration of IN medications (see attached documents for questions). A study team member will monitor the patient during the remainder of their procedure, until procedure completion, to document any adverse events (see attached documents for adverse events collected).

The administration of the midazolam alone in the PREMED group (Step #4 in the PREMED study arm description) and the administration of the midazolam/lidocaine mixture in the PREMIX group (Step #3 in the PREMIX study arm description) are the two phases which will be compared to each other to determine our primary outcome (See Figure 2).

## MISSED ELIGIBLE POPULATION

We will be doing a retrospective medical record review to identify a missed eligible population (i.e. patients who are eligible, but are not screened or enrolled). As patients come to the emergency department 24/7, it is inevitable that some eligible patients will be missed. We will collect information on these patients from the medical records to ensure scientific credibility by showing that we are not enrolling a biased sample of children with lacerations. This population will not be subjected to study procedures or interventions. The data points collected for these patients will be retrieved from existing medical records and are limited and specific. They include:

- Age (years, months - NO date of birth will be documented)
- Sex (female, male)
- Chief complaint
- Attending physician

## **Potential Risks**

There are no risks greater than that to be expected as part of the usual medical care that we provide for children with the same condition who would receive the same medications. All of the treatments you could receive in this study are considered usual practice as described in the NewYork Presbyterian Hospital Policy for intranasal medications.

## **Potential Benefits**

There are no potential direct benefits to participating in this study, but there may be benefits for children in the future who will receive intranasal midazolam.

## **Alternatives**

The parent/guardian can choose for their child not to participate in the study.

## **Data and Safety Monitoring**

Data will be reviewed on an ongoing basis by the PI with each patient enrolled. On an ongoing basis, the investigators will monitor accrual of study subjects, assess adherence to study protocol, assess data quality, and collect and review adverse events and other subject safety matters. We will submit to the IRB protocol deviations and any requested protocol modifications.

All data will be maintained on password protected computers and in locked file cabinets in a locked room to which only authorized study personnel will have access. Only approved research staff will view the clinical information of children enrolled in this study. We will retain study records, documentation and videotapes for 3 years after the last enrolled patient has completed all study procedures.

We will convene a Data Safety Monitoring Board (DSMB) comprised of two physicians unrelated to the study (members TBD). The DSMB will evaluate adherence to the protocol every 6 months and report any protocol violations to the IRB.

**Adverse Event Reporting:** An adverse event is any untoward medical occurrence by a subject. For each patient, the investigators will evaluate adverse events after completion of enrollment. All unanticipated problems (i.e. unexpected events, outcomes, or occurrences, at least possibly related to the research, and suggest an increase in risk of harm to subjects or others) will be reported to the IRB. This reporting will be done promptly, but no later than one week after the occurrence or after the PI acquiring knowledge of the unanticipated problem, and will also be reported at time of continuing review. All serious adverse events (i.e. airway obstruction requiring airway repositioning or adjunct airway; positive pressure ventilation; apnea) will be reviewed by the investigators and reported to the IRB within 96 hours

**END OF STANDALONE PROTOCOL**