Standalone Protocol

Dose-Finding Study of Intranasal Midazolam for Procedural Sedation in Children

Aug 6 2021

NCT04586504

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Study Purpose and Rationale

Procedural sedation is an integral part of providing definitive medical care for children in the emergency department (ED). Children often find common medical procedures, such as laceration repairs, to be painful and highly distressing. If this pain and distress is not treated with procedural sedation, children will suffer both the short- and long-term consequences of poorly managed pain and distress. They may also risk an unsatisfactory outcome or personal harm related to performing the procedure on an uncooperative patient under suboptimal conditions.

Over the past two decades, intranasal (IN) midazolam has emerged as a frequently-used sedative for procedural sedation for children in the ED.[1–4] It has advantages over more traditional routes of administering sedatives, such as having faster and more reliable onset of action and greater bioavailability than the oral route; and not requiring intravenous (IV) cannulation necessary for IV sedatives, as the cannulation may be as painful and distressing as the procedure itself.[5]

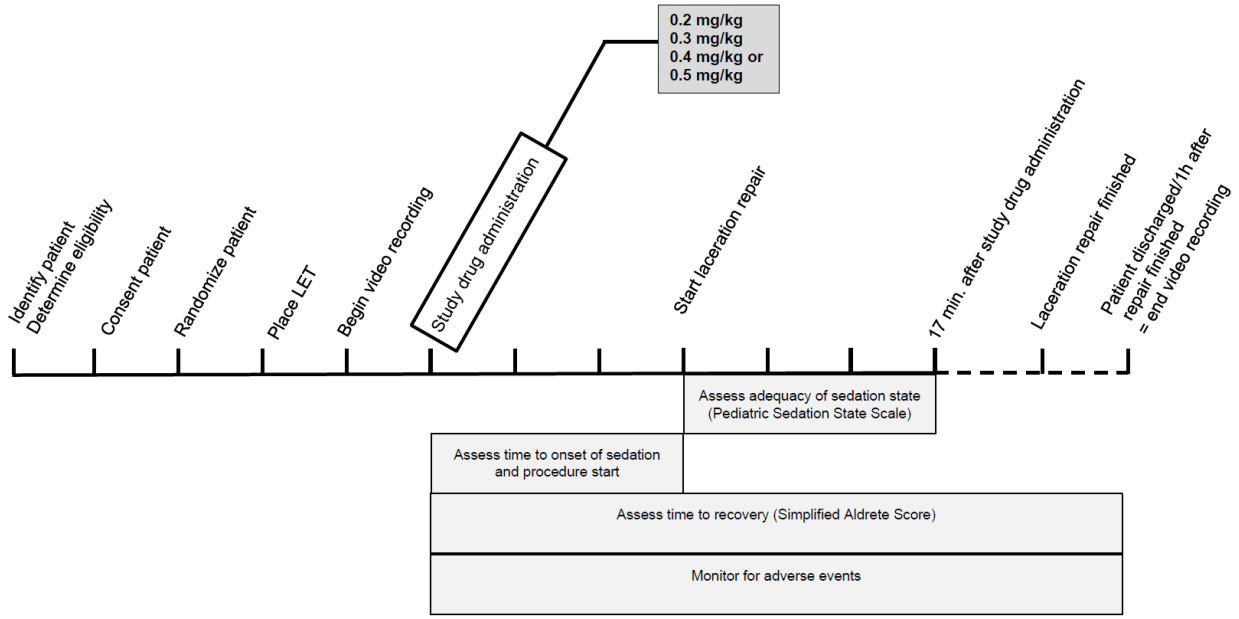
Despite the growing use of IN midazolam in EDs, there is still clinical equipoise regarding one fundamental aspect: the optimal dose of IN midazolam for procedural sedation in children. The doses of IN midazolam described in literature reviews, research studies, and clinical guidelines range from 0.2 to 0.5 mg/kg.[1–4] There is only one retrospective study from 1992 that suggests a difference in clinical efficacy between escalating doses of IN midazolam ranging from 0.2 to 0.5 mg/kg.[6] However, there has since been no prospective study or comparison of these doses to confirm or refute this observation, and there continues to be wide variation in the doses of IN midazolam used clinically and in research studies. Therefore, it is necessary to determine the optimal dose of IN midazolam for procedural sedation in the ED so that the clinical care of children can be optimized, and the correct dose be used in research studies when comparing IN midazolam to other sedatives.

Study Design

We will conduct a prospective, double-blinded, multi-arm (four groups) randomized selection trial in a single urban pediatric emergency department (ED). We will use a randomized selection trial design (a type of adaptive trial design) to randomize children to receive IN midazolam at one of the following four doses: 0.2, 0.3, 0.4 or 0.5 mg/kg. These doses were selected based on commonly-used doses recommended for IN midazolam for procedural sedation in literature reviews, research studies, and clinical guidelines.[1–4] We will use a web-based randomization and allocation system hosted by the Data Management Unit (DMU) of the Department of Biostatistics in Columbia University Mailman School of Public Health. Allocation will be concealed until a patient is enrolled. The DMU will not be involved in the assessment of outcome measures for the study.

Study Procedures

We will obtain written or electronic consent from the patient's child or legal guardian. We will collect data to describe and compare our study groups for potential confounding variables. These variables will include patient demographics (age, weight, sex, primary language, race/ethnicity); targeted medical history (prior laceration repair, painful medical procedures, and sedative exposure); and laceration characteristics (length, location, depth). We will also collect information about type(s) of local anesthesia used (if any) and level of training of person performing the repair (attending, fellow, resident, mid-level provider, subspecialist).



We will use a sequential selection procedure (a type of adaptive trial design) to block-randomize patients in blocks of 4, 3, or 2 to receive 0.2, 0.3, 0.4, or 0.5 mg/kg of IN midazolam. We will use a web-based system that will randomize patients and conceal allocation until a patient is enrolled. Clinicians, patients, families, and outcome assessors will be blinded to the dose administered.

We will enroll children aged 6 months to 7 years who present to the emergency department (ED) with a simple laceration (defined as length <5 cm and not requiring wound revision) and whose attending physician determined that IN midazolam was indicated to facilitate the repair. We will exclude children for any of the following: laceration repair using tissue adhesive (e.g. Dermabond) or staples; known or confirmed developmental delay, baseline motor neurological abnormality (e.g. motor deficit, cerebral palsy); autism spectrum disorder; illness associated with chronic pain; known allergy to midazolam or any other benzodiazepine; eyelid lacerations (i.e. repair would necessitate closed eyes); tongue or intraoral lacerations; nasal obstruction that could not be easily cleared; does not speak English or Spanish; or is a foster child or ward of the state. The data collection form will serve as source document for subject eligibility. The study physician will sign off on the data collection form as a witness.

All children will receive topical anesthesia on their laceration using lidocaine-epinephrine-tetracaine gel in a standardized fashion, as is usual care in our ED. Additional lidocaine injection for local anesthesia will be administered at the discretion of the clinician performing the laceration repair. Any use of an

integrative (i.e. non-pharmacologic) intervention, such as child life specialist, or developmentally appropriate form of active or passive distraction, will be documented.

We will use the 5 mg/mL concentration of midazolam. The study drug will be provided by the research study team. Subjects will not have to pay for the study drug. The maximum total dose to be administered for all four study arms will be 10 mg (maximum volume of 2 mL). The medication will be administered in a minimum of two equal and separate aliquots (i.e. one spray into each nostril), with a volume of administration in each nostril of no greater than 1 mL.[7] If the total volume is less than 0.4 mL, the volume will not be divided and administered into a single nostril, as dividing and administering volumes less than 0.4 mL into a nostril is technically difficult and more prone to error. The medication will be administered using an LMA Mucosal Atomization Device (MAD) Nasal (Teleflex, Morrisville, NC) device attached to a 1-mL syringe with 0.01-mL scale markings. The clinician performing the laceration repair, the caregiver, and the patient will be blinded to the dose administered.

Study subjects will be videotaped to assess the study outcome measures. The subject will be videotaped starting from prior to administration of the IN midazolam until the patient is discharged from the ED, or one hour after completion of laceration repair (whichever occurs first). Subjects will have continuous pulse oximetry throughout the procedure, starting from time of IN midazolam administration until the procedure is completed. The monitor screen displaying the subject's heart rate and oxygen saturation will also be videotaped.

After completion of the procedure, a study team member will evaluate clinician and caregiver satisfaction by speaking with the attending physician who performed the laceration repair and the child's caregiver. Clinicians and caregivers will use a 5-point Likert scale ("strongly agree," "agree," "neither agree nor disagree," "disagree," or "strongly disagree") to answer questions related to their satisfaction with the subject's comfort during the laceration repair and adequacy of sedation achieved.

The patient, caregiver, clinician performing the laceration repair, and outcome assessor will be blinded to the dose of IN midazolam administered. This blinding will be achieved using the same study procedures that have been implemented in prior and ongoing studies of IN medications (two of which studied IN midazolam) conducted in our pediatric emergency department and designed in conjunction with the Research Pharmacy (IRB protocol numbers AAAL7510, AAAQ1272, and AAAO1302). This study procedure involves having the medications prepared by a nurse who is not involved in any outcome assessments. The nurse prepares and labels the study medications in a blinded fashion in a secured location (e.g. locked medication room) and then administers the medication. They do not reveal the identity of the study medications to the patient or study team member (the outcome assessor is not present at time of study medication administration; they will be viewing the videotape at a later time). In conjunction with the Research Pharmacy, we will create standardized orders that identify that a study medication has been administered, without identifying the dose that was administered (this is the same procedure implemented for prior studies). Nurses receive orientations, serial refreshers, and real-time refreshers (i.e. at time of enrolment) on this study procedure. We have enrolled over 200 patients across three studies using this study procedure with no unblinding that has occurred.

Outcomes

The videotapes will be independently assessed by one of three trained physician outcome assessors, who will be blinded to the dose of IN midazolam that was administered. If one of the outcome assessors is involved in any way with the subject's enrollment or clinical care, they will not be eligible to evaluate the subject's videotape.

To determine the optimal dose for producing **adequate sedation state**, we will use the Pediatric Sedation State Scale (PSSS), which provides a clinically-meaningful assessment of sedation over a representative period of time (Table 1).[8] The PSSS is scored from 0 to 5, representing a continuum of sedation that spans from over-sedation associated with changes in vital signs (0) to inadequate sedation (5). This means that there is no maximum or minimum score that represents a best or worst outcome, as with other linear scales. Rather, the goal is to achieve a score of 2, 3, or 4: each of these scores would be considered sedation states that are adequate for laceration repair. The intraclass correlation determined to demonstrate interrater reliability of the PSSS was 0.949 (95% CI 0.986, 0.998).

We define a dose as having achieved "**adequate sedation state**" in a patient if a PSSS score of 2, 3, or 4 for ≥ 95% of the scored procedure. We will also assess "**ideal sedation state**", defined as having a PSSS score of 2 or 3 for 100% of the scored procedure. Another criterion for not achieving adequate (or ideal) sedation state is if a patient receives a PSSS score of 0 or 1 at any point in time during the laceration repair. From our prior research and more than 10 years of clinical experience using IN midazolam, we have never observed a patient reach a PSSS score of 0 or 1 when using the highest possible dose of 0.5 mg/kg.

Table 1: Pediatric Sedation State Scale

State	Behavior
5	Patient is moving (purposefully or non-purposefully) in a manner that impedes the proceduralist and requires forceful immobilization. This includes crying or shouting during the procedure, but vocalization is not required. Score is based on movement.
4	Moving during the procedure (awake or sedated) that requires gentle immobilization for positioning. May verbalize some discomfort or stress, but there is no crying or shouting that expresses stress or objection.
3	Expression of pain or anxiety on face (may verbalize discomfort), but not moving or impeding completion of the procedure. May require help positioning (as with a lumbar puncture) but does not require restraint to stop movement during the procedure.
2	Quiet (asleep or awake), not moving during procedure, and no frown (or brow furrow) indicating pain or anxiety. No verbalization of any complaint.
1	Deeply asleep with normal vital signs, but requiring airway intervention and/or assistance (e.g. central or obstructive apnea, etc).
0	Sedation associated with abnormal physiologic parameters that require acute intervention (ie, oxygen saturation <90%, blood pressure is 30% lower than baseline, bradycardia receiving therapy).

The PSSS will be assessed on a continuous basis from the time of procedure start until 17 minutes after administration of the study drug. Procedure start will be operationally defined as the time when the needle is inserted to when last suture is cut. The 17-minute cut off was selected to remove bias related to differences in procedure (laceration repair) duration. A prior study has shown that IN midazolam serum levels remain at ≥90% peak levels until 17 minutes after drug administration. Since adequate sedation is defined by the score assigned to a proportion of the laceration repair, procedures with longer durations (especially if extending beyond 17 minutes) may have longer periods of time when midazolam serum levels are sub-optimal, and, therefore, more likely to fail the criteria for adequate sedation. By standardizing the duration of the procedure that is evaluated for our primary outcome, we can assess the efficacy of each dose during their peak serum concentrations, without bias introduced by varying procedure durations.

To determine **time to onset of minimal sedation** associated with each dose, we will use the University of Michigan Sedation Scale (UMSS) (Table 2).[9] The UMSS is scored from 0 to 4, representing a continuum of sedation depth that spans from the deepest level of sedation (4) to being awake and alert (0). Time to onset of minimal sedation will be measured from time of IN midazolam administration until the patient achieves a UMSS score of 1. Maximal depth of sedation will also be assessed using the UMSS.

Table 2: University of Michigan Sedation Scale

Value	Patient State
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, aroused only with significant physical stimulation.
4	Unarousable.

To determine the **time to recovery**, we will use the Simplified Aldrete Score (SAS) (Table 3). This adaptation of the Aldrete Score was developed to create an outcome measure that was feasible in the ED-setting and addressed the assessment of recovery specific to minimal sedation. The SAS will be assessed every 5 minutes, starting from the time of IN midazolam administration until the patient achieves a minimum total score of 6 (with a minimum score of 2 in respiratory and O_2 saturation) after procedure start. If a patient already fulfills criteria for recovery at procedure start, then time to recovery is 0.

Adverse events will be monitored by clinical staff and study team members from time of IN midazolam administration until time of discharge from the ED. Patients will be monitored with a continuous pulse oximeter. We define adverse events using the Pediatric Emergency Research Canada (PERC) and Pediatric Emergency Care Applied Research Network (PECARN) Consensus-Based Recommendations for standardizing terminology and reporting adverse events for ED procedural sedation and analgesia in children.[11] These adverse events include oxygen desaturation; apnea (central, obstructive, laryngospasm); clinically apparent pulmonary aspiration; retching/vomiting; bradycardia; hypotension; excitatory movements; paradoxical response to sedation; unpleasant recovery reactions; and permanent complications (including death).

Table 3: Simplified Aldrete Score

Parameter	0	1	2
Level of consciousness	Nonresponsive or responsive only to painful stimuli.	Responds to verbal stimuli but falls asleep readily.	Awake and orientated (child oriented to parent) or equivalent to preoperative status.
Respiration	Apneic	Shallow, irregular breathing.	Able to breathe deeply or equivalent to preoperative status.
O_2 saturation	$SpO_2 \leq 92\%$ on oxygen	$SpO_2 \geq 92\%$ on oxygen	$SpO_2 \geq 92\%$ on room air or equivalent to preoperative.
Activity level	Unable to lift head or move extremities voluntarily or on command.	Lifts head or moves extremities on command.	Lifts head and moves all extremities spontaneously.

Statistical Procedures

We will determine the optimal dose of IN midazolam for producing adequate sedation state (defined as a PSSS score of 2, 3 or 4 for ≥95% of the procedure) by the sequential selection procedure, based on the Levin-Robbins-Leu family of sequential selection procedures for adaptive trials. The goal of the procedure is to make a correct selection which, in our study, is to select the dose that yields the greatest true probability of adequate sedation state. The procedure follows the preference zone/indifference zone approach, wherein we require the selection procedure to guarantee a probability of at least 80% correct selection of the best dose, assuming that one dose is superior to the others by a pre-specified amount (see "elimination rule" for pre-specified amount). This pre-specification defines a preference zone. If the best dose does not exceed the next best dose by the pre-specified amount, the success probabilities are said to lie in the indifference zone.

The sequential selection procedure consists of four rules: The **sampling rule, elimination rule**; **stopping rule**; and **terminal decision rule**. First, the trial begins and patients are block-randomized to a block of 4, with each patient assigned to one of the four study arms (i.e. 0.2, 0.3, 0.4 or 0.5 mg/kg). Videos are viewed and the primary outcome determined immediately after each enrolment. Analyzing data for all study arms that have not yet been eliminated is called the **sampling rule**. Patients who meet the definition of adequate sedation state will be tallied as a "success"; those who do not will be tallied as a "failure". The cumulative number of successes and failures associated with each dose is called the "success tally" for that dose.

Enrollment will continue until the first 16 patients are enrolled (i.e. 4 blocks of patients, with 4 patients in each block). The success tallies for each dose are compared to each other to see if there is one dose with 4 fewer successes than the dose with the highest number of successes. If there is, then the dose with the lower number of successes is eliminated from the study (this is called the **elimination rule**). Block-randomization would then continue in blocks of 3, with each patient assigned to one of the remaining 3 study arms. If there are no doses with 4 fewer successes than the dose with the highest number of successes, then we will proceed with the next round of block-randomization. For a hypothetical example, see Table 4. In this example, 20 patients have been enrolled (i.e. 5 blocks of patients). An analysis would have occurred after the 4th and 5th blocks enrolled. After completing enrolment of the 5th block, the largest tally of 5 (i.e. 0.5 mg/kg) exceeds the success tally of the smallest tally of 1 (i.e. 0.2 mg/kg) by 4. Based on the elimination criterion, the 0.2 mg/kg does is eliminated from the trial, and the next set of patients are randomized to a block of 3 comprised of the 0.3, 0.4, and 0.5 mg/kg doses. Note that more than one dose can be eliminated at the same time.

Table 4: Example of a hypothetical success tally for each dose after enrollment of 20 patients.

	Dose			
	0.2 mg/kg	**0.3 mg/kg**	**0.4 mg/kg**	**0.5 mg/kg**
Block 1	S	F	S	S
Block 2	F	S	F	S
Block 3	F	F	S	S
Block 4	F	S	S	S
Block 5	F	F	S	S
Total Number of Successes	1	2	4	5

S=success, F=failure.

Block-randomization and data analysis/comparison of success tallies for each remaining dose after each block is enrolled will be repeated until one of the two following conditions are met (this is the **stopping rule**): 1) When three doses are eliminated, or 2) When we have enrolled 100 patients but three doses have not yet been eliminated; this is called "truncation" and corresponds with the maximum possible total sample size.

After the study has stopped, we will use the **terminal decision rule** to decide which is the best dose. If three of the four doses are eliminated, the remaining dose is selected as the best dose. If the study ends by truncation but there is more than one dose that has not been eliminated, we will select the dose according to other considerations, such as the other outcomes measured (i.e. time to onset of minimal sedation, time to recovery).

For our study, the pre-specified amount that defines our elimination rule (i.e. a difference of 4 between the largest and smallest success tallies) was chosen to achieve a probability of correct selection of at least 80% for any true success probabilities, where the preference zone is characterized by an odds ratio of 2.25 or greater between the true success probabilities of the best two doses.

We will analyze the outcomes of **time to onset of minimal sedation** and **time to recovery** using the Kruskal-Wallis test, with follow-up pairwise comparisons between groups with the Wilcoxon rank-sum test. We chose to use a rank test so that patients who did not have a time to onset of minimal sedation documented (e.g. if they do not achieve a UMSS score of 1 or if the procedure was started before onset of minimal sedation; or if they have time to recovery of 0) could still be included in the analysis. These patients were assigned a maximal score (e.g. 999 minutes) in place of a time to onset of minimal sedation to represent a maximal time for the secondary outcome, thereby using the most conservative assumption possible. The mean of the raters' scores will be used as the time to onset of minimal sedation for each patient, and the mean time to onset of minimal sedation for each group will be determined and compared. We considered a statistically significant difference for the primary outcome at an experiment-wise alpha =0.05. For follow-up pairwise comparisons, we will use a Bonferroni adjustment for the number of comparisons needed based on the number of study arms remaining at the time of analysis, 2-tailed per comparison.

We will describe the frequency and proportion of adverse events associated with each dose and compare them using the chi square test.

Sample size: Based on this sequential selection procedure and the stopping rule defined a priori, the sample size will range from a minimum of 16 patients to a maximum of 100 patients. The minimum sample size is calculated from the fewest number of patients that would be required for one dose to have a difference of 4 in success tallies compared to the three other doses simultaneously (e.g. 0.5 mg/kg is successful in all of the first 4 consecutive rounds, but 0.2, 0.3, and 0.4 mg/kg are all failures in these first 4 rounds). The maximum sample size is based on the stopping rule. However, **it is unlikely that the study will be completed with only 16 patients**. Based on the probability of success of achieving adequate sedation state for the doses of 0.2, 0.3, 0.4 and 0.5 mg (i.e. 0.50, 0.70, 0.80, and 0.90, respectively), the probability of correct selection is 81.9% (which is above our desired threshold of 80% determined a priori) and will most likely require a total number of 91 patients to determine the optimal dose.

Potential Risks

A risk of taking part in this study is the possibility of a loss of confidentiality or privacy. There are no risks in addition to the usual risks associated with receiving intranasal IN midazolam for procedural sedation. The procedures involved in this study do not increase the risk for adverse events normally associated with receiving IN midazolam.

Potential Benefits

There is unlikely to be direct benefit to the patient. Benefits to society would include the optimization of efficacy of IN midazolam in children who required procedural sedation, and improving the care received by children by reducing the use of doses that may be less efficacious than other doses.

Alternatives

An alternative to participation in this study is to choose not to participate.

Data and Safety Monitoring

Data will be reviewed on an ongoing basis by the PI (Dr. Tsze) with each patient enrolled. A DSMB consisting of two members unrelated to the study will be formed, and will evaluate adherence to the protocol every 6 months and report any protocol violations to the IRB. One member will be an emergency medicine clinician investigator (Vice Chair of Research, Department of Emergency Medicine), and the second member will be a clinical pharmacologist (Director of Clinical Pharmacology and Toxicology Laboratory, Director of Biomarkers Core Laboratory of Irving Institution for Clinical and Translational Research).

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. The study team as a whole will meet at the start of the study, and then at least every 6 months during patient enrollment. We will submit to the IRB any protocol deviations and requested protocol modifications.

Adverse Event Reporting: An adverse event is any untoward medical occurrence by a subject. For each subject, 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 the time of continuing review. All serious adverse events (i.e. airway obstruction requiring airway repositioning or adjunct airway; positive pressure ventilation; apnea > 15 seconds or any apnea with change in vital signs) will be reviewed by the investigators and reported to the IRB within 96 hours.

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

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