Published in final edited form as:

Ann Emerg Med. 2017 May ; 69(5): 600–609. doi:10.1016/j.annemergmed.2016.08.450.

Optimal volume of administration of intranasal midazolam in children: A randomized clinical trial

Daniel S. Tsze, MD, MPH^a, Maria Ieni, MD^a, Daniel B. Fenster, MD, MS^a, John Babineau, MD^a, Joshua Kriger, MS^b, Bruce Levin, PhD^b, and Peter S. Dayan, MD, MSc^a

^aDepartment of Pediatrics, Division of Pediatric Emergency Medicine, Columbia University College of Physicians and Surgeons. New York, New York, USA

^bDepartment of Biostatistics, Columbia University Medical Center, New York, New York, USA

Abstract

Objectives—The optimal intranasal volume of administration (VOA) for achieving timely and effective sedation in children is unclear. We aimed to compare clinical outcomes relevant to procedural sedation associated with using escalating VOA to administer intranasal midazolam.

Methods—We conducted a randomized, single-blinded, three-arm, superiority clinical trial. Children 1 to 7 years old undergoing laceration repair requiring 0.5 mg/kg intranasal midazolam (5 mg/mL) were block-randomized to receive midazolam using one of three VOA: 0.2mL, 0.5mL, or 1mL. Procedures were videotaped, with outcome assessors blinded to VOA. Primary outcome was time to onset of minimal sedation (i.e. score of 1 on the University of Michigan Sedation Scale). Secondary outcomes included procedural distress; time to procedure start; deepest level of sedation achieved; adverse events; and clinician and caregiver satisfaction.

Results—Ninety-nine children were enrolled; 96 were analyzed for the primary outcome and secondary outcomes, except for the outcome of procedural distress, for which only 90 were analyzed. Time to onset of minimal sedation for each escalating VOA was 4.7 (95% CI 3.8, 5.4), 4.3 (95% CI 3.9, 4.9) and 5.2 (95% CI 4.6, 7) minutes, respectively. There were no differences in secondary outcomes except for clinician satisfaction with ease of administration: fewer clinicians were satisfied when using a VOA of 0.2mL.

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Meetings:

The current data were previously presented at: American Academy of Pediatrics National Conference & Exhibition, October 2015, Washington, DC, USA; Society for Pediatric Sedation Conference, May 2016, Hartford, CT, USA.

Clinical Trials Registration Number: NCT01948908.

Conflict of Interest: None of the authors have any conflicts of interest to disclose.

Author Contributions: DST and PSD conceptualized the study, designed the trial, and obtained research funding. DST supervised the conduct of the trial and data collection. DST, MI, DBF, and JB undertook recruitment of participating patients and viewed and analyzed the video recordings. JK and BL provided statistical advice on study design and managed the data, including quality control. DST, JK, and BL conducted the statistical analyses for the study. DST drafted the manuscript, and all authors contributed substantially to its revision. DST takes responsibility for the paper as a whole.

Conclusions—There was a slightly shorter time to onset of minimal sedation when using a VOA of 0.5mL compared to 1mL, but all three VOA produced comparable clinical outcomes. Fewer clinicians were satisfied with ease of administration using a VOA of 0.2mL.

INTRODUCTION

Background

The intranasal (IN) route is an effective means of administering sedatives to children who require procedural sedation.¹⁻³ Intranasal administration delivers the sedative to both the highly vascularized nasal mucosa, and the olfactory tissue that is in direct contact with the central nervous system (termed the “nose-brain pathway”), thereby bypassing first-pass metabolism.^{1,4} Although there are commercial products designed specifically for IN drug delivery, it is common practice in emergency departments (ED) to use parenteral formulations of a sedative for IN administration.^{1-3,5-7} However, commonly available concentrations of these sedatives often necessitate large total volumes in order to deliver the required weight-based dose in children. In the clinical setting, this total volume is often divided into smaller aliquots, or volumes of administration (VOA), that are administered repeatedly by alternating between both nostrils, until the total volume is delivered.

Importance

Although the VOA is a fundamental aspect of IN administration, it is unclear what VOA is optimal for achieving timely and effective sedation when administering IN sedatives, such as midazolam, to children. Intranasal medications are typically administered using a mucosal atomization device (MAD), with a commonly recommended optimal VOA of approximately 0.3 mL and a maximum VOA of 1 mL.^{1,8} This is in contrast to other recommendations stating that a VOA should not exceed 0.15 or 0.2 mL because of concerns that any volume in excess of these limits will become run-off and drain out of the nose and not be absorbed, or swallowed and subject to first-pass metabolism.^{4,9-15}

Goals of This Investigation

The aim of this study was to determine the optimal VOA of intranasal midazolam in children by comparing clinical outcomes relevant to procedural sedation associated with escalating volumes of administration (0.2 mL, 0.5 mL, and 1 mL) during laceration repair in an ED. Our primary outcome was time to onset of minimal sedation. Our secondary outcomes included procedural distress, time to procedure start, deepest level of sedation achieved, adverse events, and clinician and caregiver satisfaction. We hypothesized that using a VOA of 0.2 mL would be associated with a shorter time to onset of minimal sedation compared to using a VOA of either 0.5 mL or 1 mL, as we expected that a VOA of 0.2 mL would have the least amount of run-off compared to the larger VOA.^{4,9-15}

METHODS

Study Design

We conducted a randomized, outcome-assessor blinded, three-arm parallel group (1:1:1), superiority clinical trial in a single urban pediatric emergency department with an annual

census of approximately 53,000 children per year. Our institutional review board approved this study, and written informed consent was obtained from each participant's legal guardian. The study was registered on clinicaltrials.gov (NCT01948908).

Selection of Participants

Between November 2013 and September 2015, we enrolled a convenience sample of children between the ages of 1 to 7 years, inclusive, presenting to the ED with a simple laceration (defined as length <5 cm and did not require wound revision) and whose attending physician determined that IN midazolam was indicated to facilitate the repair. Patients were enrolled when a research coordinator or study physician was available (9:00am to 10:00pm on weekdays, variable on overnights and weekends). We excluded children for any of the following: a history of developmental delay, underlying neurologic abnormality or autism; illness associated with chronic pain; known allergy to midazolam or any other benzodiazepine; weight < 10 kg; eyelid lacerations (i.e. repair would necessitate closed eyes); nasal obstruction that could not be easily cleared; did not speak English or Spanish; or was a foster child or ward of the state.

Interventions

We used an online randomization program, which maintained allocation concealment, to randomize children in blocks of three to receive the total dose of midazolam using one of three volumes of administration: 0.2 mL, 0.5 mL, and 1 mL. These volumes were selected based on prior recommendations regarding optimal VOA; clinical feasibility; and current clinical practice.^{1,4,8-15} Clinicians applied lidocaine-epinephrine-tetracaine (LET) gel to all lacerations in a standardized fashion, unless contraindicated. Lidocaine injection for local anesthesia was administered at the discretion of the clinician performing the laceration repair (i.e. the "proceduralist"). All children received an integrative (non-pharmacologic) intervention, such as a Child Life Specialist, or a developmentally-appropriate form of active or passive distraction.

All children received 0.5 mg/kg of midazolam (5 mg/mL concentration), with a maximum total dose of 10 mg (maximum volume of 2 mL). The medication was administered in aliquots based on the assigned VOA by an attending pediatric emergency medicine physician using a LMA[®] MAD Nasal[™] device attached to a 1 mL syringe with 0.01 mL scale markings.⁸ Prior to every administration, the attending physician completed an "intranasal administration refresher" with a member of the study team (Supplemental Figure). During the refresher, the attending physician was required to demonstrate that they could administer the assigned VOA accurately. We made the refresher mandatory to ensure that the administration was consistently performed in a standardized fashion, and that the assigned VOA would be administered correctly.

We administered the IN midazolam first into one nostril using the assigned VOA, and then alternated between nostrils until the total volume was delivered. Since the total volume required by each patient was not always divisible by the assigned VOA into an equal number of administrations, we administered as many aliquots as possible using the assigned VOA, and then administered the remaining volume last. Medication could be delivered into the

second nostril immediately after the first, but we waited a period of 10 seconds before re-administering the medication to the same nostril again. We chose the interval of 10 seconds based on both expert consultation with otolaryngologists and pharmacologists and feasibility in a clinical setting. For example, a total dose of 8 mg (and therefore a total volume of 1.6 mL when using the 5 mg/mL concentration of midazolam) would be required for a 16 kg child. If the child was assigned to receive IN midazolam using a VOA of 0.5 mL, 0.5 mL would be administered to the first nostril, and then another 0.5 mL would be immediately administered to the second nostril. Ten seconds later, another 0.5 mL would be administered to the first nostril, and the remaining 0.1 mL immediately administered to the second nostril, thereby completing administration of the total volume.

It was at the discretion of the proceduralist, who was not blinded, as to when to begin the procedure; whether restraining the child during the procedure was indicated (and how it was implemented); and whether to abort a procedure due to perceived inadequate sedation.

Methods of Measurements and Outcomes

A member of the study team videotaped patients for a 1-minute period before IN midazolam administration (the baseline period), and then through the entirety of the procedure starting from just before administration of the IN midazolam until 1 minute after procedure completion, defined as time the last suture was cut. Steps were taken during the videotaping and video scoring to create a standardized 1-minute blinding period, starting from the time that the first aliquot was administered, in order to blind outcome assessors to both visual and auditory cues during the administration of the IN midazolam.

Three of four trained physician outcome assessors (DST, MI, DBF, JB) independently scored each video recording, blinded to the assigned VOA and to the results of the other assessors. If one of them was involved in any way with an enrollment, they were not eligible to evaluate that video recording. Outcome assessors scored the video recordings in a randomized order that was unique to each of the assessors.

Each outcome assessor evaluated the primary outcome, time to onset of minimal sedation, as defined by the University of Michigan Sedation Scale (UMSS). The UMSS is a 5-point (0-4) scale that has been validated and used in children to identify different depths of sedation, where 0 = awake and alert; 1 = minimally sedated (tired/sleepy, appropriate response to verbal conversation and/or sound); 2 = moderately sedated; 3 = deeply sedated; and 4 = unarousable.¹⁶ The primary outcome was evaluated by measuring the time starting from the administration of the first aliquot of IN midazolam until the onset of minimal sedation.

The outcome assessors evaluated procedural distress, a secondary outcome, using the Observational Scale of Behavioral Distress – revised (OSBD-r).¹⁷ The OSBD-r was used to score four predetermined clinically relevant phases: baseline, irrigation/cleaning, laceration repair, and post-procedure. The OSBD-r is an eight-factor, weighted observational scale used to measure distress associated with medical procedures which has been validated in children 1 to 20 years of age.^{5,18-22} The total OSBD-r score is the sum of the OSBD-r scores for each phase, with each phase assigned a score from 0 to 23.5 (0 = no distress, 23.5 = maximum distress), based on the frequency and types of behaviors observed during a pre-

determined number of 15-second intervals during each phase. The OSBD-r is used to identify statistically significant differences between groups, as the change in score representing a clinically meaningful difference, and the range of scores representing categories of pain intensity (i.e. mild, moderate, and severe) have not yet been clearly defined for the OSBD-r. Each outcome assessor also determined time to procedure start and deepest level of sedation achieved (as per UMSS) when scoring the video recording.

The study team member documented the presence of any adverse events during the procedure. Adverse events included vomiting; apnea (no breath for > 20 seconds); paradoxical reaction (i.e. agitation precipitated by midazolam); and the need for supplemental oxygen, airway repositioning or bag-mask-valve ventilation. We also documented whether, per the proceduralist, there was inadequate sedation during the laceration repair resulting in the inability to complete procedure. Children who did not reach adequate sedation by 20 minutes after IN administration, as per the proceduralist, were also considered to have inadequate sedation.

After completion of the procedure, a study team member evaluated clinician and caregiver satisfaction by interviewing the attending physician who administered the IN midazolam; the proceduralist who performed the laceration repair; and the child's caregiver. Clinicians and caregivers used a 5-point Likert scale ("strongly agree", "agree", "neither agree nor disagree", "disagree", or "strongly disagree") to answer questions related to their satisfaction with ease of IN administration, child comfort during IN administration, and the adequacy of sedation achieved.

Data Analyses

For our primary outcome of time to onset of minimal sedation, we compared the three groups using the Kruskal-Wallis test, with follow-up pairwise comparisons between groups using 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 not achieve adequate sedation by 20 minutes or if the procedure was started before onset of minimal sedation) 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 primary outcome, thereby using the most conservative assumption possible. The median of the three raters' scores was used as the time to onset of minimal sedation for each patient, and the median time to onset of minimal sedation for each group was 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 used a Bonferroni adjustment for three comparisons, two-tailed per comparison ($\alpha=0.0167$). We determined our sample size by designing the study to have 0.80 power to detect a clinically meaningful difference in time to onset of minimal sedation of 1.5 minutes, with an estimated standard deviation of 2 minutes for each group.^{7,23} The goal sample size was 108, but enrollment was stopped early due to constraints related to funding.

We analyzed continuous secondary outcomes (i.e. OSBD-r, time to procedure start) using the one-way ANOVA test, and ordinal and nominal outcomes (i.e. deepest level of sedation, adverse events, satisfaction) using the chi-square test.²⁴

An Interclass Correlation Coefficient (ICC) calculation was performed on the primary outcome of time to onset of minimal sedation and the secondary outcome of procedural distress (OSBD-r). The Shrout-Fleiss ICC (1,k) statistic was calculated to show the correlation of raters when each subject was rated by multiple raters, with raters assumed to be randomly assigned to subjects and all subjects have the same number of raters.²⁵

Statistical analyses were performed using SPSS (version 22; IBM SPSS Statistics, IBM Corporation, Armonk, NY) and SAS (version 9.4; SAS Institute Inc., Cary, NC).

RESULTS

We enrolled 99 patients: 96 were evaluated for the primary outcome and secondary outcomes of time to onset of procedure, deepest level of sedation, adverse events, and satisfaction; 90 patients were analyzed for procedural distress (Figure). The patient, laceration, and procedural characteristics were similar across all three groups, except there were more males in the 0.5 mL group, and fewer children who had a history of any painful or distressing medical procedure in the 0.2 mL group (Tables 1 and 2). All patients received the intervention to which they were allocated.

The median times to onset of minimal sedation when using a VOA of 0.2 mL, 0.5 mL, and 1 mL were 4.7 (95% CI 3.8, 5.4), 4.3 (95% CI 3.9, 4.9), and 5.2 (95% CI 4.6, 7) minutes, respectively (Table 3). Overall, the difference between groups was statistically significant ($p=0.048$). When conducting follow up comparisons between groups, while adjusting for multiple comparisons using the Bonferroni correction ($\alpha=0.0167$), a shorter time to onset of minimal sedation (0.9 minutes) was observed when using a VOA of 0.5 mL compared to using a VOA of 1 mL ($p=0.01$). However, this difference in time to onset was not clinically meaningful, based on the a priori threshold of 1.5 minutes. There were no statistically or clinically meaningful differences identified when comparing the remaining groups with each other. There were also no significant differences between any of the groups with regard to procedural distress, time to procedure start, and deepest level of sedation (Table 3). There were no paradoxical reactions and no serious adverse events. The only adverse events observed were vomiting and inadequate sedation, with no difference between the three groups (Table 4). Table 5 presents clinician and caregiver satisfaction. Fewer clinicians “agreed” or “strongly agreed” that they were satisfied with ease of administration when using a VOA of 0.2 mL compared to the other groups. The ICC Shrout-Fleiss ICC (1,k) statistic was 0.59 for the time to onset of minimal sedation (moderate agreement) and 0.92 for procedural distress, i.e. OSBD-r (almost perfect agreement).

LIMITATIONS

Our study has several limitations. First, the inherent subjective nature of some outcomes (i.e. time to onset of minimal sedation, procedural distress, depth of sedation, adequacy of sedation) may have potential for bias, although we attempted to minimize bias by having three separate blinded evaluators. Second, some of our secondary outcomes (e.g. time to procedure start, inadequate sedation) were determined by non-blinded participants (i.e. proceduralist). If the proceduralists believed that smaller VOA were associated with less run-

off and therefore better absorption, that could have resulted in a trend towards shorter times to procedure start and fewer patients with inadequate sedation in the smaller compared to larger VOA groups. Third, we did not standardize the decision to implement restraint on children during laceration repairs, and could not standardize when or how restraint was administered by each proceduralist. Differential use of aggressive restraint might not only contribute to a higher OSBD-r score, but could potentially precipitate or exacerbate distress in a child. Fourth, we did not achieve our desired sample size by 9 subjects (3 per group). It is possible that if we had enrolled the remaining 9 subjects, there may have been an effect size larger than that observed, or that the precision of our estimates may have improved so that a statistical difference may have become apparent between other groups. However, even if either of these scenarios occurred, it is unlikely that an increase in sample size of 10% would have resulted in an effect size 50% larger than that observed, and therefore unlikely that a clinically meaningful difference would have become apparent.

DISCUSSION

The findings of our study demonstrate the clinical outcomes associated with using escalating volumes of administration to deliver midazolam by the IN route to children undergoing laceration repairs. Although a VOA of 0.5 mL was associated with a statistically shorter time to onset of minimal sedation compared to a VOA of 1 mL (4.3 and 5.2 minutes, respectively), a clinically meaningful difference (defined a priori as 1.5 minutes) was not observed between these two groups, nor when comparing any of the groups with each other. Similarly, there was no difference in time to procedure start, which would be consistent with the absence of a clinically meaningful difference in time to onset of minimal sedation. There was also no difference when comparing procedural distress and deepest level of sedation achieved, suggesting that using any of the three volumes of administration will produce clinically comparable outcomes.

Our findings corroborate one aspect of existing guidelines regarding the VOA that should be used when administering IN medications. Our study supports the recommendation that it is acceptable to administer up to a 1 mL VOA.^{1,8} This is in light of concerns regarding run-off due to using a larger VOA that might lead to sub-optimal efficacy; our data demonstrate that the largest VOA is still associated with clinical outcomes comparable to using a smaller VOA. Our results suggest that it would be acceptable to administer IN midazolam using a VOA of 0.5 mL until a desired total volume is delivered; or to divide total volumes into two separate VOA (so that each nostril receives one aliquot and the surface area available for absorption is effectively doubled by using both nostrils), as long as the maximum VOA of each aliquot is 1 mL.

It does not appear that using a VOA as small as 0.2 or 0.3 mL is associated with any measurable advantage in clinical outcomes relevant to procedural sedation compared to using a VOA as large as 0.5 mL or 1 mL. One explanation for this lack of difference between groups could be that some of the run-off associated with using a higher VOA of midazolam may have been swallowed and absorbed orally, contributing to the clinical outcomes observed. However, the times to onset of minimal sedation we observed (Table 3) occurred much sooner than midazolam would be expected to take effect when absorbed

orally, and most of the procedures were completed before, or during, the expected time of onset of minimal sedation for oral midazolam (Table 1).^{6,26-28}

Another explanation for this lack of difference between groups may be that the VOA may not be as consequential a factor in the absorption of intranasal medications compared to other variables such as drug concentration (which remained constant) and the total volume administered. Despite our measures taken to facilitate absorption in a clinically feasible manner when multiple aliquots were required (i.e. the 10-second pause), it is possible that absorption of the administered aliquot during each pause was not complete. As a result, the amount of run-off experienced, and therefore the total volume of medication retained, may have remained similar between the three groups despite varying the VOA.

Fewer clinicians were satisfied with ease of administration when using the smallest VOA of 0.2 mL. This likely reflects the need to administer a larger number of aliquots in order to completely deliver a given total volume of midazolam when using a small VOA, such as 0.2 or 0.3 mL. For example, using a VOA of 0.2 mL would necessitate as many as 10 separate aliquots to be administered (depending on the dose required, with a maximum dose of 10 mg) to deliver the total volume, whereas using a VOA of 1 mL would only require as few as 1 to 2 aliquots. The larger number of aliquots associated with using a smaller VOA is likely to be more poorly tolerated by young children, with the problem further exacerbated by the burning sensation associated with each aliquot of midazolam. Since there is likely poorer patient acceptability without any clear clinical benefit to using a small VOA that requires a larger number of aliquots, using a larger VOA is likely preferable by clinicians because only a smaller number of aliquots would be required, and the medication could be administered over a shorter period of time.

However, our findings do not discount the potential value of using a smaller VOA in specific circumstances. For instance, minimizing the VOA may be more applicable when using medication formulations of higher concentrations, which would allow the total dose required to be administered using a single aliquot.²⁹⁻³⁴ Under these conditions, run-off would potentially reduce medication effectiveness because the patient would receive an inadequate dose. However, these concentrated formulations are not readily available. Most of the medications that are administered by the IN route in children are most commonly available in concentrations that necessitate large volumes that must be divided into smaller aliquots due to weight-based dose requirements.^{3,6,35,36}

Further study is necessary to evaluate whether our findings are generalizable to other IN medications in children. Nasal and olfactory absorption is governed by a number of factors, one of them being the physicochemical properties of a drug. With all other factors remaining similar, we expect that medications with physicochemical properties similar to midazolam would produce comparable effects when administered using the different volumes of administration described in our study. Fentanyl, for example, may potentially demonstrate comparable clinical efficacy when administered intranasally using escalating volumes of administration, given that it has a molecular weight and lipophilicity comparable to that of midazolam, and a pH that is similarly favorable for IN absorption.³⁷⁻⁴⁰

CONCLUSION

There was a statistically, but not clinically meaningful, shorter time to onset of minimal sedation when using a volume of administration (VOA) of 0.5 mL compared to 1 mL for administration of IN midazolam to children undergoing laceration repair. Using a VOA of 0.2 mL, 0.5 mL, or 1 mL produced comparable and acceptable outcomes relevant to procedural sedation in children. Fewer clinicians were satisfied with ease of administration of IN midazolam when using a VOA of 0.2 mL.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We would like to thank Dr. Pamela Flores-Sanchez, Dr. Sharon Pan, Leonor Suarez, Vartan Pahalyants, Allison Hyland, Brooke Peery, Keven Cabrera, and Jeffrey Sung for their assistance in enrolling patients; Hilary Woodward and Anita Patel for their invaluable advocacy for, and support of, the study; and the nurses, child life specialists, attendings, fellows, residents and research assistants of the Morgan Stanley Children's Hospital Pediatric Emergency Department, without whom this study would not have been possible.

Grants:

This publication was supported by the American Academy of Pediatrics Section on Emergency Medicine Ken Graff Young Investigator Award. Funding was also provided by the National Center for Advancing Translational Sciences, National Institutes of Health, through Grant Number UL1 TR000040.

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Figure. Enrolment flow diagram

^a Patients excluded because of video technical issues, medication administered in error before videotaping started, or exclusion criteria identified after randomization.

^b Patients excluded because of inadequate sedation; procedure aborted/delayed due to inadequate local anesthesia; omission of irrigation/cleaning phase; or omission of post-procedure phase due to video technical issues.

Table 1

Patient characteristics.

	0.2 mL VOA (n=32)	0.5 mL VOA (n=33)	1 mL VOA (n=31)
Age in years, median (IQR)	3 (2.4, 5.6)	2.7 (2.1, 3.5)	2.7 (1.9, 3.9)
Male, n (%)	20 (62.5%)	25 (75.8%)	19 (61.3%)
Weight in kg, median (IQR)	16 (13.7, 21.4)	14.3 (12.5, 17.6)	15.6 (12.9, 18.5)
Ethnicity/Race, n (%)	22 (68.8%)	25 (75.8%)	25 (80.6%)
Hispanic	6 (18.8%)	5 (15.2%)	5 (16.2%)
Non-Hispanic, White	3 (9.4%)	2 (6%)	1 (3.2%)
Non-Hispanic, Black	1 (3%)	1 (3%)	0
Non-Hispanic, Other ^a			
Primary language, n (%)	19 (59.4%)	20 (60.6%)	21 (67.7%)
English	13 (40.6%)	13 (39.4%)	10 (32.3%)
Spanish			
History of any prior painful or distressing medical procedure, n (%) ^b	16 (51.6%) ^c	23 (69.7%)	26 (83.9%)
Laceration repair	2 (6.2%)	1 (3%)	2 (6.4%)
Immunization	13 (41.9%) ^c	22 (66.7%)	24 (77.4%)
Other medical procedure	7 (21.9%)	4 (12.1%)	5 (16.1%)
History of receiving a sedative, n (%)	7 (21.9%)	5 (15.2%)	5 (16.1%)

^a Asian, more than one^b Laceration repair, immunization, or other medical procedure (e.g. blood draw, intravenous line placement, fracture reduction); patients could have had more than one distressing or painful medical procedure^c n=31

Table 2

Laceration repair procedure characteristics.

	0.2 mL (n=32)	0.5 mL (n=33)	1 mL (n=31)
Laceration length, cm, mean (SD)	2 (1.1)	1.3 (0.7)	1.9 (0.9)
Laceration location, n (%)	26 (81.2%)	26 (78.8%)	25 (80.6%)
Face	3 (9.4%)	3 (9.1%)	2 (6.4%)
Upper extremity, including hands and fingers	1 (3.1%)	3 (9.1%)	1 (3.3%)
Lower extremity, including feet and toes	2 (6.3%)	1 (3%)	3 (9.7%)
Other ^a			
Laceration depth, n (%)	2 (6.3%)	5 (15.2%)	1 (3.3%)
Epidermis	10 (31.2%)	10 (30.3%)	10 (32.3%)
Dermis	11 (34.4%)	16 (48.5%)	13 (41.9%)
Subcutaneous fat	5 (15.6%)	1 (3%)	5 (16.1%)
Muscle	4 (12.5%)	1 (3%)	2 (6.4%)
Bone			
Proceduralist, n (%)	20 (62.5%)	21 (63.6%)	19 (61.3%)
Attending	5 (15.6%)	9 (27.3%)	5 (16.1%)
Fellow, resident	0	0	1 (3.2%)
Mid-level provider	7 (21.9%)	3 (9.1%)	6 (19.4%)
Subspecialist ^b			
No LET administered, n (%)	4 (12.5%)	5 (15.2%)	4 (12.9%)
Lidocaine injection administered, n (%)	8 (25%)	9 (27.3%)	6 (19.4%)
Other injuries ^c	1 (3.1%)	0	0
Total dose of midazolam administered, mg, mean (SD)	8.2 (1.5)	7.5 (1.6)	7.7 (1.6)
Volume of midazolam administered, mL, mean (SD), [range]	1.6 (0.3), [1.1-2.0]	1.5 (0.3), [1.0-2.0]	1.5 (0.3), [1.0-2.0]
Procedure started before onset of minimal sedation, n (%)	1 (3.1%)	0	2 (6.5%)
Did not achieve minimal sedation by 20 minutes after IN midazolam administration, n (%)	0	0	0
Pre-emptive physical restraint administered, n (%) ^d	5 (15.6%)	5 (15.2%)	2 (6.5%)
Procedure duration in minutes, median (IQR)	12.5 (9.5, 22.4)	12.5 (9, 22.3)	14.3 (9.2, 22.7)

LET = lidocaine-epinephrine-tetracaine.

^aOther includes: scalp, ear, tongue, buccal mucosa^bOrthopedics, plastic surgery, otolaryngology, or oromaxillofacial surgery.^cFinger fracture^dPhysical restraint (e.g. papoose, forcibly pinning down patient's arms) that is applied prior to initiating procedure, and without any preceding indication of patient distress or un-cooperation.

Table 3

Outcomes based on volumes of administration.

	0.2 mL (n=32)	0.5 mL (n=33)	1 mL (n=31)
Time to onset of minimal sedation, minutes, median (95% CI)	4.7 (3.8, 5.4)	4.3 (3.9, 4.9)	5.2 (4.6, 7)
Total OSBD-r score, units, mean (95% CI) ^{a,b}	6.06 (3.68, 8.44)	7.90 (4.95, 10.85)	8.56 (5.75, 11.37)
Baseline ^d	0.02 (0, 0.07)	0.01 (0, 0.04)	0.10 (0, 0.21)
Irrigation/cleaning ^d	3.16 (1.83, 4.5)	3.44 (1.87, 5.02)	3.74 (2.34, 5.14)
Laceration repair ^d	2.67 (1.51, 3.82)	4.26 (2.65, 5.86)	4.2 (2.79, 5.6)
Post-procedure ^d	0.55 (0, 1.15)	0.45 (0, 0.91)	0.52 (0, 1.08)
Time to onset of procedure, minutes, mean (95% CI)	10.2 (9.1, 11.3)	9.9 (8.0, 11.8)	10.4 (9.0, 11.9)
Deepest level of sedation, UMSS, median (IQR) ^e	1 (1, 1)	1 (1, 1)	1 (1, 1)

^aTotal OSBD-r score range from 0 to 94: 0 = no distress, 94 = maximum distress^bn=30, 29, and 31 for 0.2 mL, 0.5 mL, and 1 mL VOA, respectively.^dOSBD-r score range for each phase from 0 to 23.5; 0 = no distress, 23.5 = maximum distress.^eUMSS (University of Michigan Sedation Scale) score from 0 to 4: 0 = awake and alert; 1 = minimal sedation; 2 = moderate sedation; 3 = deep sedation; 4 = unarousable.

Table 4

Adverse events.

	0.2 mL (n=32)	0.5 mL (n=33)	1 mL (n=31)
Vomiting, n (%, [95% CI])	0 (0, [0, 10.7])	2 [/] (6.1, [0, 19.6])	1 (3.2, [0, 16.2])
Sedation inadequate, could not complete procedure, n (%, [95% CI])	0 (0, [0, 10.7])	2 [/] (6.1, [0, 19.6])	0 (0, [0, 11])

[/]The two patients who experienced vomiting were not the same patients that experienced inadequate sedation.

Table 5

Clinician and caregiver satisfaction associated with volumes of administration.

	0.2 mL (n=32)	0.5 mL (n=33)	1 mL (n=31)
It was easy to administer the entire dose of medication using this method [as per attending who administered medication], n (% , [95% CI]) ^a	13 (40.6, [23.6, 57.6])	30 (90.9, [81.1, 100])	30 (96.8, [90.6, 100])
I was satisfied with the sedation achieved using this method [as per proceduralist], n (% , [95% CI]) ^a	25 (78.1, [63.8, 92.4])	23 (69.7, [54, 85.4])	21 (67.7, [51.2, 84.2])
I was satisfied with how comfortable my child was when they received the medication through the nose [as per caregiver], n (% , [95% CI]) ^a	20 (62.5, [45.7, 79.3])	23 (69.7, [54, 85.4])	19 (63.3, [46.3, 80.3]) ^c
I was satisfied with how well my child stayed still and/or was comfortable during the procedure [as per caregiver], n (% , [95% CI]) ^a	26 (81.2, [67.7, 94.7])	25 (78.1, [64, 92.2]) ^b	23 (76.7, [61.8, 91.6]) ^c

^a Individuals who answered, "Agree" or "Strongly agree", to the statements posed.^b n=32^c n=30