JAMA Pediatrics | Original Investigation

Optimal Dose of Intranasal Midazolam for Procedural Sedation in Children
A Randomized Clinical Trial

Daniel S. Tsze, MD, MPH; Hilary A. Woodward, MS; Son H. McLaren, MD, MS; Cheng-Shiun S. Leu, PhD; April M. R. Venn, MD; Nina Y. Hu, MD, MS; Pamela L. Flores-Sanchez, MD; Bianca R. Stefan, MD; Sripriya T. Shen, MD; Mina J. Ekladios, MD, MS; Joseph P. Cravero, MD; Peter S. Dayan, MD, MSc

IMPORTANCE Intranasal (IN) midazolam is commonly used for procedural sedation in children, but the optimal dose is unclear. Insufficient dosing may result in inadequate sedation, leading to short- and long-term consequences associated with poorly managed procedural pain and distress, whereas doses that are too high may be associated with more adverse events.

OBJECTIVE To determine the optimal dose of IN midazolam for procedural sedation in children undergoing laceration repair.

DESIGN, SETTING, AND PARTICIPANTS This prospective, double-blind, adaptive selection randomized clinical trial used the Levin-Robbins-Leu sequential selection procedure and was conducted between September 2021 and May 2024 at a tertiary care pediatric emergency department. Participants were children aged 6 months to 7 years with a simple laceration who required IN midazolam to facilitate the repair. The sequential selection procedure eliminated doses when they failed to achieve a prespecified rate of adequate sedation state compared with the best-performing dose. If more than 1 dose survived elimination, secondary outcomes of remaining doses were compared. Data were analyzed from June to August 2024.

INTERVENTIONS Doses of 0.2, 0.3, 0.4 or 0.5 mg/kg of IN midazolam.

MAIN OUTCOMES AND MEASURES The primary outcome was adequate sedation state, defined as Pediatric Sedation State Scale (PSSS) score of 2, 3, or 4 (of 5) for at least 95% of the procedure; no PSSS score of 0 or 1; procedure start within 17 minutes of IN midazolam administration; and procedure completion. Secondary outcomes included ideal sedation state (PSSS score of 2 or 3 for 100% of the procedure), time to onset of minimal sedation, adverse events, time to recovery, and clinician and caregiver satisfaction.

RESULTS Following the sequential selection procedure, a total of 101 children (38 [37.6%] female; median [IQR] age, 3 [2-4] years) were enrolled. The 0.2 and 0.3 mg/kg doses were eliminated, with 19 children receiving 0.2 mg/kg and 24 children receiving 0.3 mg/kg. The 0.4- and 0.5-mg/kg doses remained at enrollment completion, with 29 children receiving 0.4 mg/kg and 29 children receiving 0.5 mg/kg. There were no differences in secondary outcomes between the 2 remaining doses and no serious adverse events with any dose.

CONCLUSIONS AND RELEVANCE In this randomized clinical trial, the optimal doses of IN midazolam for procedural sedation in children undergoing laceration repair were 0.4 and 0.5 mg/kg. This finding can inform clinical practice and future studies of IN midazolam for procedural sedation.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT04586504

Visual Abstract

Supplemental content

Author Affiliations: Division of Pediatric Emergency Medicine, Department of Emergency Medicine, Columbia University Vagelos College of Physicians and Surgeons, New York, New York (Tsze, McLaren, Venn, Hu, Flores-Sanchez, Stefan, Shen, Ekladios, Dayan); Department of Child Life, NewYork-Presbyterian Morgan Stanley Children's Hospital, New York, New York (Woodward); Department of Biostatistics, Mailman School of Public Health, Columbia University, New York, New York (Leu); Department of Anesthesiology, Critical Care and Pain Medicine, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts (Cravero).

Corresponding Author: Daniel S. Tsze, MD, MPH, Division of Pediatric Emergency Medicine, Department of Emergency Medicine, Columbia University Vagelos College of Physicians & Surgeons, 530 W 166th St, First Floor, New York, NY 10032 (dst2141@cumc.columbia.edu).

JAMA Pediatr. doi:10.1001/jamapediatrics.2025.2181
Published online July 28, 2025.

Intranasal (IN) midazolam is commonly used in children for procedural sedation in the emergency department (ED).[1-7] Midazolam is an effective sedative and anxiolytic, and the IN route uses the nose-brain pathway and highly vascularized respiratory epithelium of the nasal cavity to facilitate rapid uptake of medications directly into the central nervous system and systemic circulation.[8,9] IN administration results in better bioavailability and more reliable effects than the oral route by bypassing first-pass metabolism and can achieve plasma concentrations comparable to intravenous (IV) administration, leading to the timely onset of clinical effects (eg, onset of minimal sedation within 5 minutes).[1,8-10] In addition, IN administration obviates the painful needle stick necessary for IV and intramuscular (IM) administration, allowing children to avoid what they have identified to be among their most feared medical experiences.[11-16]

Despite its reported use in children for more than 20 years, the optimal dose of IN midazolam remains unclear. Doses commonly described in literature reviews, research studies, and clinical guidelines range from 0.2 to 0.5 mg/kg.[1,2,5,7,8,17-32] There is a paucity of data comparing different doses of IN midazolam in children undergoing procedural sedation to identify the optimal dose for achieving clinically important outcomes, such as adequacy of sedation state, adverse events, time to onset of minimal sedation, and time to recovery. It is necessary to identify the optimal dose of IN midazolam because children who receive an insufficient dose may experience inadequate sedation and the short- and long-term consequences associated with poorly managed procedural pain and distress.[33-42] Similarly, children who receive too high a dose may experience an increased rate of adverse events or suboptimal outcomes, such as prolonged time to recovery.

The primary aim of this study was to determine the optimal dose of IN midazolam for procedural sedation in children undergoing laceration repair by comparing doses of 0.2, 0.3, 0.4, and 0.5 mg/kg using an adaptive selection trial to assess efficacy and safety. We hypothesized that 0.5 mg/kg is the optimal dose to achieve an adequate sedation state. Achieving this aim will optimize sedation-related outcomes associated with IN midazolam, facilitate standardization of its use for procedural sedation, and generate the evidence needed for rigorous and valid trials of IN midazolam in children.

Key Points

Question What is the optimal dose of intranasal midazolam for procedural sedation in children?

Findings This randomized clinical trial used an adaptive selection design to compare intranasal midazolam doses of 0.2, 0.3, 0.4 and 0.4 mg/kg in 101 children undergoing laceration repair. The 2 lower doses were eliminated due to lower rates of achieving adequate sedation state and there were no differences in secondary outcomes between the 0.4- and 0.5-mg/kg doses.

Meaning This randomized clinical trial found that the 0.4- and 0.5-mg/kg doses of intranasal midazolam were superior for procedural sedation in children undergoing laceration repair.

Methods

This randomized clinical trial was approved by the Columbia University institutional review board. Written informed consent was obtained from each participant's legal guardian. The trial protocol and statistical analysis plan are provided in Supplement 1. This study is reported following the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline for randomized clinical trials.[43]

Study Design and Participants

We conducted a prospective double-blind, adaptive selection, randomized clinical trial comparing 0.2-, 0.3-, 0.4-, and 0.5-mg/kg doses of IN midazolam. Between September 2021 and May 2024, we enrolled children presenting to a tertiary care children's hospital ED aged 6 months to 7 years 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. Exclusion criteria included developmental delay, underlying neurologic anomaly, or autism spectrum disorder; illness associated with chronic pain (eg, sickle cell disease); known allergy to any benzodiazepine; eyelid, tongue, or intraoral lacerations; nasal obstruction that could not be easily cleared; not English- or Spanish-speaking; or being a foster child or ward of the state. Race and ethnicity were collected directly from caregivers using federally defined categories and used to describe the population enrolled.

Randomization, Allocation Concealment, and Blinding

Patients were randomized using a web-based data system that used a real-time assignment algorithm to facilitate the adaptive selection trial and conceal allocation. The clinician performing the laceration repair, patient, caregivers, and outcome assessors were blinded to the assigned dose.

Study Procedures

We initially randomized patients in blocks of 4 to receive 0.2, 0.3, 0.4, or 0.5 mg/kg of IN midazolam. A 5 mg/mL concentration of midazolam was used (maximum dose, 10 mg). We used a mucosal atomization device (Wolfe-Tory Medical) for all IN administrations. The use of local anesthetic (eg, lidocaine-epinephrine-tetracaine gel, lidocaine injection) was documented. Children received at least 1 form of integrative intervention during the laceration repair (eg, child life specialist, digital device for distraction).

Patients were monitored using continuous pulse oximetry and videotaped beginning from prior to IN midazolam administration until ED discharge. The decisions of when to begin the procedure and whether to abort a procedure were at the discretion of the clinician performing the laceration repair. After laceration repair completion, clinicians and caregivers were assessed for their satisfaction with the sedation. Videos were scored by 1 of 3 blinded outcome assessors as soon as possible so that the results of the enrollment (ie, whether the dose achieved an adequate sedation state) could be incorporated into the dose-selection algorithm prior to the completion of each randomization block.

Outcome Measures

The primary outcome was adequate sedation state, defined as a Pediatric Sedation State Scale (PSSS) score of 2, 3, or 4 (on a scale from 0 to 5) for at least 95% of the scored procedure; no PSSS score of 0 or 1; procedure start within 17 minutes of IN midazolam administration; and procedure completion. The PSSS is a 6-point scale that measures the effectiveness and quality of procedural sedation in children and has strong criterion validity, construct validity, interrater reliability, and intrarater reliability (**Table 1**).[44] PSSS scores represent a continuum of sedation that spans from oversedation associated with changes in vital signs (0) or requiring airway intervention and/or assistance (1) to inadequate sedation requiring forceful immobilization (5) and facilitates an assessment of both benefit (ie, adequate sedation) and harm (ie, inadequate sedation, adverse events).

The period defined as the scored procedure encompassed the time from IN midazolam administration until 17 minutes after administration or until procedure completion, whichever occurred first. The 17-minute threshold was chosen to remove bias related to differences in laceration repair duration. Serum levels of IN midazolam remain at least 90% of peak levels until 17 minutes after administration.[26] Procedures with longer durations would be susceptible to greater periods of time with waning serum levels and clinical effect, thereby creating more opportunities for inadequate sedation state. Standardizing the duration of procedure evaluated for our primary outcome allowed us to compare the doses during their expected periods of peak effectiveness without the bias introduced by varying procedure durations. The inability to start the procedure by 17 minutes was also chosen as a criterion for adequate sedation state based on the assumption that if a procedure could not be started when a dose's effect was at its peak, then the dose was inadequate for starting the procedure in a timely fashion.

Secondary outcomes assessed included ideal sedation state, time to onset of minimal sedation, deepest level of sedation, time to recovery, clinician satisfaction, caregiver satisfaction, and adverse events. We defined ideal sedation state in the same way as adequate sedation state except the PSSS score had to be a 2 or 3 for 100% of the scored procedure. Minimal and deepest level of sedation were defined using the University of Michigan Sedation Scale.[45] Time to recovery was measured from time to procedure completion until time that recovery criteria were fulfilled. We assessed recovery using the Simplified Aldrete Score, which was adapted from the Modified Aldrete Scale to facilitate feasibility of use in the ED setting and scored from 0 to 8 (eTable 1 in Supplement 2).[46] Recovery was defined as a score of at least 6 and a minimum score of 2 in the respiration and oxygen saturation categories. If the patient fulfilled recovery criteria before or at time of procedure completion, the time to recovery was zero. We assessed clinician and caregiver satisfaction by asking the following questions using a 5-item Likert scale: "I was satisfied with the sedation achieved using this dose" and "I was satisfied with how well the medicine worked in helping my child stay calm for the procedure," respectively. Adverse events were defined per the Quebec Guidelines, which report sedation events that result in an intervention or a change in disposition from the ED.[47]

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 (eg, 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).

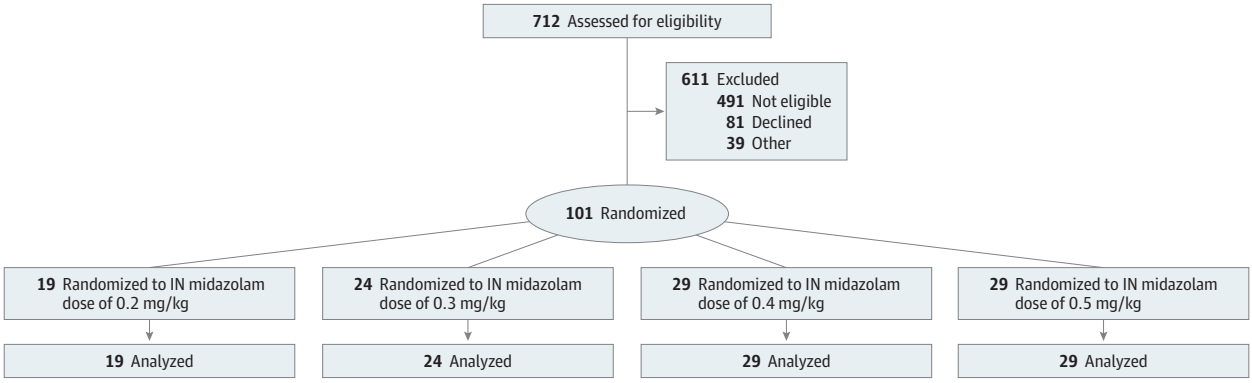
Reproduced with permission from Journal *Pediatrics*, Vol. 239, page e20162897. © 2017 by the AAP.

Statistical Analysis

For the primary outcome, we used the Levin-Robbins-Leu sequential selection procedure to select the dose most likely to be superior to the others for achieving an adequate sedation state.[48,49] For this 4-group adaptive selection trial, patients were initially randomized in blocks of 4 to 1 of the 4 doses. Patients who met the definition of adequate sedation state were tallied as success; those who did not were tallied as failure. After completion of each block, the outcome of each sedation was determined and added to the success tally (ie, number of successes) for each dose. Enrollment continued until the success tally for the dose with the largest number of successes exceeded the success tally of the dose with the smallest number of successes by 4, at which time the latter dose would be eliminated (ie, no further patients would be randomized to that dose). The prespecified difference of 4 was chosen to guarantee a probability of at least 80% correct selection of an optimal dose that is superior to the other doses by a prespecified amount, ie, an odds ratio of 2.25 or greater comparing the odds of success between the 2 best doses.

When a dose was eliminated, patients were randomized in block sizes corresponding to the remaining number of doses (eg, after the first dose was eliminated, patients were randomized to blocks of 3 to receive 1 of the 3 remaining doses). This procedure would continue until 3 doses were eliminated or the truncation threshold of 100 patients was reached. The truncation threshold was selected to allow the highest probability of identifying the optimal dose based on the primary outcome while balancing feasibility. The truncation threshold was also chosen to allow enrollment of a sufficient number of patients (ie, 100 patients) to compare doses not eliminated and detect statistical and clinically meaningful differences in proportion of patients who achieved an ideal sedation state (ie, 20%), time to onset of minimal sedation (ie, 1.77 minutes), and

Figure. Participant Enrollment Flowchart



IN indicates intranasal.

time to recovery (ie, 15 minutes) with 0.80 power.[1] If more than 1 dose remained when the truncation threshold was met, the remaining doses would be compared using secondary outcomes to identify the optimal dose based on a hierarchy that was determined a priori by a consensus group of 9 individuals representing pediatric emergency medicine, acute care pediatrics, and child life. The hierarchy of secondary outcomes (in descending order) was ideal sedation state, time to onset of minimal sedation, minor adverse events, clinician satisfaction, time to recovery, and caregiver satisfaction. If there was no difference in the first secondary outcome (ie, ideal sedation state), then the next secondary outcome would be compared, and so forth. If 1 dose was superior based on a secondary outcome, the subsequent secondary outcome would not be compared and the superior dose would be considered optimal. Additional information about this study design is provided in the eAppendix in Supplement 2.

For the secondary outcomes, categorical outcomes were compared using the χ^2 test. Satisfaction was analyzed by grouping strongly agree and agree responses together as satisfied. Time to onset of minimal sedation and recovery were analyzed using the Wilcoxon rank-sum test. We analyzed median (instead of mean) time so that patients who did not have a time to onset of minimal sedation or recovery documented could still be included in the analysis. These patients were assigned a maximal score (ie, 999 minutes) in place of a time to onset of minimal sedation or recovery. A finding was statistically significant at 2-sided $P \leq .05$. Statistical analyses were conducted using SPSS version 29 (IBM) from June to August 2024.

Results

Characteristics of Study Participants

We enrolled and randomized 101 children (38 [37.6%] female; median [IQR] age, 3 [2-4] years), with 19 children receiving 0.2 mg/kg, 24 children receiving 0.3 mg/kg, 29 children receiving 0.4 mg/kg, and 29 children receiving 0.5 mg/kg IN midazolam (**Figure**). Patient characteristics are presented in **Table 2**, and procedure characteristics are shown in **Table 3**. Patient characteristics were similar across all 4 groups, with median age ranging from 2 to 4 years old. Procedure characteristics were also similar, with most lacerations occurring on the face and having a median (IQR) length of 1.5 (1.0-2.0) cm. Most laceration repairs were performed by an attending physician, and more than 90% of children received lidocaine-epinephrine-tetracaine. Any patient who did not receive lidocaine-epinephrine-tetracaine received injected lidocaine for local anesthesia.

Main Results

The number of patients who received each dose is shown in the Figure. Following the sequential selection procedure, the 0.2- and 0.3-mg/kg doses were eliminated after enrolling 19 blocks of 4 and an additional 6 blocks of 3, respectively (eFigure 1 and eFigure 2 in Supplement 2). The 0.4- and 0.5-mg/kg doses remained when enrollment was completed; 101 patients were enrolled to allow the final randomization block (of 2 patients) to be completed after reaching the truncation threshold of 100 patients. **Table 4** shows the secondary outcomes used to determine an optimal dose from the 2 remaining doses; no differences were observed. As a result, both 0.4 and 0.5 mg/kg of IN midazolam were considered superior to the lower doses. There were no serious adverse events. There was 1 paradoxical reaction in a child who received 0.4 mg/kg of IN midazolam. eTable 2 in Supplement 2 displays the clinical outcomes associated with all 4 doses. The deepest level of sedation associated with all 4 doses was a University of Michigan Sedation Scale score of 1 (ie, minimally sedated). The patient and procedure characteristics of children who received 0.4 or 0.5 mg/kg of IN midazolam based on sedation state adequacy are shown in eTable 3 and eTable 4 in Supplement 2.

Discussion

In this randomized clinical trial, we used an adaptive selection design to identify 0.4 and 0.5 mg/kg as the optimal doses of IN midazolam for children undergoing procedural seda-

Table 2. Patient Characteristics

Characteristic	Patients by intranasal midazolam dose, No. (%)			
	0.2 mg/kg (n = 19)	0.3 mg/kg (n = 24)	0.4 mg/kg (n = 29)	0.5 mg/kg (n = 29)
Age, median (IQR), y	2 (1-3)	3 (2-3.8)	4 (2.5-5)	3 (2.5-5)
Sex				
Female	6 (32)	11 (46)	10 (35)	11 (38)
Male	13 (68)	13 (54)	19 (65)	18 (62)
Weight, median (IQR), kg	14.6 (12.7-18.1)	16.5 (13.7-18.8)	17.2 (15.1-20.9)	17 (14.1-20.1)
Primary language				
English	12 (63)	16 (67)	18 (62)	22 (76)
Spanish	7 (37)	8 (33)	11 (38)	7 (24)
Race and ethnicity				
Asian	1 (5)	0	0	1 (3)
Black	2 (11)	0	2 (7)	4 (14)
Hispanic	13 (68)	17 (71)	24 (83)	21 (72)
White	2 (11)	7 (29)	1 (3)	3 (10)
>1 Race	1 (5)	0	2 (7)	0
History of painful or distressing procedure				
Laceration	1 (5)	1 (4)[a]	2 (7)	0
Immunization	9 (47)	12 (50)	11 (38)	16 (57)[b]
Other medical procedure	4 (21)	5 (21)	4 (14)	5 (18)[b]
History of receiving a sedative	1 (5)	3 (12)	4 (14)	3 (11)[b]

[a] Number of participants evaluated = 23.

[b] Number of participants evaluated = 28.

Table 3. Procedure Characteristics

Characteristic	Procedures by intranasal midazolam dose, No. (%)			
	0.2 mg/kg (n = 19)	0.3 mg/kg (n = 24)	0.4 mg/kg (n = 29)	0.5 mg/kg (n = 29)
Laceration location				
Face	17 (89)	21 (88)	28 (97)	26 (90)
Upper extremity	0	2 (8)	1 (3)	1 (3)
Lower extremity	1 (5)	0	0	2 (7)
Other[a]	1 (5)	1 (4)	0	0
Laceration length, median (IQR), cm	1.5 (1-2)	1.5 (1-2)	1.5 (1-2)	1.5 (1-2.3)
Laceration depth				
Epidermis	4 (21)	10 (42)	4 (14)	9 (31)
Dermis	7 (37)	10 (42)	15 (52)	11 (38)
Subcutaneous fat	7 (37)	2 (8)	6 (21)	5 (17)
Muscle	1 (5)	1 (4)	4 (14)	4 (14)
Bone	0	1 (4)	0	0
Proceduralist				
Attending physician	4 (21)	16 (67)	18 (62)	15 (52)
Fellow or resident	3 (16)	2 (8)	4 (14)	3 (10)
Nurse practitioner or physician assistant	4 (21)	3 (12)	3 (10)	5 (17)
Subspecialist	8 (42)	3 (12)	4 (14)	6 (21)
LET administered	19 (100)	24 (100)	28 (97)	27 (93)
Lidocaine injected	4 (21)	5 (21)	8 (28)	7 (24)

Abbreviation: LET, lidocaine-epinephrine-tetracaine.

[a] Included ear and lower back.

tion for laceration repairs. Although these doses are commonly used clinically and in research, lower doses (ie, 0.2 and 0.3 mg/kg) are also used and included in guidelines.[5,7,17-23,25] Our findings support the use of 0.4 or 0.5 mg/kg of IN midazolam to optimize the chance of achieving adequate sedation state in children undergoing laceration repair. These higher

Table 4. Secondary Outcomes Associated With 0.4 and 0.5 mg/kg of Intranasal Midazolam for Terminal Decision Rule of Sequential Selection Procedure

Outcome	Intranasal midazolam dose		Difference (95% CI)
	0.4 mg/kg (n = 29)	0.5 mg/kg (n = 29)	
Ideal sedation state, No. (%) [95% CI]	15 (52) [33 to 71]	13 (44) [27 to 64]	8 (−18 to 34)
Onset of minimal sedation, median (IQR), min	3.9 (3.1 to 4.4)	3.9 (3.3 to 5)	0.2 (−0.4 to 0.9)[a]
Adverse events, No. (%) [95% CI]	2 (7) [1 to 23]	0	7 (−2 to 16)
Vomiting	1 (3) [0 to 18]	0	3 (−3 to 9)
Paradoxical reaction	1 (3) [0 to 18]	0	3 (−3 to 9)
Clinician satisfied with sedation, No. (%) [95% CI]	24 (83) [64 to 94]	21 (72) [53 to 87]	11 (−10 to 32)
Time to recovery, median (IQR), min	0	0	0[a]
Caregiver satisfied with sedation, No. (%) [95% CI]	27 (96) [82 to 100][b]	25 (86) [68 to 96]	10 (−5 to 25)

[a] Independent samples Hodges-Lehman median difference.

[b] Number of participants evaluated = 28.

doses were not observed to be different from the lower doses with regard to time to recovery or adverse events. Our study did not provide data supporting the preferential use of 0.4 or 0.5 mg/kg, as neither dose was eliminated as part of the sequential selection procedure (indicating that neither dose was considered superior to the other in achieving adequate sedation state), and there were no differences between the 2 doses in the secondary outcomes evaluated.

Our findings regarding the comparative sedative efficacy of different doses of IN midazolam are similar to those described in prior studies. A retrospective study of 408 children who received IN midazolam for laceration repair in an ED showed a difference based on dose in the proportion of children who experienced satisfactory sedation (defined as being cooperative, sleepy, or with good to excellent sedation and not requiring restraint).[29] Of patients who received 0.20 to 0.29, 0.30 to 0.39, or 0.40 to 0.50 mg/kg of IN midazolam in the retrospective study by Yealy et al,[29] 27%, 80%, and 100% achieved satisfactory sedation, respectively. Similarly, a prospective randomized clinical trial comparing 0.3 mg/kg to 0.5 mg/kg of IN midazolam in children undergoing dental extractions showed that children who received the higher dose demonstrated less uncooperative behavior and anxiety.[24]

Concerns with using higher doses of IN midazolam (ie, 0.4 or 0.5 mg/kg) include the potential for increased rate of adverse events and prolonged recovery time. We did not observe any differences in either of these outcomes among the 4 doses studied, but our sample size may not have been large enough to identify a difference in adverse events, given their infrequency in children who receive IN midazolam. Prior studies describing the use of 0.4 and 0.5 mg/kg reported no serious adverse events involving clinically significant changes in vital signs or requiring airway or breathing interventions (eg, airway repositioning, supplemental oxygen, bag-valve-mask ventilation).[1,2,24,26-30] In a cumulative sample of 645 children aggregated from these studies, adverse events observed in the ED included 5 episodes of vomiting (0.78%) and 1 paradoxical reaction (0.15%); of these events, 2 episodes of vomiting and the paradoxical reaction occurred in patients who received 0.4 mg/kg. A comparison of recovery times associated with different doses of IN midazolam was described in 2 studies, neither of which showed a difference between 0.4 or 0.5 mg/kg compared with lower doses.[24,29]

Adequate sedation state was achieved in 65% to 70% of children who received 0.4 or 0.5 mg/kg of IN midazolam. This degree of success may seem less desirable when compared with IV or IM sedatives (eg, ketamine, propofol), which are typically associated with higher rates of adequate sedation.[50,51] However, the benefits and risks of IN midazolam need to be compared with these more potent sedatives. For example, higher rates of adequate sedation state are typically due to deeper levels of sedation, which are associated with higher rates of adverse events, prolonged recovery time, and additional resources for performing the sedation, monitoring, and recovery. In addition, the IN route of administration is needle-sparing and obviates the need for the child to receive an IM injection or undergo IV line insertion. The observed rate of adequate sedation state in our study may prompt consideration of more potent sedatives instead of IN midazolam when performing more sensitive or noxious procedures (eg, eyelid or tongue laceration repairs). In addition, this finding should prompt future investigation of ways to improve the rate of achieving adequate sedation state when using IN midazolam. For example, higher doses (eg, 0.6 mg/kg) and higher maximum total doses (eg, >10 mg) have been described but not studied, the latter of which may benefit heavier patients who may receive lower milligram per kilogram doses.[5,7,28,29] Future studies could identify patient characteristics (eg, temperament) that predict a child's response to IN midazolam to aid in choosing the most appropriate medication for a child requiring sedation. The effect of different procedural adjuncts or strategies (eg, integrative therapies, mitigating environmental stimuli) when used in conjunction with IN midazolam to achieve an adequate or ideal sedation state should also be evaluated.

Limitations

This study has limitations. We did not enroll children with developmental delay or autism spectrum disorder. It is unclear whether our findings are generalizable to these populations; future studies should address these populations. Similarly, we

did not enroll children younger than 6 months. Neonates and young infants have reduced clearance and less mature respiratory-reflex responses to hypercapnia and hypoxemia compared with those 6 months and older, so it is unclear whether the doses we identified as optimal would perform similarly with regards to efficacy and safety in a newborn population. Our study only evaluated children undergoing laceration repairs, so it is unclear whether our findings are generalizable to more noxious procedures (eg, abscess incision and drainage).

Conclusions

This randomized clinical trial using an adaptive selection design found that the optimal doses of IN midazolam for procedural sedation in children undergoing laceration repairs were 0.4 and 0.5 mg/kg. This finding can inform both clinical practice and future studies of IN midazolam for pediatric procedural sedation.

ARTICLE INFORMATION

Accepted for Publication: May 28, 2025.

Published Online: July 28, 2025. doi:10.1001/jamapediatrics.2025.2181

Author Contributions: Dr Tsze had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Tsze, Leu, Cravero, Dayan.
Acquisition, analysis, or interpretation of data: Tsze, Woodward, McLaren, Leu, Venn, Hu, Flores-Sanchez, Stefan, Shen, Ekladios, Dayan.
Drafting of the manuscript: Tsze.
Critical review of the manuscript for important intellectual content: All authors.
Statistical analysis: Tsze, Leu.
Obtained funding: Tsze, Woodward, Leu, Dayan.
Administrative, technical, or material support: Leu, Cravero.
Supervision: Tsze, Dayan.

Conflict of Interest Disclosures: Dr Tsze reported grants from Emergency Medicine Foundation during the conduct of the study and grants from National Institute of Neurological Disorders and Stroke (NINDS) and Eunice Kennedy Shriver National Institute of Child Health and Human Development outside the submitted work. Dr Woodward reported grants from Emergency Medicine Foundation during the conduct of the study. Dr Leu reported grants from Emergency Medicine Foundation during the conduct of the study. Dr Dayan reported grants from Columbia University Emergency Medicine Foundation during the conduct of the study and grants from Columbia University, Health Resources and Services Administration, and NINDS outside the submitted work. No other disclosures were reported.

Funding/Support: This study was supported by funding from the Emergency Medicine Foundation and Columbia University's CTSA grant No. UL1TR000040 from the National Institutes of Health National Center for Advancing Translational Sciences.

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Data Sharing Statement: See Supplement 3.

Additional Contributions: We thank Richard Buchsbaum, MS (Columbia University), for his administrative and technical support. Mr Buchsbaum is employed by the institution and was not compensated for his work for this study outside of his normal salary.

REFERENCES

1. Tsze DS, Ieni M, Fenster DB, et al. Optimal volume of administration of intranasal midazolam in children: a randomized clinical trial. *Ann Emerg Med*. 2017;69(5):600-609. doi:10.1016/j.annemergmed.2016.08.450

2. Malia L, Laurich VM, Sturm JJ. Adverse events and satisfaction with use of intranasal midazolam for emergency department procedures in children. *Am J Emerg Med*. 2019;37(1):85-88. doi:10.1016/j.ajem.2018.04.063

3. Sahyoun C, Cantais A, Gervaix A, Bressan S, Löllgen R, Krauss B; Pediatric Emergency Medicine Comfort and Analgesia Research in Europe (PemCARE) group of the Research in European Pediatric Emergency Medicine. Pediatric procedural sedation and analgesia in the emergency department: surveying the current European practice. *Eur J Pediatr*. 2021;180(6):1799-1813. doi:10.1007/s00431-021-03930-6

4. Kumar K, Ali S, Sabhaney V, et al; Pediatric Emergency Research Canada. Anxiolysis for laceration repair in children: a survey of pediatric emergency providers in Canada. *CJEM*. 2022;24(1):75-83. doi:10.1007/s43678-021-00210-y

5. Borland M, Esson A, Babl F, Krieser D. Procedural sedation in children in the emergency department: a PREDICT study. *Emerg Med Australas*. 2009;21(1):71-79. doi:10.1111/j.1742-6723.2008.01150.x

6. Choudhary D, Dhillon R, Chadha K, Cross K, Carnevale FP. National survey to describe the current patterns of procedural sedation practices among pediatric emergency medicine practitioners in the United States. *Pediatr Emerg Care*. 2022;38(1):e321-e328. doi:10.1097/PEC.0000000000002275

7. Trotter Z, Mecham C, Bhattarai B. Physician self-reported practice patterns: midazolam for minor procedures in pediatric patients. *Clin Pediatr (Phila)*. 2023;62(6):605-614. doi:10.1177/00099228221132020

8. Wolfe TR, Braude DA. Intranasal medication delivery for children: a brief review and update. *Pediatrics*. 2010;126(3):532-537. doi:10.1542/peds.2010-0616

9. Pires A, Fortuna A, Alves G, Falcão A. Intranasal drug delivery: how, why and what for? *J Pharm Pharm Sci*. 2009;12(3):288-311. doi:10.18433/J3NC79

10. Bregstein JS, Wagh AM, Tsze DS. Intranasal lorazepam for treatment of severe agitation in a pediatric behavioral health patient in the emergency department. *Ann Emerg Med*. 2020;75(1):86-89. doi:10.1016/j.annemergmed.2019.05.020

11. Fradet C, McGrath PJ, Kay J, Adams S, Luke B. A prospective survey of reactions to blood tests by children and adolescents. *Pain*. 1990;40(1):53-60. doi:10.1016/0304-3959(90)91050-S

12. Humphrey GB, Boon CM, van Linden van den Heuvell GF, van de Wiel HB. The occurrence of high levels of acute behavioral distress in children and adolescents undergoing routine venipunctures. *Pediatrics*. 1992;90(1)(Pt 1):87-91. doi:10.1542/peds.90.1.87

13. Cummings EA, Reid GJ, Finley AG, McGrath PJ, Ritchie JA. Prevalence and source of pain in pediatric inpatients. *Pain*. 1996;68(1):25-31. doi:10.1016/S0304-3959(96)03163-6

14. Van Cleve L, Johnson L, Pothier P. Pain responses of hospitalized infants and children to venipuncture and intravenous cannulation. *J Pediatr Nurs*. 1996;11(3):161-168. doi:10.1016/S0882-5963(96)80049-2

15. Carlson KL, Broome M, Vessey JA. Using distraction to reduce reported pain, fear, and behavioral distress in children and adolescents: a multisite study. *J Soc Pediatr Nurs*. 2000;5(2):75-85. doi:10.1111/j.1744-6155.2000.tb00089.x

16. Goodenough B, Thomas W, Champion GD, et al. Unravelling age effects and sex differences in needle pain: ratings of sensory intensity and unpleasantness of venipuncture pain by children and their parents. *Pain*. 1999;80(1-2):179-190. doi:10.1016/S0304-3959(98)00201-2

17. Pansini V, Curatola A, Gatto A, Lazzareschi I, Ruggiero A, Chiaretti A. Intranasal drugs for analgesia and sedation in children admitted to pediatric emergency department: a narrative review. *Ann Transl Med*. 2021;9(2):189. doi:10.21037/atm-20-5177

18. Rech MA, Barbas B, Chaney W, Greenhalgh E, Turck C. When to pick the nose: out-of-hospital and emergency department intranasal administration of medications. *Ann Emerg Med*. 2017;70(2):203-211. doi:10.1016/j.annemergmed.2017.02.015

19. Williams JM, Schuman S, Regen R, et al. Intranasal fentanyl and midazolam for procedural analgesia and anxiolysis in pediatric urgent care centers. *Pediatr Emerg Care*. 2020;36(9):e494-e499. doi:10.1097/PEC.0000000000001782

20. Mayel M, Nejad MA, Khabaz MS, Bazrafshani MS, Mohajeri E. Intranasal midazolam sedation as an effective sedation route in pediatric patients for radiologic imaging in the emergency ward: a single-blind randomized trial. *Turk J Emerg Med*. 2020;20(4):168-174. doi:10.4103/2452-2473.297461

21. Smith D, Cheek H, Denson B, Pruitt CM. Lidocaine pretreatment reduces the discomfort of intranasal midazolam administration: a randomized, double-blind, placebo-controlled trial. *Acad Emerg Med*. 2017;24(2):161-167. doi:10.1111/acem.13115

22. Klein EJ, Brown JC, Kobayashi A, Osincup D, Seidel K. A randomized clinical trial comparing oral, aerosolized intranasal, and aerosolized buccal midazolam. *Ann Emerg Med*. 2011;58(4):323-329. doi:10.1016/j.annemergmed.2011.05.016

23. Chang H, Yuan Y, Yang G, Liao X, Chen C, Ding G. Comparison of sedative effects of intramuscular and intranasal midazolam for pediatric laceration repair in dental emergency department: a randomized controlled study. *J Stomatol Oral Maxillofac Surg*. 2023;124(3):101396. doi:10.1016/j.jormas.2023.101396

24. Peerbhay F, Elsheikhomer AM. Intranasal midazolam sedation in a pediatric emergency dental clinic. *Anesth Prog*. 2016;63(3):122-130. doi:10.2344/15-00016.1

25. Chang JG, Regen RB, Peravali R, Harlan SS, Smeltzer MP, Kink RJ. Intranasal fentanyl and midazolam use in children 3 years of age and younger in the emergency department. *J Emerg Med*. 2021;61(6):731-739. doi:10.1016/j.jemermed.2021.09.006

26. Mellion SA, Bourne D, Brou L, et al. Evaluating clinical effectiveness and pharmacokinetic profile of atomized intranasal midazolam in children undergoing laceration repair. *J Emerg Med*. 2017;53(3):397-404. doi:10.1016/j.jemermed.2017.05.029

27. Everitt IJ, Barnett P. Comparison of two benzodiazepines used for sedation of children undergoing suturing of a laceration in an emergency department. *Pediatr Emerg Care*. 2002;18(2):72-74. doi:10.1097/00006565-200204000-00002

28. Lane RD, Schunk JE. Atomized intranasal midazolam use for minor procedures in the pediatric emergency department. *Pediatr Emerg Care*. 2008;24(5):300-303. doi:10.1097/PEC.0b013e31816ecb6f

29. Yealy DM, Ellis JH, Hobbs GD, Moscati RM. Intranasal midazolam as a sedative for children during laceration repair. *Am J Emerg Med*. 1992;10(6):584-587. doi:10.1016/0735-6757(92)90190-9

30. Neville DNW, Hayes KR, Ivan Y, McDowell ER, Pitetti RD. Double-blind randomized controlled trial of intranasal dexmedetomidine versus intranasal midazolam as anxiolysis prior to pediatric laceration repair in the emergency department. *Acad Emerg Med*. 2016;23(8):910-917. doi:10.1111/acem.12998

31. Nocera Kelley M, Lynders W, Pelletier E, et al. Increasing the use of anxiolysis and analgesia for paediatric procedures in a community emergency department network: a quality improvement initiative. *Emerg Med J*. 2024;41(2):116-122. doi:10.1136/emermed-2023-213232

32. Nemeth M, Jacobsen N, Bantel C, Fieler M, Sümpelmann R, Eich C. Intranasal analgesia and sedation in pediatric emergency care—a prospective observational study on the implementation of an institutional protocol in a tertiary children's hospital. *Pediatr Emerg Care*. 2019;35(2):89-95. doi:10.1097/PEC.0000000000001017

33. Taddio A, Katz J, Ilersich AL, Koren G. Effect of neonatal circumcision on pain response during subsequent routine vaccination. *Lancet*. 1997;349(9052):599-603. doi:10.1016/S0140-6736(96)10316-0

34. Weisman SJ, Bernstein B, Schechter NL. Consequences of inadequate analgesia during painful procedures in children. *Arch Pediatr Adolesc Med*. 1998;152(2):147-149. doi:10.1001/archpedi.152.2.147

35. Bijttebier P, Vertommen H. The impact of previous experience on children's reactions to venipunctures. *J Health Psychol*. 1998;3(1):39-46. doi:10.1177/135910539800300103

36. Pate JT, Blount RL, Cohen LL, Smith AJ. Childhood medical experience and temperament as predictors of adult functioning in medical situations. *Child Health Care*. 1996;25(4):281-298. doi:10.1207/s15326888chc2504_4

37. Nixon RDV, Nehmy TJ, Ellis AA, Ball SA, Menne A, McKinnon AC. Predictors of posttraumatic stress in children following injury: the influence of appraisals, heart rate, and morphine use. *Behav Res Ther*. 2010;48(8):810-815. doi:10.1016/j.brat.2010.05.002

38. Brodzinski H, Iyer S. Behavior changes after minor emergency procedures. *Pediatr Emerg Care*. 2013;29(10):1098-1101. doi:10.1097/PEC.0b013e3182a5ff07

39. Pearce JI, Brousseau DC, Yan K, Hainsworth KR, Hoffmann RG, Drendel AL. Behavioral changes in children after emergency department procedural sedation. *Acad Emerg Med*. 2018;25(3):267-274. doi:10.1111/acem.13332

40. Fortier MA, Del Rosario AM, Martin SR, Kain ZN. Perioperative anxiety in children. *Paediatr Anaesth*. 2010;20(4):318-322. doi:10.1111/j.1460-9592.2010.03263.x

41. Kain ZN, Mayes LC, Caldwell-Andrews AA, Karas DE, McClain BC. Preoperative anxiety, postoperative pain, and behavioral recovery in young children undergoing surgery. *Pediatrics*. 2006;118(2):651-658. doi:10.1542/peds.2005-2920

42. Kain ZN, Wang SM, Mayes LC, Caramico LA, Hofstadter MB. Distress during the induction of anesthesia and postoperative behavioral outcomes. *Anesth Analg*. 1999;88(5):1042-1047. doi:10.1097/00000539-199905000-00013

43. Schulz KF, Altman DG, Moher D; CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ*. 2010;340:c332. doi:10.1136/bmj.c332

44. Cravero JP, Askins N, Sriswasdi P, Tsze DS, Zurakowski D, Sinnott S. Validation of the Pediatric Sedation State Scale. *Pediatrics*. 2017;139(5):e20162897. doi:10.1542/peds.2016-2897

45. Malviya S, Voepel-Lewis T, Tait AR, Merkel S, Tremper K, Naughton N. Depth of sedation in children undergoing computed tomography: validity and reliability of the University of Michigan Sedation Scale (UMSS). *Br J Anaesth*. 2002;88(2):241-245. doi:10.1093/bja/88.2.241

46. Aldrete JA. The post-anesthesia recovery score revisited. *J Clin Anesth*. 1995;7(1):89-91. doi:10.1016/0952-8180(94)00001-K

47. Bhatt M, Kennedy RM, Osmond MH, et al; Consensus Panel on Sedation Research of Pediatric Emergency Research Canada (PERC) and the Pediatric Emergency Care Applied Research Network (PECARN). Consensus-based recommendations for standardizing terminology and reporting adverse events for emergency department procedural sedation and analgesia in children. *Ann Emerg Med*. 2009;53(4):426-435.e4. doi:10.1016/j.annemergmed.2008.09.030

48. Leu CS, Levin B. On the probability of correct selection in the Levin-Robbins sequential elimination procedure. *Stat Sin*. 1999;9(3):879-891.

49. Leu CS, Levin B. On a conjecture of Bechhofer, Kiefer, and Sobel for the Levin-Robbins-Leu binomial subset selection procedures. *Sequential Anal*. 2008;27(2):106-125. doi:10.1080/07474940801989079

50. Green SM, Roback MG, Kennedy RM, Krauss B. Clinical practice guideline for emergency department ketamine dissociative sedation: 2011 update. *Ann Emerg Med*. 2011;57(5):449-461. doi:10.1016/j.annemergmed.2010.11.030

51. Miller KA, Andolfatto G, Miner JR, Burton JH, Krauss BS. Clinical practice guideline for emergency department procedural sedation with propofol: 2018 update. *Ann Emerg Med*. 2019;73(5):470-480. doi:10.1016/j.annemergmed.2018.12.012