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Incidence and predictors of nonresponse to intranasal midazolam in children undergoing laceration repair

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Abstract

Background/objective: Pediatric laceration repairs are common in the emergency department (ED) and often associated with significant procedural anxiety. Despite the increased use of intranasal midazolam (INM) prior to pediatric ED procedures, there is limited, real-world data on the effects of INM on anxiety. This study aimed to describe the proportion of children who were nonresponsive to INM (i.e., exhibited extreme anxiety) and identify factors associated with INM nonresponse.

Methods: This cross-sectional study included a sample of 102 children (ages 2–10 years) who received 0.2 mg/kg INM prior to laceration repair in the ED. Procedural anxiety was assessed using the modified Yale Preoperative Anxiety Scale (mYPAS). Children exhibiting extreme procedural anxiety (mYPAS score ≥72.91) when procedure started were labeled as INM nonresponders. Bivariate and multivariable logistic regression analyses explored associations between child age, temperament, laceration location, time from INM administration, and likelihood of INM nonresponse.

Results: In this sample, 45.1% of the children were classified as INM nonresponders, exhibiting extreme procedural anxiety. Bivariate analyses indicated that nonresponders were younger, had lower sociability temperament, longer delay between INM administration and the procedure, and were more likely to have extremity lacerations. In the logistic regression, younger age (odds ratio [OR] 0.79, $p = 0.034$), lower sociability temperament (OR 0.28, $p = 0.002$), and extremity lacerations (OR 8.04, $p = 0.009$) were significantly associated with likelihood of INM nonresponse.

Conclusions: Nearly half of the children in our sample exhibited extreme procedural anxiety despite receiving INM. The high incidence of nonresponse to INM has important clinical practice implications and suggests that 0.2 mg/kg INM alone may not be sufficient to manage all pediatric procedural anxiety in the ED. Findings highlight a need for further research examining multimodal strategies to manage procedural anxiety in the pediatric ED, particularly for younger children with low sociability temperament or extremity lacerations.

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INTRODUCTION

Each year, millions of children present to the emergency department (ED) after an injury. Facial and extremity lacerations represent some of the most common pediatric injuries treated in the ED.[1] These visits often result in children undergoing invasive procedures, which can cause significant anxiety.[2] The detrimental short and long-term consequences of pediatric procedural anxiety have been documented in a variety of pediatric medical settings, with data indicating that heightened anxiety is associated with increased procedural pain, interference with procedure completion, and adverse psychological and clinical outcomes.[3–6]

Midazolam is one of the most common pharmacological interventions for managing pediatric procedural anxiety in the United States. Evidence of the anxiolytic effects of midazolam has primarily been derived from studies examining oral and intravenous midazolam. Results from these studies largely support the efficacy of oral and intravenous midazolam as an anxiolytic for procedural anxiety.[7–10] However, variability in children's response to midazolam remains a concern, with some data from perioperative and ED samples suggesting that a notable proportion of children display high levels of anxiety following oral midazolam administration.[7,9,11,12] In the ED specifically, midazolam has demonstrated favorable effects on distress and sedation in children; however, collective evidence on the effectiveness of midazolam as an anxiolytic for ED procedures is mixed and limited by variability of sample size, outcome measures, comparators, and route of administration across studies.[9,10]

The use of intranasal midazolam (INM) prior to pediatric ED procedures has increased in recent years due to its faster therapeutic onset relative to oral administration, which allows for more efficient patient flow in a fast paced ED setting.[9,13,14] Existing evidence on the effects of INM surrounding pediatric ED procedures primarily stems from randomized controlled trials, often focusing on sedation and procedural satisfaction as primary outcomes.[13–19] Fewer studies have specifically assessed INM effectiveness in managing procedural anxiety during common ED procedures like laceration repair. A recent systematic review of INM for pediatric ED procedures reported mixed results for the efficacy of INM for laceration repair and highlighted a lack of data on INM effectiveness utilizing validated measures of anxiety.[19] Although data indicate that INM is a safe sedative premedication for pediatric ED procedures and has shown favorable effects compared to placebo, there is limited real-world evidence specifically examining the effects of INM on procedural anxiety.[14–16]

Given the increased use of INM in children undergoing laceration procedures in the ED, there is a need to expand clinical evidence on the effectiveness of INM on procedural anxiety in the ED using real-world, observational data. Such work may better inform clinical practice through characterizing variability in children's anxiety response to INM and identifying factors associated with nonresponse, enabling more targeted interventions that improve pediatric procedural anxiety management in the ED. Therefore, the current study examined procedural anxiety in children who received INM prior to undergoing laceration repair in the ED. Specifically, the study aimed to describe the proportion of children who were nonresponsive to INM (i.e., exhibited extreme procedural anxiety) and identify clinical and child factors, including age and temperament,[11,20] associated with INM response.

METHODS

Study design and participants

This cross-sectional study was conducted within a Level I pediatric trauma center ED in the southwestern United States. Eligible participants included children 2 to 12 years old admitted to a pediatric ED for a laceration repair and their caregivers. Children undergoing suture repair with an Emergency Severity Index (ESI)[21] of 3–5 and families who were fluent in English or Spanish were eligible to participate. Children were excluded if they underwent a noninvasive repair (e.g., tissue adhesive); were scheduled to be admitted to an inpatient floor following the ED procedure; were being seen for cooccurring psychiatric concerns; were being treated for injuries related to maltreatment; had a cognitive impairment or developmental delay; or had a history of diabetes, cancer, thyroid, or pain related chronic conditions.

Measures

Demographics

Demographics, including age, gender, ethnicity, race and primary language, were collected via caregiver report.

Clinical and treatment variables

ESI,[22] laceration location, length of laceration, INM dose, number of sutures placed, medications administered, and length of stay were obtained from the medical record. Time from INM administration to procedure start was calculated from video data.

Sedation

Level of sedation at the start of the procedure was assessed via the University of Michigan Sedation Scale (UMSS).[23] The UMSS has demonstrated reliability and validity in the assessment of sedation after midazolam administration, including prior to laceration repairs in ED.[15,24] Sedation scores range from 0 (awake and alert) to 4 (unarousable), with a score of 1 (minimally sedated) indicating a sedative effect.[25]

Child temperament

Child temperament was assessed via the parent-reported Emotionality Activity Sociability Temperament Survey (EAS-TS).[26] The EAS-TS is a 20-item measure that includes four subscales (i.e., emotionality, activity, sociability, shyness) and has demonstrated acceptable validity in pediatric samples. Parents were asked to rate their child's typical behavior on a 5-point, Likert-type scale. Higher scores indicated higher baseline emotionality, activity, sociability, or shyness temperament.

Child procedural anxiety

Child procedural anxiety was measured using the modified Yale Preoperative Anxiety Scale–Short Form (mYPAS-SF) observational measure.[27] The mYPAS-SF is an adapted and validated version of the mYPAS[28,29] that assesses four different domains of anxiety (activity, emotional expressivity, state of apparent arousal, and vocalizations) surrounding pediatric medical procedures. The modified versions of the YPAS have been used across diverse health fields (e.g., anesthesia, emergency medicine, pediatrics, and dentistry).[5,30–33] The mYPAS-SF score ranges from 22.5 to 100. Higher scores indicate higher anxiety and scores ≥72.91 indicate extreme anxiety.[11]

A research assistant who was trained in mYPAS using a standardized protocol requiring inter-rater reliability weighted kappa coefficients >0.60 completed the mYPAS-SF from study video data. The mYPAS was scored at surrounding the start of the procedure (i.e., the point when the provider touches the patient's skin with forceps prior to the first suture).

Procedures

Study procedures were approved by the institutional review board (#210108). Families underwent recruitment procedures once they had been admitted to the ED and were awaiting assignment to a procedure room. Caregivers completed written HIPAA authorization and informed consent forms, while children between the ages of 7 and 12 years were asked to complete an assent form. After families completed informed consent, caregivers completed demographics and child temperament surveys using REDCap, a secure web-based data collection tool, on a digital tablet. Child anxiety during the procedures were captured on high-definition video via cameras mounted in the ED procedure rooms. The video recordings were securely transferred to a password-protected server. Trained research personnel independently coded the video data. All clinical procedures followed the institution's standard of care guidelines. The need for suture repair and the order for INM was at the discretion of the treating provider. Administration of INM was completed by a registered nurse. Midazolam concentration of 5 mg/mL was given at a dosage of 0.2 mg/kg, up to 6 mg total (max of 1 mL per nostril), using an intranasal mucosal atomization device and syringe.

Data analyses

Descriptive analyses were conducted to characterize the sample. Prior to conducting primary analyses, mYPAS scores were dichotomized based on a previously established, clinical cutoff for identifying response to midazolam.[11] Specifically, mYPAS scores ≥72.91 indicated a child was exhibiting extreme anxiety and thus labeled a nonresponder to INM whereas mYPAS scores <72.91 indicated that anxiety did not qualify as extreme anxiety and thus denoted that the child was an INM responder. Sedation at the start of the procedure was also assessed to characterize level of sedation in the current sample. Normality tests indicated that age, temperament, and anxiety data did not follow a normal distribution. Therefore, for primary analyses, chi-square and Mann-Whitney U mean difference analyses were conducted to examine bivariate associations among independent variables and anxiety response. Variables significantly associated with anxiety response were included in a subsequent logistic regression model to identify factors independently associated with likelihood of INM nonresponse. An a priori power analysis was conducted using G*power.[34] Based on an approximated incidence of extreme anxiety of 14%,[11] a two-sided alpha level of 0.05, and power of 0.80, the power analysis indicated that a sample of 88 would be sufficient to detect a medium effect for a multivariable logistic regression. Statistical analyses were conducted using IBM SPSS Statistics for Windows, Version 29.0 (IBM Corp.).

RESULTS

The study sample included 102 children ages 2–10 years old (mean±SD age 4.71±2.17 years). Approximately 40% ($n=41$) of children were female, 61.6% ($n=61$) were Latinx, and 85.3% ($n=87$) presented with a facial laceration. Sample characteristics are presented in Table 1.

Procedural anxiety

During laceration repair, mYPAS procedural anxiety scores ranged from 22.92 to 100 (mean±SD 68.28±20.71, median [IQR] 68.75 [30.2]). In this sample of children who received INM, 45.1% ($n=46$) displayed extreme anxiety (i.e., mYPAS score ≥72.91) during laceration repair and were labeled as midazolam nonresponders. Approximately 90% ($n=92$) of children were at least minimally sedated at the start of the procedure, and children who were minimally sedated were significantly more likely to be an INM responder (59.8%) compared to children who were not minimally sedated (0%; $\chi^2=11.81$, $p<0.001$).

Factors associated with midazolam response

Bivariate analyses indicated that age, temperament, laceration location, and time from midazolam administration to the start of procedure were all significantly associated with response to midazolam. Specifically, midazolam nonresponders (i.e., children who displayed

TABLE 1 Sample descriptives.

Variable	
Child age (range 2–10 years)	4.71 (±2.17)
Child gender[a]	
Female	41 (40.20)
Male	61 (59.80)
Child ethnicity	
Latinx	61 (61.30)
Non-Latinx	38 (38.40)
Child race	
African American, Black	1 (1.10)
Asian, Pacific Islander	9 (10.10)
Hawaiian or Pacific Islander	2 (2.20)
White	2 (2.20)
Multiracial or other	49 (55.10)
Language	26 (29.20)
English	95 (93.10)
Spanish	7 (6.90)
ESI	
3	2 (2.00)
4	100 (98.00)
Laceration location	
Face	87 (85.30)
Upper extremity	8 (7.80)
Lower extremity	7 (6.90)
Laceration length (cm)	1.76 (±0.93)
INM dose (mg/kg)	0.21 (±0.03)
Sedation score	
0	9 (8.90)
1	87 (86.10)
2	5 (5.00)
INM-to-procedure time (min)	22.48 (±7.95)
Child temperament	
Emotionality	2.43 (±0.83)
Activity	4.18 (±0.71)
Sociability	3.48 (±0.61)
Shyness	2.36 (±0.77)
Child anxiety (mYPAS)	68.28 (±20.71)

Note: Data are reported as mean (±SD) or *n* (%).

Abbreviations: ESI, Emergency Severity Index; INM, intranasal midazolam; mYPAS, modified Yale Preoperative Anxiety Scale.

[a]Gender response options included nonbinary options in addition to female and male.

extreme anxiety) were younger ($Z = -1.96$, $p = 0.050$), had less sociable temperament ($Z = -2.77$, $p = 0.006$), and were more likely to have an extremity laceration ($\chi^2 = 8.65$, $p = 0.003$). Time from midazolam administration to procedure start was also significantly longer for nonresponders ($Z = -2.10$, $p = 0.035$). Results of bivariate analyses are presented in Table 2.

Additional analyses were conducted to explore the effects of midazolam-to-procedure start time and child age on procedural anxiety. Figure 1 and Table 3 display mean procedural anxiety scores across midazolam-to-procedure start times. Results of an analysis of variance (ANOVA) comparing anxiety across all time duration groups indicated that procedural anxiety did not significantly differ across groups (F [5, 96] = 1.92, $p = 0.075$). However, pairwise difference tests showed that children whose procedure started 10–15 min or 15–20 min after midazolam administration had significantly lower anxiety than children whose procedure started 25–30 min ($p = 0.022$, $p = 0.030$, respectively) or 30–35 min ($p = 0.031$, $p = 0.046$, respectively) after INM administration. To further examine the effect of child age on procedural anxiety, age was converted to an ordinal variable reflecting developmental age ranges (i.e., 2–4, 5–7, 8–12 years old).[35,36] Mean procedural anxiety scores and proportion of INM nonresponders across child age groups are displayed in Tables 4 and 2, respectively. Procedural anxiety scores did not significantly differ across age groups in ANOVA nor pairwise difference tests (F[2,99] = 0.21, $p = 0.81$). Although the proportion of INM nonresponders was slightly higher in the 2- to 4-year group (51.6%) compared to the 5- to 7- (32.0%) and 8- to 12-year (38.5%) groups, these differences were not significant ($X^2 = 3.04$, $p = 0.22$).

A logistic regression was then conducted to examine independent effects of child age, temperament, laceration location, and time from INM administration to procedure on likelihood of not responding to INM. The overall regression model explained 28.2% of the variance (Nagelkerke R^2) in midazolam response ($X^2(4) = 23.87$, $p < 0.001$). Regression results indicated that younger age and having an extremity laceration were significantly associated with an increased likelihood of not responding to INM whereas a more sociable temperament was significantly associated with a decreased likelihood of not responding to INM (OR 0.79, $p = 0.034$; OR 8.04, $p = 0.009$; OR 0.28, $p = 0.002$). INM administration-to-procedure time was not associated with likelihood of INM nonresponse (Table 5).

DISCUSSION

In this study, nearly half (45.1%) of the children who received INM for laceration repair in the ED were classified as nonresponders, exhibiting extreme anxiety during the procedure. Current findings suggest that a considerable proportion of children may not experience the expected anxiolytic effects of INM during ED laceration procedures. The incidence of nonresponse in the current sample is notably higher than the 14% reported in previous studies of midazolam in perioperative settings.[11] This discrepancy may be attributed to the differences between the ED and perioperative environments. The ED is a fast-paced, unfamiliar and unpredictable medical setting where children are treated immediately following an injury and not based on a predetermined operating rooms schedule.

In the pediatric ED literature, midazolam has shown favorable effects on distress and sedation compared to placebo, but data on the anxiolytic response to INM for laceration repair using validated

TABLE 2 Proportion of midazolam responders and nonresponders across study variables.

Variable	Responder (mYPAS <72.91)	Nonresponder (mYPAS ≥72.91)	*p*-value
Child age (years)	5.02 (±2.13)	4.33 (±2.18)	0.050
2–4	31 (48.40)	33 (51.60)	0.218
5–7	17 (68.00)	8 (32.00)	
8–12	8 (61.50)	5 (38.50)	
Child gender			0.55
Female	24 (58.50)	17 (41.50)	
Male	32 (52.50)	29 (47.50)	
Child ethnicity			0.49
Latinx	31 (50.80)	30 (49.20)	
Non-Latinx	22 (57.90)	16 (42.10)	
Child race			0.56
African American, Black	1 (100.00)	0 (0)	
Asian, Pacific Islander	7 (63.60)	4 (36.40)	
White	28 (57.10)	21 (42.90)	
Multiracial or other	13 (50.00)	13 (50.00)	
Language			0.90
English	52 (54.70)	43 (45.30)	
Spanish	4 (57.10)	3 (42.90)	
Laceration location			0.003
Face	53 (60.90)	34 (39.10)	
Extremity	3 (20.00)	12 (80.00)	
Laceration length (cm)	1.75 (±0.92)	1.78 (±0.96)	0.83
INM dose (mg/kg)	0.21 (±0.03)	0.21 (±0.03)	0.62
INM-to-procedure time (min)	21.39	23.81	0.035
Sedation			<0.001
Score 0	0 (0.0)	9 (100.0)	
Score ≥1	55 (59.80)	37 (40.20)	
Child temperament			
Emotionality	2.44 (±0.88)	2.42 (±0.78)	0.94
Activity	4.23 (±0.68)	4.13 (±0.75)	0.60
Sociability	3.64 (±0.66)	3.29 (±0.49)	0.006
Shyness	2.48 (±0.79)	2.22 (±0.73)	0.08
mYPAS score	56.25 (43.75–65.63)	87.50 (83.34–93.75)	<0.001

Note: Data are reported as mean (±SD), *n* (%), or median (IQR).

Abbreviations: INM, intranasal midazolam; mYPAS, modified Yale Preoperative Anxiety Scale.

measures of anxiety in clinical practice are sparse, which challenges the interpretation of current results in the context of the ED literature.[10,19] One previous randomized controlled trial by Neville et al.[17] utilized the mYPAS to compare INM with intranasal dexmedetomidine and reported that 89% of children receiving INM exhibited procedural anxiety. While this rate is higher than 45.1% of extreme anxiety in the current study, key methodological differences likely explain this discrepancy. Notably, the study by Neville et al. included a relatively small INM sample and used a low threshold for anxiety, which may not adequately account for the heightened anxiety levels common in ED settings. Collectively, results highlight the need for further research that applies clinically meaningful and validated measures to better understand the effectiveness of INM in managing procedural anxiety in real-world ED settings.

Study analyses identified several factors associated with INM response. Bivariate analyses revealed that INM response was associated with child age, sociability temperament, laceration location, and delay time from midazolam administration to the start of the procedure. In the multivariable logistic regression model, child age, temperament, and laceration location remained significantly associated with INM response. Specifically, children who were younger, had lower sociability temperament, and with an extremity laceration

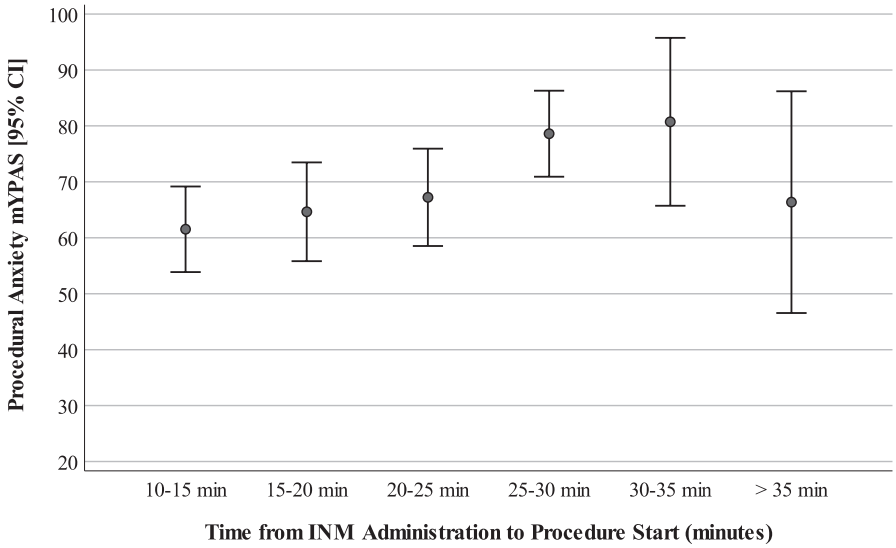

FIGURE 1 Mean procedural anxiety scores across INM-to-procedure start times. INM, intranasal midazolam.

TABLE 3 Procedural anxiety by midazolam-to-procedure duration.

Time (min)	*N*	Mean	95% CI
10–15	15	61.53	53.88–69.18
15–20	31	64.65	55.83–73.47
20–25	26	67.23	58.52–75.93
25–30	15	78.61	70.92–86.31
30–35	8	80.73	65.72–95.73
>35	7	68.28	64.21–72.35

TABLE 4 Procedural anxiety by child age.

Age range (years)	*N*	Mean	95% CI
2–4	64	69.01	63.12–74.91
5–7	25	65.92	60.10–71.73
8–12	13	69.23	59.22–79.24

were significantly more likely to exhibit extreme procedural anxiety and be classified as an INM nonresponder.

Current results are consistent with previous work demonstrating the effects of child age and temperament on various procedural anxiety outcomes. Collective results indicate that younger children and those with a temperament characterized by higher emotionality and lower activity and sociability are more likely to exhibit heightened procedural anxiety.[4,5,11,20,31,37] To our knowledge, only one other study has examined associations between child age, temperament styles, and anxiety response to midazolam. That study, conducted in children undergoing surgery, identified younger age and emotionality temperament as significant predictors of midazolam nonresponse.[11] In the current study, sociability was the only temperament dimension associated with INM response in the ED. Sociability reflects a tendency to seek out social interactions and a preference for being around others.[38] Undergoing a procedure in the ED may be especially challenging and anxiety provoking for child low in sociability who may struggle with adapting to a fast-paced, crowded ED environment and interacting with unfamiliar providers. The high incidence of extreme anxiety in our sample may have reduced the ability to detect a significant association between emotionality (i.e., tendency to become easily upset and exhibit distress) and midazolam response.

Children with extremity lacerations were also significantly more likely to be nonresponders compared to those with facial lacerations. The visibility of the injury and repair procedure for children with extremity lacerations may have contributed to increased anxiety, as they are more likely to observe the treatment process compared to those with facial lacerations. Additionally, extremity lacerations were less common in this sample, which could have influenced the observed effect. Future research should explore how injury location impacts anxiety and response to INM and whether procedural modifications (e.g., shielding the injury site) could mitigate this effect.

This study contributes important effectiveness data to the pediatric ED literature by describing the effect of INM on procedural anxiety in real-world practice. Unlike efficacy trials, which test treatment effects under controlled conditions, the current findings derived from real-world, observational data may offer a more accurate reflection of INM effectiveness in typical pediatric ED setting where variability in patient characteristics and treatment circumstances exist. Compared to the analyses of treatment group mean, the current observational design allows for the examination of variability in anxiety response and the influence of specific factors like age and temperament on INM response. These data may help clinicians better understand which children may benefit most from INM and where alternative or supplementary interventions may be needed.

LIMITATIONS

Several study limitations should be considered. First, the cross-sectional design of the study does not allow for causal conclusions. Although the observational study design and examination of effects

TABLE 5 Logistic regression identifying factors associated with midazolam nonresponse.

Variable	*B*	*SE*	OR (95% CI)	*p*-value
Child age	−0.23	0.11	0.79 (0.64–0.98)	0.034
Laceration location (extremity)	2.09	0.80	8.04 (1.69–38.32)	0.009
Sociability temperament	−1.28	0.42	0.28 (0.12–0.63)	0.002
Midazolam-to-procedure time	0.04	0.03	1.04 (0.99–1.10)	0.136

of standard of care practices has implications for INM effectiveness, the lack of control or manipulation over INM dosing and administration limits the ability to examine effects of these variables. The current study utilized an INM dose of 0.2 mg/kg, which aligns with our institution's standard dosing guidelines but represents the lower end of the dosing range (0.2–0.5 mg/kg) recommended by the American Academy of Pediatrics and commonly reported in recent literature for pediatric laceration repair.[19] The lower dose may have contributed to rates of nonresponse and may limit generalizability. That said, the findings of this study suggest that perhaps institutions that are using INM at lower range should consider increasing the dosing recommendations. Although time from INM administration to the procedure was accounted for in regression analyses, the variability in time is a potential confounding factor as delays may affect INM efficacy. Additionally, mean anxiety in the >35-min group should be interpreted cautiously due to the small sample size, which increases susceptibility to random variability and may limit the generalizability of results. Moreover, provider discretion in administering INM may have introduced selection bias, with more anxious children receiving treatment, potentially influencing response rates. Further, the sample age range was limited to 2–12 years old to align with the validated age range for the mYPAS and children being admitted inpatient following the procedure were excluded, which may limit the generalizability of findings to younger children or those with more severe injuries.

CONCLUSIONS

Study results highlight the variability in children's anxiety response to intranasal midazolam during laceration repair in the ED. The high rate of nonresponse to intranasal midazolam has important implications for clinical practice. Current findings suggest that factors such as child age and temperament play a significant role in intranasal midazolam effectiveness, underscoring the need for tailored, multimodal strategies. Future research should focus on optimizing treatment approaches, such as adjusting intranasal midazolam dosage for younger children, to improve procedural anxiety management in ED settings.

AUTHOR CONTRIBUTIONS

Sarah R. Martin conceptualized the objective of the study, directed the collection, analysis and interpretation of the data, prepared and drafted the manuscript, and revised the manuscript for intellectual content and important clinical implications. Kelly Bauer assisted with drafting the manuscript, contributed to the acquisition of the data and interpretation of the results, and critically reviewed and revised the manuscript for intellectual content. Theodore W. Heyming contributed to the conceptualization of the study, supervised data collection, assisted with analysis and interpretation of the data, and critically reviewed and revised the manuscript for intellectual content and important clinical implications. Jenny Zhu contributed to the contributed to the acquisition of the data and interpretation of the results, and critically reviewed and revised the manuscript for intellectual content. Helen Lee contributed to the acquisition, and interpretation of the data, assisted with drafting results tables, and critically reviewed and revised the manuscript for intellectual content. Zeev N. Kain contributed to the conceptualization and design the study, supervised and contributed to manuscript preparation, critically reviewed and revised the manuscript for important intellectual content and clinical implications. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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