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Original Contribution

Adverse events and satisfaction with use of intranasal midazolam for emergency department procedures in children☆

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ABSTRACT

Purpose: Procedural sedation is commonly performed in the emergency department (ED). Having safe and fast means of providing sedation and anxiolysis to children is important for the child's tolerance of the procedure, parent satisfaction and efficient patient flow in the ED.
Objective: To evaluate fasting times associated with the administration of intranasal midazolam (INM) and associated complications. Secondary objectives included assessing provider and caregiver satisfaction scores.
Methods: A prospective observational study was conducted in children presenting to an urban pediatric emergency department who received INM for anxiolysis for a procedure or imaging. Data collected included last solid and liquid intake, procedure performed, sedation depth, adverse events and parent and provider satisfaction.
Results: 112 patients were enrolled. The mean age was 3.8 years. There were no adverse events experienced by any patients. Laceration repair was the most common reason for INM use. The median depth of sedation was 2.0 (cooperative/tranquil). The median liquid NPO time was 172.5 min and the median NPO time for solids was 194.0 min. 29.8% were NPO for liquids ≤2 h and 62.5% were NPO for solids ≤2 h. Parent and provider satisfaction was high: 90.4% of parents' and 88.4% of providers' satisfaction scores were a 4 or 5 on a 5 point Likert scale.
Conclusion: Our data suggest that short NPO of both solids and liquids are safe for the use of INM. Additionally, parent and provider satisfaction scores were high with the use of INM.

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1. Introduction

Procedural sedation is commonly performed in the pediatric emergency department (ED). Minor procedures such as laceration repairs in children are among of the most frequently performed procedures in the ED. These procedures can cause significant anxiety in both the child and caregiver and thus can make the procedure more challenging for the provider and lead to parental dissatisfaction. Having safe and fast means of providing sedation and anxiolysis to children is important for the child's tolerance, parent satisfaction and efficient patient flow in the ED. Medications that have a quick onset and short duration are ideal in the ED setting. Intranasal medications can be used without the need for intravenous line placement and may obviate the need for the use of physical restraint during ED minor procedures.

Intranasal midazolam (INM) is a commonly used sedative in the ED to help achieve anxiolysis and amnesia during procedures [1-3]. INM is a water-soluble drug that has rapid onset (10–15 min) and a short half-life (20–40 min) [1,4,5]. INM has been shown to be easy to administer and is effective at decreasing anxiety and easing the procedural process [4,6,7]. These characteristics make it a useful drug in the ED setting.

The American Society of Anesthesiologists recommends NPO times of 6 h for solids and 2 h for clear liquids prior to procedural sedation/anesthesia for elective procedures [8]. The American College of Emergency Physicians clinical policy states that fasting time has not been shown to decrease risk of emesis or aspiration in ED procedural sedation and that lack of fasting is not a contraindication to perform procedural sedation [9]. Nonetheless, at many institutions the ASA guidelines form the basis for procedural sedation protocols [8,10]. Abiding by these strict recommendations can result in significant delays in a busy ED. Research regarding short fasting times is limited although recent studies have shown no increased risk of adverse events with shorter fasting times in pediatric patients. Many of these studies however, still had long fasting times, averaging four to 6 h and most have not evaluated intranasal medications [11-16]. Studies specifically evaluating fasting times and associated adverse events with INM are limited. One prior ED based study on INM and short fasting times by Lane et al. in

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2008 showed no adverse events in a small cohort of ED patients. However, in this study, fasting times were still relatively long, with an average of 3.5 h and by study protocol patients over 60 months were excluded [3]. There are no existing studies that evaluate both patient safety and parent/provider satisfaction.

The primary objective of our study was to evaluate fasting times (both last liquid oral intake and last solid oral intake) associated with the administration of intranasal midazolam and associated adverse events in a broader pediatric age range. Secondary objectives included assessing both provider and caregiver satisfaction scores with the use of INM for procedures.

2. Methods

A prospective observational study was conducted at an urban pediatric emergency department with an annual census of 65,000 patients. All children ages birth to 18 years presenting to the ED from January 2017 to October 2017 who received INM as sedation for a procedure or imaging were included. Children who received INM for issues other than procedures/imaging (i.e. seizure), received more than one medication for sedation, patients who eloped from the ED, or patients previously enrolled in the study were excluded. Patients with incomplete information that could not be found in the electronic medical record were excluded.

A convenience sample was collected using patients who met inclusion criteria and were enrolled in the study when providers (attending physicians, fellows and residents) were available. INM dose was generally based on dosing guidelines in the electronic ordering system as 0.4–0.5 mg/kg with a max total dose of 10 mg. To maximize enrollment during the study period, residents were emailed information about the study and inclusion exclusion criteria. The administration of INM was performed by the nurse with the child sitting up. Using a 1 mL (mL) syringe, intravenous midazolam (5 mg/mL) is drawn up and delivered via atomizer (MAD Nasal™ Intranasal Mucosal Atomization Device) by the intranasal route. The atomizer requires an extra 0.1 mL as it is lost within the device. Although some experts recommend using lidocaine first as INM can cause some burning on administration, it is not the standard of care at this institution and was not used in these study patients. When using INM alone at this institution, by policy it is termed anxiolysis and not sedation, therefore by policy, patients do not require formal written consent or additional nursing staff for in the room monitoring. Additionally, the ED sedation policy with Nil per Os (NPO) guidelines and specific monitoring and recovery requirements do not apply in these patients as they are receiving anxiolysis. It is the standard that patients are placed on a pulse oximetry monitor while in the ED after receiving INM. For pain control with lacerations, as part of our nursing triage protocol, the ED the nurse can apply topical LET (lidocaine 4%, epinephrine 0.1%, tetracaine 0.5%) to wounds without a physician order.

A data collection form was created to collect patient medical record number, weight, gender, last solid and liquid intake, procedure performed, sedation depth (using the Ramsey Sedation Scale (anxious/agitated, cooperative/oriented/tranquil, asleep/response to light stroke, asleep/sluggish response to stroke, no response to light stroke, no response to painful stimuli)), adverse events (vomiting, hypoxia (<90%), paradoxical reaction, apnea, stridor, or laryngospasm), parent satisfaction and provider satisfaction on a Likert scale (Tables 1 and 2) [15,17]. Following the procedure, the physician approached the caregiver using a standardized script to ask about their satisfaction regarding the use of INM. Providers were asked to fill out the form for any patient undergoing a procedure and receiving INM. The study was approved by the institutional review board.

Table 1
Likert scale for parent/provider satisfaction.

1 = very satisfied
2 = somewhat satisfied
3 = unsure
4 = somewhat dissatisfied
5 = very dissatisfied

Table 2
Ramsey sedation score.

1 = anxious/agitated
2 = cooperative/tranquil
3 = asleep/response to light stroke
4 = asleep/sluggish response to light stroke
5 = no response to light stroke
6 = no response to painful stimuli

Electronic medical record (EMR) review was conducted by the primary author. Confirmation of patients' age, gender, weight, procedure performed, INM dose (in mg/kg) and time of administration was obtained from the EMR. Using time stamps in the EMR, time from ED arrival to INM dose and time from INM dose to ED discharge were calculated. Additionally, we reviewed the EMR to ensure no patients returned to the ER within 3 days of the procedure for an adverse event to the sedation.

Data were collected from the electronic medical record then analyzed using IBM SPSS Statistics 22.00. Data is presented as mean ± standard deviation or median with 25–75% interquartile range depending on the distribution of the data. The Sharpiro-Wilk test was used to assess normality. Frequencies (%) were rounded to the nearest whole number. A p-value of <0.05 was consider significant.

3. Results

There were 405 patients who received INM during the study period. Of these, 112 patients were enrolled in the INM study who received INM as sedation for a procedure in the ED. One was excluded for age > 18 years, and seven were excluded for unrecorded fasting times. No excluded patient experienced an adverse event. The study group was comprised of the remaining 104 children. No enrolled patients dropped out during the study.

The study patient population was 53.8% male, 50% Caucasian, 32% Hispanic, 9% Black or African American, 2% Asian, and 9% Other. The mean age of study patients was 3.8 years (SD, 2.7 years) with a range of 0.9 to 14 years and a mean weight of 19 kg (SD, 9.8 kg; range, 9.1–59.3 kg) (Table 3). The median INM dose was 0.4 mg/kg (SD, 0.07 mg/kg). Table 4 shows the procedures performed under the use of INM. Laceration repair was the most common reason for INM use in this cohort (83.7%). 99% (86 of 87) of patients undergoing laceration repair received documented analgesia with LET applied at least 20–30 min prior to the procedure. There were no adverse events experienced by any patients who received INM in this study.

Depth of sedation scores were recorded on 100% of patients. The median depth of sedation was 2.0 (cooperative/tranquil) with a range of 1.0–4.0 (anxious/agitated to asleep/sluggish response to light stroke). The median depth of sedation was 2 (cooperative/tranquil), which was achieved in 79% of all patients, with range from 1 to 4. Only one patient in the cohort required an additional sedative medication to

Table 3
Demographics.

	N (%)
N	104
Sex (Male)	56 (53.8)
Caucasian	52 (50.0)
Hispanic or Latino	32 (30.7)
Black or African American	9 (8.7)
Asian	2 (1.9)
Other	9 (8.7)
Age	M 3.8, SD 2.7

Table 4
Procedure performed.

	N (%)	Adverse events
Laceration repair	87 (83.7)	0
Incision & drainage	3 (2.9)	0
Imaging	5 (4.8)	0
Other	9 (8.7)	0
Casting	1	0
Digital block	1	0
Finger fracture reduction (4yo, no digital block)	1	0
Foreign body removal	2	0
IV insertion	1	0
Nailbed repair (4yo & 9yo, digital block given)	2	0
Paraphimosis reduction	1	0

complete a procedure. This was a toddler undergoing head and face computed tomography (CT) who required escalation to ketamine sedation to complete the procedure. Internal dosing guidelines at our institution recommend 0.4–0.5 mg/kg for anxiolysis, and most study patients received a dose of 0.4 mg/kg or above with a maximum dose of 10 mg. However, 11 patients received <0.4 mg/kg (without reaching the max dose of 10 mg due to weight).

NPO status was captured in 100% of patients. The median liquid NPO time was 172.5 min (SD, 148.3 min; range 0–720 min) and the median NPO time for solids was 194.0 min (SD, 180.6 min; range 9–946 min). Of all patients, 29.8% were NPO for liquids ≤2 h and 62.5% were NPO for solids ≤2 h prior to the dose of INM.

Using a five point Likert scale, parent and provider satisfaction were assessed. The vast majority of both parents and providers were somewhat to very satisfied, 90.4% and 88.4% respectively. A small percentage of both parents and providers were unsure of their satisfaction with the use of INM, 5.8% ($n = 6$) and 2.9% ($n = 3$) respectively. Only 1.9% ($n = 2$) of parents were somewhat dissatisfied with the use of INM, both patients were undergoing laceration repair and both patients were <3 years old. No parents were extremely dissatisfied. Of providers 5.8% ($n = 6$) were somewhat dissatisfied and 1.9% ($n = 2$) were extremely dissatisfied (Table 5). In the 8 patients, whose providers were either somewhat dissatisfied or extremely dissatisfied, 3 received a dose lower than 0.4 mg/kg INM. Those patients with low provider satisfaction were more like to have received a dose less than the recommended dose of 0.4 mg/kg ($p = 0.04$).

In the study cohort, the mean length of stay from ED arrival to discharge was 175 min (SD7.1, range [78–567]). Once patients were placed in a room, the mean time to INM administration was 103 min (SD 4.3, range [20–227]). From the time INM was administered and the procedure performed the mean time to discharge was 58 min (SD 4.5, range [21–337]).

Discussion

Ensuring appropriate sedation for children undergoing procedures in the ED is an important attribute in providing quality care and parental satisfaction. INM is an increasingly common medication being used in both the pediatric and general ED to provide sedation to children undergoing procedures [1-3]. Potential advantages are minimizing physical restraint of patients, obviating need for intravenous lines for sedation, faster throughput compared to intravenous sedation, rare occurrence of adverse events, and high patient and provider satisfaction. Fasting times during the use of INM has been evaluated in prior studies, however previous studies have had limited age ranges and on average long fasting times (up to 6 h) [11-16]. Our study is the first to evaluate safety of shorter fasting times in a wide pediatric age range and document high objective measures of parent and provider satisfaction.

Table 5
Provider and parent satisfaction.

Satisfaction	Provider N(%)	Parent N(%)
Very satisfied	77 (74.0)	83 (79.8)
Somewhat satisfied	15 (14.4)	11 (10.6)
Unsure	3 (2.9)	6 (5.8)
Somewhat dissatisfied	6 (5.8)	2 (1.9)
Very dissatisfied	2 (1.9)	0 (0)
Missing	1 (1.0)	2 (1.9)

In our study, no patient, regardless of fasting time, suffered any side effects or adverse outcome. Although the median fasting times for liquids and solids were 172.5 min and 194.0 min respectively, 29.8% and 62.5% in each group had fasting times ≤2 h. Further, there were 5 patients who had a <10-minute liquid NPO time and no adverse outcomes were experienced. Our data suggests that short NPO times (≤2 h) of both solids and liquids are safe for the use of INM.

The one patient who required an additional agent for sedation was undergoing a CT scan of the brain and face. The patient had a fasting time >2 h for both solids and liquids. Per review of his record it appears that the patient was moving and talking too much to obtain the CT scan. There were 4 other patients who underwent CT imaging where INM was successfully used. INM would still be recommended and deemed safe in children undergoing imaging, however due to INM's disinhibition properties, excessive movement is possible but in this study, was a rare occurrence.

Further, providing appropriate sedation for the child during procedures performed in the ED is vital to ensuring that parents are satisfied with the care their child receives. In this study, the majority of parents and providers were somewhat to very satisfied with the use of INM during their child's procedure. In the rare case where satisfaction was low, the total administered dose of INM was more likely to be <0.4 mg/kg. While 0.4 mg/kg (and 10 mg max dose) is higher than IV dosing for midazolam, providers should be aware that 0.4 mg/kg is a safe and effective dose.

Factors including pain management, wait time, communication, and attentive staff have also been shown to be associated with parent satisfaction in EDs [18-20]. A busy ED setting can pose challenges to achieving high parent satisfaction especially in cases where their child is undergoing a painful procedure, as this creates excess stress on the parent [21,22]. Patient and parental satisfaction has become more of a focus in for management EDs for many reasons including the increasing use of patient surveys such as Press Ganey to judge ED performance. Studies evaluating factors associated with higher Press Ganey scores have shown that shorter ED stays were associated with higher satisfaction scores [23,24]. Using INM for procedural sedation has the potential to allow completion of the procedure much more efficiently than moderate sedation as it avoids the delays to meet NPO requirements and recovery time. Additional advantages include, less physical restraint of patients and not needing to extend the ER stay to place intravenous lines for sedation and recover these patients, both parent satisfiers. Furthermore, this study showed that patients can be discharged home quickly and safely after receiving INM. Compared to children needing recovery from intravenous sedation with agents such as Ketamine the recovery time and time to discharge after medication administration is shorter with INM. Prior studies have shown time to discharge after intravenous ketamine averages 2.1 h and up to 2.7 h when using intramuscular ketamine [25,26]. A mean time of 55 min from INM dose to discharge in our study paired with high parent and provider satisfaction make INM an attractive alternative in certain circumstances.

There are limitations to our study. First, this study was conducted at a single center tertiary pediatric ED and thus our results may not be applicable to other practice settings. Second, we recognize that this was a convenience sample and patients were enrolled at the physicians' convenience therefore, there may have been some bias with regard to which patients were enrolled. Further, missing fasting times were unable to be obtained as they are not routinely documented in the chart when using INM, thus it is possible that these excluded patients could

alter the results. However, a review of excluded patients shows no adverse events in this group. Finally, adverse events in sedation are rare (laryngospasm aspiration, hypoxia), thus this smaller sample may not have captured such events. Additional prospective studies using a larger sample size with shorter fasting times is needed to further delineate these results.

4. Conclusion

In conclusion, INM, used for sedation in the emergency department setting is safe even when used with relatively short fasting times. Parent and provider satisfaction are high with the use of INM when used with topical anesthetics for laceration repairs and other minor common pediatric ED procedures. In busy ED settings, using the intranasal route involves less staff, less physical restraint of patients, and likely a faster throughput of patients than other forms of sedation.

Abbreviations

CT	computed tomography
EMR	electronic medical record
ED	emergency department
INM	intranasal midazolam
NPO	Nil per os

Author contributions

LM and JS conceived the study. LM, JS and VML supervised the conduct of conduct of the trial and data collection. JS provided statistical advice on study design and analyzed the data. LM drafted the manuscript and all authors contributed substantially to its revision. LM takes responsibility for the paper as a whole.

Conflict of interest

LM reports no conflict of interest.
VML reports no conflict of interest.
JS reports no conflict of interest.

References

[1] Krauss B, Green SM. Procedural sedation and analgesia in children. Lancet 2006;367(9512):766Y780.
[2] Pena BM, Krauss B. Adverse events of procedural sedation and analgesia in a pediatric emergency department. Ann Emerg Med 1999;34 ((4 pt 1):483Y491).
[3] Lane RD, Schunk JE. Intranasal midazolam use for minor procedures in the pediatric emergency department. Pediatr Emerg Care 2008;24:300–3.
[4] Walbergh EJ, Eckert J. Pharmacokinetics of intravenous (IV) and intranasal (IN) midazolam in children. Anesthesiology 1989;71:A1066.
[5] Rey E, Delaunay L, Pons G, et al. Pharmacokinetics of midazolam in children: comparative study of intranasal and intravenous administration. Eur J Clin Pharmacol 1991;41:355–7.
[6] Knoester PD, Jonker DM, van der Hoeven RTM, et al. Pharmokinetics and pharmacodynamics of midazolam administered as a concentrated intranasal spray. A study in healthy volunteers. J Clin Pharmacol 2002:501–7.
[7] Harbord MG, Kyrkou NE, Jyrkou MR, et al. Use of intranasal midazolam to treat acute seizures in paediatric community settings. J Paediatr Child Health 2004;40:556–8.
[8] American Society of Anesthesiologists Committee. Practice guidelines for preoperative fasting and the use of pharmacologic agents to reduce the risk of pulmonary aspiration: application to healthy patients undergoing elective procedures: an updated report by the American Society of Anesthesiologists Committee on Standards and Practice Parameters. Anesthesiology 2016;126:376–93.
[9] Godwin SA, Burton JH, Gerardo CJ, et al. Clinical policy: procedural sedation and analgesia in the emergency department. Ann Emerg Med 2014;63:247.
[10] Coté CJ, Wilson S, American Academy Of Pediatrics, American Academy Of Pediatric Dentistry. Guidelines for monitoring and management of pediatric patients before, during and after sedation for diagnostic and therapeutic procedures: update 2016. Pediatrics 2016:138.
[11] Agrawai D, Manzi SF, Gupta R, et al. Preprocedural fasting state and adverse events in children undergoing procedural sedation and analgesia in a pediatric emergency department. Ann Emerg Med 2003;42:636–46.
[12] Treston G. Prolonged pre-procedure fasting time is unnecessary when using titrated intravenous ketamine for paediatric procedural sedation. Emerg Med Australas 2004;16:145–50.
[13] Ghaffar S, Haverland C, Ramasciotti C, et al. Sedation for pediatric echocardiography: evaluation of preprocedure fasting guidelines. J Am Soc Echocardiogr 2002;15:980–3.
[14] Kennedy RM, Porter FL, Miller P, et al. Comparison of fentanyl/midazolam with ketamine/midazolam for pediatric orthopaedic emergencies. Pediatrics 1998;102:956–63.
[15] Roback MG, Bajaj L, Wathen JE, et al. Preprocedural fasting and adverse events in procedural sedation and analgesia in a pediatric emergency department: are they related? Ann Emerg Med 2004;44:454–9.
[16] Babl FE, Puspitadewi A, Barnett P, et al. Preprocedural fasting state and adverse events in children receiving nitrous oxide for procedural sedation and alalgesia. Pediatr Emerg Care 2005;21(11):736–43.
[17] Mondello E, Siliotti R, Noto G, Cuzzocrea E, Scollo G, Trimarchi G, et al. Bispectral index in ICU: correlation with Ramsay score on assessment of sedation level. J Clin Monit Comput 2002;17:271–7.
[18] Margaret ND, Clark TA, Warden CR, et al. Patient satisfaction in the emergency department – a survey of pediatric patients and their parents. Acad Emerg Med 2002;9:1379–88.
[19] Pagnamenta R, Benger JR. Factor influencing parent satisfaction in a children's emergency department prospective questionnaire-based study. Emerg Med J 2008;24:417–9.
[20] Locke R, Stefano M, Koster A, et al. Optimizing patient/caregiver satisfaction through quality of communication in the pediatric emergency department. Pediatr Emerg Care 2001;27:1016–21.
[21] Byckowski TL, Fitzgerald M, Kennebeck S, et al. A comprehensive view of parental satisfaction with pediatric emergency department visits. Ann Emerg Med 2013;62(4):340–50.
[22] Institute of Medicine. Committee on the Future of Emergency Care in the United States Health System. Emergency Care for Children: Growing Pains. Washington, DC: National Academies Press; 2007.
[23] Pang PS, McCarthy D, Schmidt M, et al. 440 factors associated with perfect press ganey satisfaction scores for discharged emergency department patients. Ann Emerg Med 2011;58((4):S327–28.
[24] Nichol J, Robert BS, Fu R, et al. Association between patient and emergency department operational characteristics and patient satisfaction scores in a pediatric population. Pediatr Emerg Care 2016;32(3):139–41.
[25] Green SM, Rothrock SG, Lynch EL, et al. Intramuscular ketamine for pediatric sedation in the emergency department: safety profile in 1,022 cases. Ann Emerg Med 1998;31(6):688–97.
[26] Ramaswamy P, Babl F, Deasy C, et al. Pediatric procedural sedation with ketamine: time to discharge after intramuscular versus intravenous administration. Acad Emerg Med 2008;16(2):101–7.