

Role of intranasal midazolam as a procedural sedative in children aged 6 months to 12 years: An open-label randomized controlled study

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ABSTRACT

Objectives: The objectives of the study were to evaluate the efficacy and the adverse effects of intranasal midazolam compared to intravenous (IV) midazolam for procedural sedation in children between 6 months and 12 years of age using the University of Michigan sedation scale. **Design:** Prospective open-label randomized controlled trial. **Setting:** Children requiring sedation for any invasive or non-invasive procedure in the Department of Paediatrics, between June 2012 and May 2014. **Participants:** A total of 246 children aged between 6 months and 12 years of age were enrolled and sequentially allocated into the study by computer-generated block randomization. **Intervention:** As per randomization, participants were administered intranasal or IV midazolam before the procedure. Procedure was done 5 min after IV and 15 min after intranasal administration. **Main outcome measures:** Sedation score was rated using the University of Michigan Sedation Score. The ease of performance, numbers of successfully completed procedures, and adverse effects were noted. **Results:** Intranasal midazolam provided better sedation scores ($p < 0.001$) and ease of procedure scores ($p = 0.026$) compared to IV, especially in the age group from 6 months to 6 years. Both groups gave comparable successful procedure completion rates. The most commonly encountered side effect with intranasal was nasal irritation ($p < 0.001$). **Conclusion:** Intranasal midazolam provided significantly better sedation and ease of procedure scores when compared to IV, with fewer adverse effects. Hence, it can be put to use in resource-limited settings.

Key words: *Minor surgical procedures, Pain management, Parents, Patient care*

Pain perception in young infants and newborns did not receive much attention until recently. There have been valid concerns regarding the safety of administering potent opiates and sedatives to children due to the potential risk of airway compromise and respiratory depression. Inadequate sedation and analgesia for painful procedures in children are also aided by the fact that the adult health-care providers can often physically overpower children.

The increasing number of procedures being performed in children has led to a phenomenal demand for safe, predictable, efficacious, and cost-effective sedation in varied settings. A non-invasive route of drug administration may be useful to obtain short-term sedation for procedures in uncooperative children. Intranasal delivery offers unique advantages that may allow more efficient use of resources, more rapid patient care, and higher patient, and provider satisfaction. Delivery of intranasal medication is also relatively painless, inexpensive, and easy to administer with a minimum of training [1].

Midazolam is the most commonly used benzodiazepine as it possesses many properties desirable for use in children such as short half-life, faster onset of action, wide toxic and therapeutic ratio, safety margin, and dose-dependent anxiolytic action.

Previous studies have shown that therapeutic levels of midazolam in the cerebrospinal fluid indicate a more rapid rate of absorption through intranasal administration compared to the oral route, due to the rich vascular plexus cavity that communicates with the subarachnoid space through the olfactory nerve [2]. Intranasal midazolam has been used successfully in a variety of pediatric clinical situations, such as laceration repair, dental extractions, ophthalmological tests, burns patients, and venepuncture. The onset of action of intranasal midazolam is within 10–20 min of administration and the duration of its effect lasts for 30–60 min [3].

Most of the previous studies have used the undiluted parenteral formulation containing 5 mg/ml midazolam through intranasal route with a syringe by drop instillation; this reduces its bioavailability and increases the discomfort. A mucosal atomizer device delivers the medication through a fine spray over a broad surface area in the nasal cavity. By this technique, the absorption of midazolam through the nasal mucosa has been reported to be virtually complete (83%), because very little of the drug is swallowed unlike through the drop instillation technique [4]. Midazolam given intranasally has been shown to be safe, easy to administer, and effective in children undergoing various procedures. There were hardly any studies comparing the

effectiveness of intranasal midazolam versus intravenous (IV) midazolam for procedural sedation in children; hence, an attempt was made to study the efficacy and safety profile of intranasal midazolam as a procedural sedative.

MATERIALS AND METHODS

This was a prospective open-label randomized controlled study conducted in the Department of Pediatrics, Kerala Institute of Medical Sciences, Trivandrum, during the period between June 2012 and May 2014. The study was approved by the Hospital Ethical Committee. As literature review did not show any similar previous studies, a pilot study was conducted on 50 children, based on which the sample size was calculated. A sample size of 123 children each in the groups receiving intranasal and IV midazolam was calculated [5].

All children between the ages of 6 months and 12 years, who underwent any invasive (lumbar puncture, central line insertion, suture removal, burns wound care, wound dressing changes, liver biopsy, skin biopsy, IV cannulation in apprehensive children, intercostal drainage, or esophagogastroduodenoscopy,) or non-invasive procedures (magnetic resonance imaging [MRI], computed tomography [CT], echocardiography, and ultrasonography) in our hospital were included in the study. Children with allergy to benzodiazepines or any of its components, hemodynamically or neurologically unstable children and critically ill children were excluded from the study.

A computer-generated block randomization table was created by personnel with no clinical involvement in the trial. This allocation list was held by the pediatric intensive care unit (PICU) in-charge nurse. Children fulfilling the inclusion criteria were formally enrolled in the study after informed parental consent. After enrolment, the PICU in-charge nurse was contacted to assign allocation to each new participant, based on the allocation list.

A predation evaluation was carried out. One group received 0.3 mg/kg of intranasal midazolam with mucosal atomizer device (Insed atomizer, 5 mg/ml, 0.5 mg/puff, Samarth pharma) while the second group received 0.15 mg/kg of IV midazolam for sedation. A lidocaine-prilocaine (prilox) patch was applied for topical analgesia 45 min before procedure for all children in both groups undergoing invasive procedures. Prilox was also applied before securing IV access in children who did not previously have an IV line so that the confounding effect of needlestick could be avoided. Sedation was administered to all children by a pediatric resident under the supervision of a pediatric intensivist. Routine behavior management techniques such as tender loving care and minimal physical restraint were required to manage children of both groups during various procedures. As per hospital protocol, parents were not allowed to be with the children during any invasive procedures.

Baseline demographic variables and vitals were noted. Vitals were then continuously monitored and recorded in a structured data collection sheet every 30 min till recovery from sedation. Sedation score was rated only once, after administering the drug, just before performing the procedure, using the University of

Michigan Sedation Score (0 - awake, alert; 1 - minimally sedated, responds to verbal conversation; 2 - moderately sedated, responds to tactile stimulation; 3 - deeply sedated; responds to significant physical stimulation; and 4 - unarousable) in both the groups [6]. Procedure was done 15 min after intranasal and 5 min after IV administration of midazolam.

The ease of performance was scored during the procedure (1 - violent movements; 2 - continuous movements; 3 - controllable movements; and 4 - no movements, no crying) [7]. The number of successfully completed procedures was noted. The child was monitored until he/she was able to walk (if age appropriate) and gave age-appropriate responses to verbal commands, but the time to recovery was not recorded [8]. If the sedation was not adequate in either group of children, the child was reverted to standard PICU sedation protocol and was taken as a case of "sedation failure." Adverse events were noted and defined as follows:

- Hypoxemia: SpO₂ (using pulse oximetry) <90% at any time after drug administration [9].
- Hypoventilation/apnea: Poor breathing efforts or cessation of respiration for more than 20 s [10].
- Upper airway obstruction in the form of excessive secretions or spasm.
- Hemodynamic changes: Tachycardia, bradycardia, or hypotension (systolic blood pressure <5th percentile of normal for patients' age) [10].
- Hypersensitivity to the sedation agent used.
- Paradoxical agitation: Sustained severe irritability for 30 min or more after procedure [11].
- Nasal irritation: Increased irritability or watery nasal discharge after drug administration by intranasal route, which was transient [4].

The results of the sedation scores, ease of procedure scores, number of completed cases, and adverse effects noted in both groups were tabulated and statistically analyzed using SPSS version 11. Mean age was compared between the two groups using Student's t-test. The comparison of procedures between two groups was done by Chi-square test. Ordinal data obtained with the scoring scales were analyzed using the non-parametric Mann-Whitney U Test at the 95% significance level, to compare the effectiveness of the groups. $p < 0.05$ was considered as the level of statistical significance.

RESULTS

Baseline characteristics such as age, sex, and procedure distribution were comparable between the two groups (Table 1 and Fig. 1). Of the 246 children enrolled in the study, 75% children were in the age group between 6 months and 6 years and 57% of the total children underwent invasive procedures. The median interquartile range for age was 4 years.

Intranasal midazolam provided significantly better sedation scores (deeply sedated and unarousable) than IV midazolam for all procedures ($p < 0.001$) (Table 2). The sedation scores were better with intranasal midazolam, especially, in the younger age

Table 1: Baseline characteristics of study subjects

Baseline data	Intranasal midazolam n=123 (%)	Intravenous midazolam n=123 (%)
Mean age (years), SD*	3.3, 3.4	4.3, 3.5
Male	71 (57.7)	63 (51.2)
Female	52 (42.3)	60 (48.8)
Invasive procedures	73 (59.3)	69 (56.1)
Non-invasive procedures	50 (40.7)	54 (43.9)
Procedures		
Lumbar puncture	60 (48.8)	55 (44.7)
MRI	18 (14.6)	35 (28.5)
CT	23 (18.7)	7 (5.7)
Others	22 (17.9)	26 (21.1)

*: Standard deviation. Baseline characteristics such as age, sex, and procedure distribution were comparable between the two groups, CT: Computed tomography, MRI: Magnetic resonance imaging

Table 2: Comparison of sedation scores in total

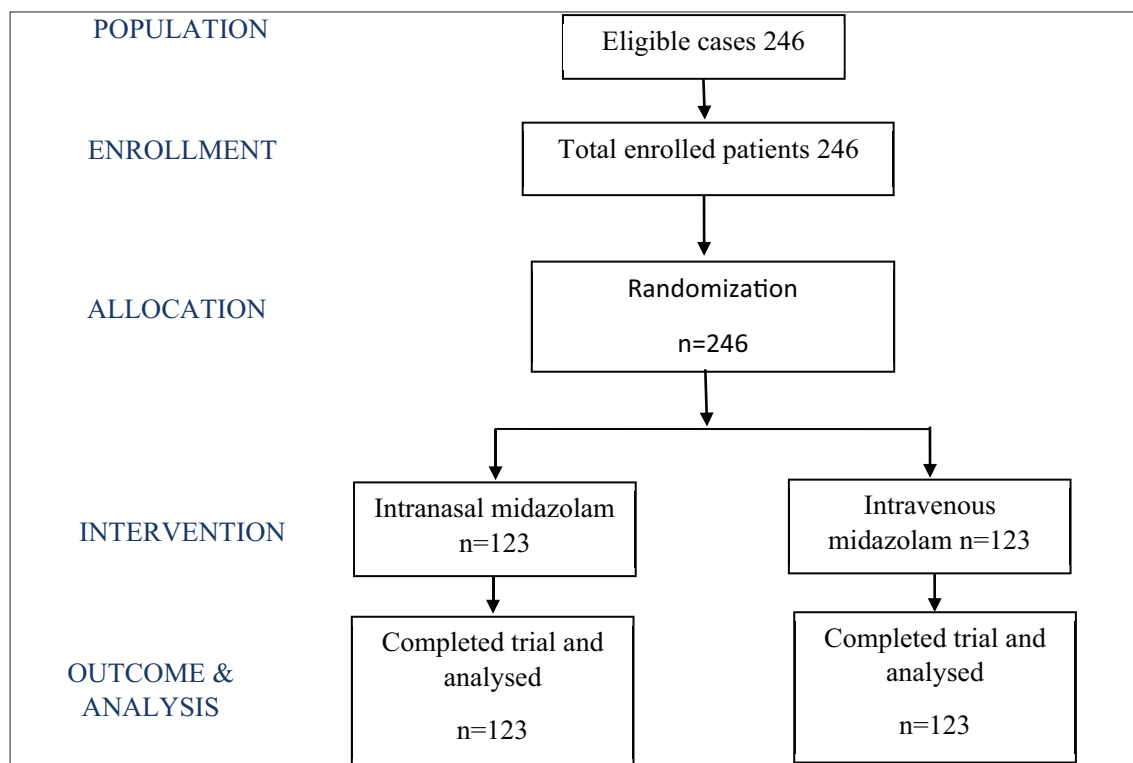
Sedation score	Intranasal n=123 (%)	Intravenous n=123 (%)	P
0=Awake alert	9 (7.3)	9 (7.3)	p<0.001
1=Minimally sedated	10 (8.1)	10 (8.1)	p<0.001
2=Moderately sedated	24 (19.5)	66 (53.7)	p<0.001
3=Deeply sedated	67 (54.5)	28 (22.8)	p<0.001
4=Unarousable	13 (10.6)	10 (8.1)	p<0.001

group of 6 months–6 years ($p<0.001$); while in the age group from 6 years to 12 years, IV midazolam achieved significantly better sedation scores ($p<0.001$) (Fig. 2).

Intranasal midazolam provided better ease of procedure scores compared to IV midazolam for all procedures ($p=0.026$). For invasive procedures, intranasal midazolam provided better ease of procedure scores compared to IV midazolam ($p=0.023$). For non-invasive procedures, although not statistically significant, intranasal midazolam provided better ease of procedure scores compared to IV midazolam. The ease of procedure scores for both invasive and non-invasive procedures were significantly better with intranasal midazolam in the age group between 6 months and 6 years while above 6 years to 12 years, scores were significantly better with IV midazolam ($p<0.001$) (Table 3).

For invasive procedures, both intranasal midazolam and IV midazolam showed comparable rates of successful procedure completion. For non-invasive procedures, even though intranasal midazolam showed a higher successful procedure completion rate when compared to IV midazolam, it was not found to be statistically significant.

The most commonly done procedures were lumbar puncture and CT scan for which intranasal midazolam gave higher successful procedure completion compared to IV midazolam although this was not statistically significant. Nasal irritation was

**Figure 1: Consort flowchart - trial profile of midazolam in procedural sedation**

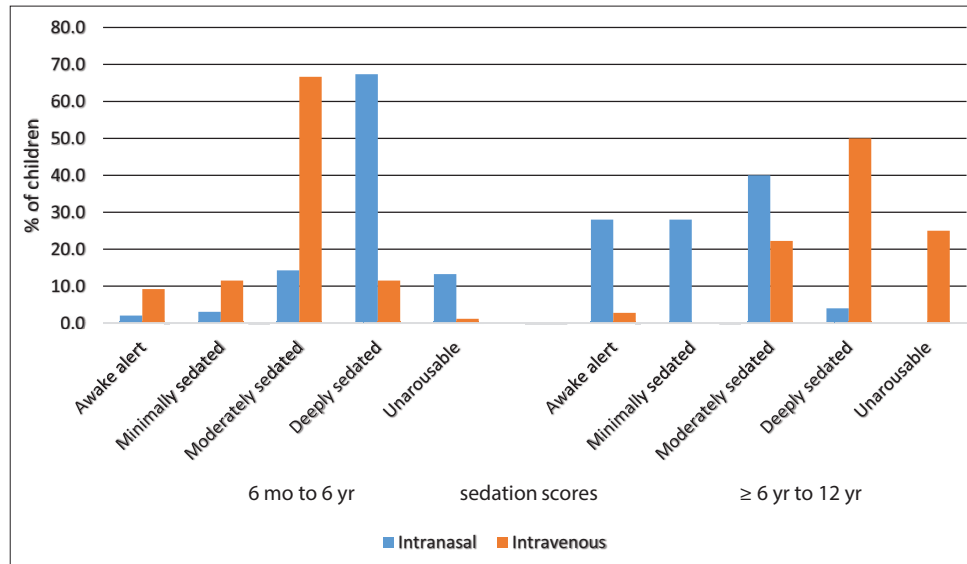


Figure 2: Comparison of sedation scores based on group and age

Table 3: Comparison of ease of procedure in different age groups for invasive and non-invasive procedures

Ease of procedure*	Invasive procedures				Non-invasive procedures			
	6 months–6 years n (%)		≥6 years–12 years n (%)		6 months–6 years n (%)		≥6 year–12 years n (%)	
	INM [#]	IVM [§]	INM [#]	IVM [§]	INM [#]	IVM [§]	INM [#]	IVM [§]
1	2 (3.2)	6 (11.5)	3 (30)	1 (5.9)	1 (2.9)	7 (20)	5 (33.3)	0 (0)
2	1 (1.6)	16 (30.8)	5 (50)	2 (11.8)	4 (11.4)	18 (51.4)	9 (60)	1 (5.3)
3	40 (63.5)	26 (50)	2 (20)	4 (23.5)	9 (25.7)	9 (25.7)	1 (6.7)	5 (26.3)
4	20 (31.7)	4 (7.7)	0 (0)	10 (58.8)	21 (60)	1 (2.9)	0 (0)	13 (68.4)
p	<0.001		<0.001		<0.001		<0.001	

*Ease of procedure scores 1: Violent movements; 2: Continuous movements; 3: Controllable movements; 4: No movements, no crying. INM[#]: Intranasal midazolam, IVM[§]: Intravenous midazolam

a common side effect with intranasal midazolam (p<0.001). No serious side effects were noted with intranasal midazolam.

DISCUSSION

This study compared the role of midazolam in pediatric procedural sedation when administered by two different routes, the standard established IV and the newer intranasal route. Notably, previous studies have compared different routes of administration of midazolam, but no study could be identified where intranasal midazolam was compared with IV midazolam for pediatric procedural sedation.

Our study showed that intranasal midazolam provided better sedation and ease of doing procedures for both invasive and non-invasive procedures compared to IV midazolam, especially in young children between 6 months and 6 years of age. In our study population of 246 children, procedural sedation was most commonly given for CT, lumbar puncture, and MRI. Although not statistically significant, for CT and lumbar puncture, intranasal midazolam showed higher procedure completion rates. Reduced efficacy for MRI may have been due to the longer duration of sedation required for completion of MRI. Importantly, intranasal midazolam showed a better safety profile compared to the IV route; nasal irritation being the only frequent side effect was

self-limited. There were limitations to our study. First, we did not measure the time of onset of sedation, duration of sedation, and the recovery time. Furthermore, we could not objectively measure the depth of sedation achieved. The intervention could not be blinded as the routes of drug administration were different; hence, observers could differentiate between the wide variability of response to the different routes.

Studies have been conducted in different parts of the world regarding the use of intranasal midazolam for minor invasive procedures such as laceration repair, abscess drainage, suturing, venepuncture, and dental procedures as well as for non-invasive procedures such as CT scans and audiometry. All these studies showed good degrees of sedation enabling procedures to be completed without additional drugs, which were reflected in our study as well [12-14]. Regression analysis in some earlier studies has also shown that in younger children, the onset of sedative effect of intranasal midazolam is quicker. Such variability among different age groups may be explained by age-related variation in the pharmacodynamics and pharmacokinetics of midazolam due to both genetic polymorphisms and maturation of drug metabolizing enzymes. Parents as well as doctors have shown high levels of satisfaction with the efficacy of intranasal midazolam [2]. Most of the other studies used intranasal midazolam at a higher dose of 0.4–0.5mg/kg [13,14]. At a higher dose, the duration of action of

intranasal midazolam would perhaps be longer. Some previous studies have also considered repeating the dose of intranasal midazolam till the desired level of sedation is achieved [14]. Thus, we found that intranasal midazolam can be safely administered in younger children for pediatric procedural sedation. This may be especially useful in resource-limited peripheral centers. Furthermore, it provided increased patient compliance, rendering aggressive physical retention unnecessary.

CONCLUSION

Intranasal midazolam is an effective procedural sedative; especially, in young children between 6 months and 6 years of age with no significant adverse effects. It will be particularly useful in resource-limited settings.

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