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ORIGINAL ARTICLE

Atomised intranasal midazolam spray as premedication in pediatric patients: comparison between two doses of 0.2 and 0.3 mg/kg

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Abstract
Purpose Midazolam premedication administered by the intranasal route is noninvasive with good bioavailability. Atomised intranasal midazolam spray ensures accurate drug dosage and better patient acceptability, with rapid onset of action and virtually complete absorption.
Methods Sixty pediatric patients scheduled for elective surgeries were administered atomised intranasal midazolam. Two doses of midazolam, of 0.2 and 0.3 mg/kg, were compared. Children were observed for achieving satisfactory sedation and separation scores, and face mask acceptance.
Results At 10 and 20 min of nasal administration, 70 and 76% of the children, respectively, in the 0.3 mg/kg dose group, while 40 and 63% of the children, respectively, in the 0.2 mg/kg group were adequately sedated. Similarly, at 10 and 20 min after administration, 66.6 and 73.3% of children, respectively, in the 0.3 mg/kg group, and 30 and 60% in the 0.2 mg/kg group were easily separated from their parents. With regard to face mask acceptance, 33.3% of patients in the 0.3 mg/kg group and 16.6% in the 0.2 mg/kg group accepted the mask easily.
Conclusion Atomised midazolam at 0.3 mg/kg is safe, and achieves faster sedation and better separation scores as compared to 0.2 mg/kg.

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Introduction

Fears of operation, injections, physicians, and the peculiar operation theatre environment where children are separated from their parents prior to anesthesia invariably produces traumatic experiences in the tender minds of young children [1]. Preanesthetic medication may decrease the adverse psychological and physiological sequelae of induction of anesthesia in a distressed child.

The ideal agent for premedication should have rapid onset, predictable duration of action and rapid recovery. The search for such agents still continues. Midazolam has almost all these properties; namely, sedative, hypnotic, and anxiolytic actions. Owing to its high mucosal vascularity, the intranasal route offers rapid and virtually complete absorption of midazolam within 1–2 h into the systemic circulation.

Traditionally, intranasal midazolam has been administered with a syringe, which reduces its bioavailability and increases discomfort. In most studies on intranasal midazolam, the undiluted, commercially available parenteral formulation containing 5 mg/ml midazolam has been used. Given as an intranasal atomised spray, instead of drops, the absorption of midazolam via the nasal mucosa has been reported to be virtually complete (83%), because little of the substance is swallowed [2]. This study was planned to assess the efficacy and safety of intranasal midazolam administered as a spray with a metered dose atomiser for premedication in pediatric patients. We compared two doses, 0.2 and 0.3 mg/kg, to find out the optimum dose avoiding any undesirable side effects.

Patients, materials, and methods

Institutional Ethics Committee approval was obtained, informed consent was taken from the parents of participating children, and assent from the children was obtained whenever applicable. Sixty patients of American Society of Anesthesiologists (ASA) physical status I and II in the age group of 1–12 years scheduled for elective surgeries were included.

Children with upper respiratory tract infections, those with systemic disorders (cardiac, neurological, renal, hepatic, coagulopathy) and those with local nasal pathology were excluded.

Preoperatively, intranasal midazolam was administered with an atomiser delivering 0.5 mg/puff (Insed®, Samarth Pharma, India) by spraying in alternate nostrils. Patients were allocated to 2 groups by computer generated randomisation:

- Group A ($n = 30$): received intranasal midazolam 0.2 mg/kg.
- Group B ($n = 30$): received intranasal midazolam 0.3 mg/kg.

Patient acceptability was graded as:

- Good: easily allowing administration of all doses.
- Fair: allowing administration with persuasion.
- Poor: not allowing administration or administration with restraint.

Cardiorespiratory monitoring (heart rate, respiratory rate, SpO_2) was done, and sedation and separation scores were noted at 10 and 20 min after drug administration by an observer blinded to the study drug dose.

The level of sedation was graded as shown in Table 1.

The separation score was graded as shown in Table 2.

Table 1 Level of sedation

Level of sedation	Score
Agitated, clinging to the parent/crying	1
Alert but anxious, not clinging to the parent, may whimper but not cry	2
Calm, sitting or lying comfortably with eyes open	3
Drowsy, eyes closed but responds to verbal or tactile stimulation	4
Asleep, not responding to minor stimulation	5

Table 2 Separation score

Criteria	Grade	Score
Patient unafraid, cooperative, asleep	Excellent	1
Slight fear or crying, quiet with reassurance	Good	2
Moderate fear, crying, quiet with reassurance	Fair	3
Crying, need for restraint	Poor	4

The scores were considered to be satisfactory when the sedation score achieved was ≥ 3 and the separation score was <3. Time for achieving a sedation score of ≥ 3 and a separation score of <3 was noted. After 20 min, patients were taken inside the operation theatre (OT). All observations were done by an independent observer who was blinded to the study.

General anesthesia was induced with sevoflurane in oxygen administered via mask. Acceptance of the sevoflurane face mask was graded as:

- Agitated: refusal to accept.
- Fair: accepting after persuasion.
- Good: easily accepting.

Subsequent anesthetic management was tailored to the requirement of the surgery. The incidence of side effects, if any (bradycardia, hypoventilation, desaturation, nasal discharge, excessive sedation, etc.) was noted and postoperative recovery was observed.

Demographic parameters were compared using Student's *t*-test. The percentage of patients with good acceptability of the nasal route of administration was calculated. The differences between the two groups in the proportions of patients achieving satisfactory sedation and separation scores at 10 and 20 minutes were compared by the χ^2 test. Numbers of patients accepting the sevoflurane face mask satisfactorily were compared between the two groups by the χ^2 test. A p value of <0.05 was considered significant.

Results

The demographic parameters cardiorespiratory (age, gender, weight) of the patients in the two groups were comparable (p value >0.05). In group A 36.7% of the patients had prior surgical experience, which was comparable to that of 33.4% in group B (Table 3).

As shown in Table 4, 23.4% of the patients had good acceptance of the nasal route, whereas 43.4% had fair acceptance, and 33.4% had poor acceptance of the nasal route.

Most of the patients in group B (70%) were adequately sedated at 10 min, as compared to 40% of the patients in group A, and the difference between them was statistically significant.

Similarly, separation from parents was faster in group B; 30% of the patients in group A achieved a separation score of <3 at 10 min, as compared to 66.67% in group B, and the difference between them was statistically highly significant ($p = 0.005$) (Table 5).

At 20 min, 63.3% of the patients in group A had reached a sedation score of ≥ 3, compared to 76.67% in group B,

Table 3 Demographic data

Parameters	Group A Midazolam 0.2 mg/kg ($n = 30$)	Group B Midazolam 0.3 mg/kg ($n = 30$)	p value[a]
Age (years)			
Mean ± SD	5.40 ± 3.22	4.23 ± 2.46	0.114
Gender			
Male	27 (90.0%)	28 (87.5%)	0.756
Female	03 (10.0%)	4 (12.5%)	
Weight (kg)			
Mean ± SD	10.12 ± 5.44	12.95 ± 4.10	0.823
Prior surgical experience (percentage of patients)	36.7	33.4	0.78

[a] By Student's t-test

$p > 0.05$, not significant

Table 4 Profile of acceptance of nasal route

Assessment	No. of patients ($n = 60$)	Percentage
Good	14	23.4
Fair	26	43.34
Poor	20	33.34

Table 5 Sedation and separation scores at 10 min

Groups, number of patients	A	B	p value[a]
Sedation score ≥3	12 (40%)	21 (70%)	0.04*
Separation score <3	9 (30%)	20 (66.67%)	0.005*

[a] By χ^2 test

*$p < 0.05$, significant

Table 6 Sedation and separation scores at 20 min

Groups, number of patients	A	B	p value[a]
Sedation score ≥3	19 (63.34%)	23 (76.67%)	0.1
Separation score <3	18 (60%)	22 (73.34%)	0.147

[a] By χ^2 test

$p > 0.05$, not significant

but the difference between them was not statistically significant ($p = 0.1$). Similarly, 60.0% of the patients in group A could be separated from their parents at 20 min, which was less than the percentage of patients in group B (73.34%), but the difference between them was not statistically significant ($p = 0.147$) (Table 6).

Regarding mask acceptance, 16.6% in group A had good mask acceptance compared to 33.3% in group B and the difference between the two groups was statistically significant ($p = 0.007$). Similarly, the percentage of patients in group A who were agitated with mask placement was 46.6%, which was more than that of group B (16.6%), and the difference between them was statistically significant. The percentage of patients fairly accepting face mask was comparable in the two groups (Table 7).

Table 7 Profile of mask acceptance

Assessment	Midazolam 0.2 mg/kg ($n = 30$) No. (%)	Midazolam 0.3 mg/kg ($n = 32$) No. (%)	p value[a]
Good	5 (16.6)	10 (33.3)	0.007*
Fair	11 (36.6)	15 (50)	0.36
Agitated	14 (46.6)	5 (16.6)	0.04*

[a] By χ^2 test

*$p < 0.05$, significant

Side effects

Side effects with the intranasal midazolam spray were transient nasal secretions (60%), conjunctival congestion (42%), and salivation (30%). None of the patients had any serious side effects such as desaturation (<92%), bradycardia, or delayed postoperative recovery.

Discussion

Separation from the parents to a totally unknown operating room environment with unknown faces makes the operative experience traumatic for young children. Psychological stress because of forced separation from parents can cause nightmares and postoperative behavioral abnormalities [3]. The main medical consequences include a stormy anesthetic induction, reduced defence against infections, and increased need for anesthetics in the intraoperative period and of analgesics in the postoperative period. Maladaptive behavioral responses such as general anxiety, nighttime crying, enuresis, and separation anxiety occur in up to 44% of children 2 weeks after an operation. Twenty percent of these children will continue to demonstrate negative behavior even 6 months after surgery [4].

In addition to behavioral manifestations, preoperative anxiety activates the human stress response, leading to increased serum cortisol, epinephrine, and natural killer cell activity [5]. Children are particularly vulnerable to the global surgical stress response because of their limited energy reserves, larger brain mass relative to body size, and obligatory glucose requirements [6].

Midazolam is a potent imidazo-benzodiazepine that has a rapid onset of action and an elimination half-life of about 2 h. Midazolam can be administered via intramuscular, intravenous, oral, rectal, and intranasal routes. The necessity for venous cannulation may be a disadvantage of intravenous administration. The intramuscular route is painful and children dislike needles. Rectal administration is associated with unpredictable absorption and discomfort to the child. The oral route, though now most popular, has low bioavailability due to the high first-pass metabolism of midazolam. The oral bioavailability of midazolam is only 15–27%, so a larger dose (0.5–1 mg kg^{-1}) is required and the peak effect is also delayed. Bitter taste is also a limiting factor and cause for rejection as well as low compliance. The sublingual route is more beneficial in this regard. But for desirable effect the drug must be held under the tongue for at least 30 s. This requires cooperation and that is difficult to achieve in preschool children.

The bioavailability of intranasal midazolam is very high, and there is no significant formation of a pharmacologically active metabolite [7]. Midazolam is rapidly absorbed from the highly vascular nasal mucosa directly into the systemic circulation and, therefore, has higher systemic availability than that for other routes of administration ($\approx$50%), with an onset of action within minutes, which was also confirmed in our study [8]. The rapid onset of action has also been explained by direct connections between the nasal mucosa and brain via the perineurium of the olfactory nerves [8]. Given by the intranasal route, midazolam bypasses the portal system and does not undergo the high hepatic first-pass elimination.

In most studies on intranasal midazolam, the undiluted, commercially available parenteral preservative-free formulation containing 5 mg/ml midazolam has been used with a syringe. This requires a relatively large volume, 1–2 ml in older children, which may account for the lacrimation, coughing, sneezing, burning, and general discomfort that is associated with intranasal midazolam [9]. In smaller children the titration of doses as per weight is a problem. A significant amount of the fluid can be swallowed and absorbed from the gastrointestinal tract, which decreases the bioavailability and therefore reduces efficacy [10]. Furthermore, treatment failure may occur due to poor technique in delivering an adequate volume of midazolam liquid.

In our study, intranasal midazolam was administered with a metered dose atomiser (Insed®) containing 50 metered doses. Each metered dose is 100 µl and delivers 0.5 mg midazolam. Unlike intranasal liquid applied with a syringe, the spray is not partly swallowed and absorption from the nasal mucosa is virtually complete. It has been surmised that the fine aerosol would allow greater contact with the absorbing surface and that such application would be better than the use of drops. Thus, with the use of spray, the potency of midazolam is improved, with faster onset of action than that seen with the use of drops. The advantages of intranasal midazolam spray (rapidity of onset, ease of administration, and avoidance of an IV injection) outweigh the single disadvantage of a moderate transient burning of the nasal mucosa.

Intranasal midazolam is irritant due to its acidic pH, leading to a low reported acceptance rate. This drawback can be overcome by the use of midazolam as a nasal spray or as a solution in cyclodextrin [11]. In our study, the acceptance rate was 67%. Many children above 5 years self-administered the drug. Similarly a 62% acceptance rate of intranasal midazolam was reported in preschool children in a study done by Vivarelli et al. [12]. In our study, for better results, the procedure was initially explained or demonstrated to the children and parents during preanesthetic assessment a day prior to the surgery. The children were pacified by explaining that it would act like a spray. Most of the patients would get mild nasal burning with the first dose. But we observed that with subsequent doses the older children actually became more calm and cooperative and accepted the repeated doses better, and some children self-administered the drug.

In our study, most of the children in group B (0.3 mg/kg) achieved a satisfactory sedation score at 10 min after administration. Our results are consistent with those of Yearly et al. [13], who studied intranasal midazolam for laceration repair. They found that 27% [confidence limits (CL) 6–60%] of children receiving 0.2 mg/kg midazolam had adequate sedation as compared with 80% (CL 52–95%) in the 0.3 mg/kg group at the end of 12 $\pm$ 4 min. However, contrary results were reported by Bhakta et al. [14]. They concluded that intranasal midazolam 0.2 mg/kg had a quicker onset than 0.3 mg/kg. They, however, administered the parenteral preparation with a syringe.

We found that the majority of children in group B could be easily separated from their parents at the end of 10 min. Similarly, face mask acceptance was better in group B as compared to group A. However, at 20 min of administration, both groups were comparable in terms of sedation and separation scores.

The most common side effects seen with intranasal midazolam were nasal secretions, conjunctival congestion, and salivation. No episode of desaturation or bradycardia was seen, nor was excessive sedation seen in any of the patients in the study. Thus, midazolam used intranasally in this dose range is quite safe [15].

There is some concern regarding the use of midazolam intranasally. Neurotoxicity has been reported in rabbits after the use of midazolam in a study [16]. This neurotoxicity was reported only after chronic administration of the drug by the intrathecal route. There is no major human study in this regard.

There are few reports of the use of atomised intranasal midazolam for premedication. Lane and Schunk [17] evaluated atomised intranasal midazolam for procedural sedation in a pediatric emergency unit ($n = 205$) in the dose range of 0.3–0.8 mg/kg and achieved a median sedation score of 2. Only 5.4% of their patients required additional sedation to complete the procedure [17].

Tschirch and Gopfert [18] compared intranasal midazolam with the oral route for claustrophobic patients undergoing magnetic resonance imaging (MRI), and in 97% of the patients in the intranasal group MRI could be successfully completed with better image quality, without relevant adverse effects.

Conclusion

We conclude that atomised intranasal midazolam spray is a safe and effective method of premedication in pediatric patients. Acceptability of the nasal route of drug delivery is fair. The atomised dose of 0.3 mg/kg achieves faster sedation and separation scores at 10 min as compared to 0.2 mg/kg. Face mask acceptance is better in patients receiving 0.3 mg/kg as compared to those receiving 0.2 mg/kg. No serious complications were encountered with either dose.

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