

ORIGINAL RESEARCH

Comparative Study of Oral and Intranasal Midazolam for Premedication In Children

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ABSTRACT

Introduction: Pre anesthetic management of children can be a challenge for anesthesiologist. Pre-operative anxiety can largely affect the smoothness of induction, emergence from anesthesia. The ideal premedicant in children would be available in a preparation that has good patient and parent acceptance, have a relatively rapid and reliable onset, free of cardiovascular or respiratory depression effects, and provide rapid recovery. Among benzodiazepines, midazolam is probably most widely used premedicant in children due to certain unique advantages, recently, the nasal mucosa has seriously emerged as a therapeutically viable route for the systemic drug delivery. The nasal delivery seems to be a favorable way to circumvent the obstacles for blood-brain barrier (BBB) allowing the direct drug delivery in the bio phase of central nervous system (CNS)-active compounds. The purpose of this study is to evaluate and compare the acceptability and efficacy of midazolam by oral and intra nasal routes as pre-medicants in children in alleviating anxiety and fear and to produce sedation.

Material and method: Fifty pediatric patients belonging to ASA physical status I and II within the age group of 2 – 10 years scheduled for surgeries were randomly taken, Children were divided in to two equal groups, twenty-five in each group. Group IN: Patients received nasal midazolam 0.3mg/kg. Group OM: Patients received oral midazolam 0.5mg/kg. All children were received standard identical general Anesthesia with similar drugs except study drugs. In both the groups we have observed and compared for A) Acceptability of drug by oral and intranasal spray B) Time of onset of sedation C) Ease of separation from parents.

Results: A) Acceptability was much better for oral route of administration than nasal. B) Time of onset of action was rapid with nasal route than oral with mean onset time of 7.61 minutes compared to oral mean onset time of 16.11 minutes.

Conclusion: Our study concludes that both oral and intranasal routes of midazolam as premedicant in children were equally effective and provided adequate sedation and the ease of separation of the child from parent. Oral midazolam was more acceptable and acceptability of intranasal midazolam was poor.

Keywords: Intranasal, midazolam, premedication, paediatric

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INTRODUCTION

Pre anesthetic management of children can be a challenge for anesthesiologist. Most of the children suffer from anxiety and apprehension when they are separated from their parents for induction of anesthesia.¹ The unfamiliar faces and the environment inside the operating room compound the sense of insecurity in the child.² Pre-operative anxiety can largely affect the smoothness of induction, emergence from anesthesia and also psychological and emotional state of the child in the remote future. The pre anesthetic visit marks the commencement of the anesthetic management of a patient. The goal of premedication of each patient must be individualized. Multiple techniques may be used to accomplish in children peri operatively. They include administration of sedative premedicant, parental presence during induction, administration of sweeteners, giving lollypops; facilitate music in operation theatre etc.,

Ideal premedication should have rapid onset and rapid recovery, predictable effect, good patient acceptance, no side effects. Various pharmacological agents like

Fentanyl, Ketamine, Midazolam, Clonidine, etc. were used in the past. Midazolam is probably most widely used premedicant in children due to certain unique advantages like high water solubility, high lipophilic nature at physiological pH, short duration of action, anterograde amnesic effect, and reduction of sympathetic response to surgical stress and rapid recovery. Midazolam has been used for preoperative sedation by various routes, intramuscular,^{3,4} rectal,⁵ oral⁶ and sublingual⁷ routes but each has its own advantages and disadvantages. Intranasal drug delivery is now recognized to be a useful and reliable alternative to oral and parenteral routes.⁸ Because of high vascularity onset of action is rapid and since it bypasses hepatic pre-systemic metabolism, enhancing drug bioavailability. On the other hand, intranasal administration also offers several practical advantages either from the viewpoint of patients (non-invasiveness, essentially painless, ease drug delivery and favorable tolerability profile) or pharmaceutical industry (unnecessary sterilization of nasal preparations). Hence, bearing in mind the intrinsic value of intranasal route to overcome patient compliance concerns together with its pharmacokinetic advantages, it appears to be an appropriate route for the treatment. Aim of the study was to evaluate and compare the acceptability and efficacy of midazolam by oral and intranasal routes as pre-medication in children in alleviating anxiety and fear and to produce sedation.

MATERIALS AND METHODS

After obtaining the institutional ethical committee approval and informed parent consent, fifty pediatric patients belonging to ASA (American society of anesthesiologists) physical status I and II within the age group of 2 – 10 years scheduled for surgeries are randomly taken and studied in Mahatma Gandhi Memorial Hospital in between JAN 2011 to FEB 2012. Informed and written consent was obtained from parents regarding the study. Surgeries include Hydrocele, Hernia, Circumcision, Laceration repair, Lymph node biopsy, rectal prolapse etc.

Study Design

A prospective, controlled, randomized study was conducted. Children are divided in to two equal groups, twenty-five in each group

Group IN: Patients received nasal midazolam 0.3mg/kg,⁹ 15 minutes before induction.

Nasal midazolam is available as metered dose containing 50 metered doses. Each

metered dose delivers 0.5 mg midazolam per dose. Calculated drug with regard to patient body weight is divided in to two equal aliquots and given in both nostrils. Drug is administered in the form of puff in each nostril by occluding the other nostril, so that drug wastage can be prevented.

Group OM: Patients received oral midazolam 0.5mg/kg,¹¹ 30 minutes before induction.

Oral MIDAZOLAM is supplied as a clear, pink syrup containing midazolam equivalent to 2 mg of midazolam/mL in bottles of 15 ml. All children were allowed to take clear fluids up to 2 hours before surgery. All children were planned to receive general Anesthesia with similar drugs. In both the groups we have observed and compared for

1. Acceptability of drug by oral and intranasal spray
2. Time of onset of sedation
3. Ease of separation from parents
4. Acceptability of the child for shifting to operation theatre

Inclusion criteria

1. ASA grades I and II.
2. Both sexes of pediatric patients.
3. Age range 2 to 10 years
4. Elective surgeries

Exclusion criteria

Includes ASA grade III and IV, age > 10 years, full stomach, Gastrointestinal disorders that might affect absorption of drug, known allergic reactions to midazolam, presence of otorhinolaryngeal diseases such as nasal polyp, rhinitis, nasal pathology, nasal trauma, children with respiratory and cardiac diseases, children having upper respiratory tract infection, children participating in another study, any condition that would compromise the safety of patient or interfere with interpretation of results and patients taking cytochrome P450 3A4 inhibitors or inducers are excluded from the study.

All children are monitored for acceptability of drug, time of onset of action of drug, time of onset of satisfactory sedation, cooperation at the time of separation from parents, cooperation at the time of mask application. Heart rate and respiratory rate were monitored during 1,2,3,4,5,10,20 minutes, Continuous oxygen saturation monitoring was done during administration of drug, intra operative and postoperatively

Acceptability of spray/syrup scale¹¹

1 = accepted readily

- 2 = accepted with grimace
 3 = accepted with verbal complaint
 4 = rejected entirely

Using a five-point sedation scale the degree of sedation was assessed.¹¹

1. Agitated: patient clinging to parents and/or crying.
2. Alert: patient is aware but not clinging to parent, may whimper but not cry.
3. Claim: Sitting or lying comfortably with spontaneous eye opening.
4. Drowsy: comfortable with eyes closed, but responding to minor stimulation.
5. Asleep: Eyes closed, arousable but does not respond to minor stimulation.

Four point Separation score was assessed

1. Patient un afraid, cooperative, asleep – Excellent
2. Slight fear or crying, quite with reassurance – Good
3. Moderate fear, crying not quite with reassurance – Fair
4. Crying, need for restraint – Poor

Patients were induced with oxygen (O₂), nitrous oxide (N₂O) and sevoflurane by face mask. Intravenous line was started. Pre medication with Inj. Atropine 20ug/kg I.V, Inj.Paracetamol 15mg/kg I.M, Inj.Ondansetron 0.1mg/kg I.V to a maximum of 4mg in children. Inj.Thiopentone sodium 3-5mg/kg I.V

Response to mask placement assessed by another scale.¹¹

1. Agitated: patient clinging to parents and/or crying and/or refuses mask.
2. Alert: patient is aware but not clinging to parent, may whimper but not cry and/or initially refuses mask, but accept after persuasion.
3. Calm: comfortable with spontaneous eye opening and accept mask.
4. Drowsy: comfortable with eyes closed, but responding to minor Stimuli and accept mask.
5. Asleep: Eyes closed, arousable but does not respond to minor stimulation and accept mask.

Thus, if a patient was drowsy but refused mask induction, then the patient was recorded on score 1 and not 4. Intubated with appropriate size cuffed or uncuffed endotracheal tube after administration of Inj. succinyl choline 2mg/kg and maintained with N₂O and O₂, Fentanyl, Sevoflurane (2%) and Inj. Atracurium 0.5mg/kg. Ventilation was controlled by Jackson-Ree's modification of Ayre's T-piece.

Residual neuromuscular paralysis was reversed at the end of operation by appropriate dose of neostigmine (50- 80 ug/kg) and glycopyrrolate (20ug/kg). Child is shifted to postoperative room for observation.

STATISTICAL ANALYSIS

The independent variable in the study was the choice of drug route (oral or intranasal).

The dependent variables in assessment of the effectiveness of each route were the sedation level, respiratory & hemodynamic parameters

ANALYSIS

- Descriptive statistics was used to describe the data.
- Inferential statistics such as 'chi-square' test (descriptive data), student "t" test (continuous data) and other appropriate statistical tests were used.

A two tailed p-value < 0.05 was considered to be significant

RESULTS

Of the fifty patients, twenty five patients belong to intranasal group (Received 0.3mg/kg of intranasal midazolam) and other twenty five patients belong to Oral group (Received 0.5 mg/kg of oral midazolam)

Both intranasal and oral midazolam groups are evaluated for Mean onset of time for satisfactory sedation, Mean sedation score and grading of sedation among individual children.

Both Intranasal and oral midazolam groups are compared for Respiratory rate variations during midazolam administration. It was compared during 1min, 2min, 3min,4min,5min,10min,20min. Its mean is taken in to consideration.

Intranasal and oral midazolam groups are compared for heart rate variations during midazolam administration. It was compared during 1min, 2min, 3min, 4min, 5min,10min,20min. Its mean is taken in to consideration.

Age, sex, weight distribution in both groups compar-

	Intranasal midazolam N=25		Oral Midazolam N=25		
	Number	%	Number	%	
Acceptability score	1	7	28%	14	56%
	2	8	32%	9	36%
	3	10	40%	2	8%
	4	0	0%	0	0%
Chi square = 7.725, P value = 0.021, p value < 0.005, significant for acceptability scale.					
Table-1: Acceptability Scale					

	Intranasal	Oral
Mean(min)	7.61	16.11
Standard Deviation	1.42	1.29
t value = 22.08, P value = < 0.0001, P value statistically significant.		
Table-2: Time of onset of action		

	Intranasal	Oral
Mean	9.44	17.25
Standard deviation	1.19	1.22
t value = 22.77, P value <0.001 statistically significant.		
Table-3: Mean time of satisfactory sedation		

	Intranasal midazolam N=25		Oral Midazolam N=25		
	Number	%	Number	%	
Mean sedation score	2	4	16.0%	4	16.0%
	3	9	36.0%	9	36.0%
	4	8	32.0%	7	28.0%
	5	4	16.0%	5	20.0%
Chi square = 0.178, P value = 0.981					
Table-4: Mean sedation score:					

	Intranasal	Oral
1 Minute	22.60	23.24
2 Minute	22.52	23.32
3 Minute	21.92	22.72
4 Minute	21.24	21.96
5 Minute	20.08	20.76
10 Minute	18.52	19.12
20 Minute	18.92	19.08
t value = 0.181, P value = 0.035		
Table-5: Respiratory rate		

	Intranasal	Oral
1 Minute	113.12	113.52
2 Minute	113.72	114.64
3 Minute	112.88	113.12
4 Minute	112.36	111.52
5 Minute	110.80	110.88
10 Minute	109.28	109.12
20 Minute	109.32	108.96
t value = 0.221, P value = 0.035		
Table-6: Heart rate		

ble. Mean cooperation at the time of separation from parents is comparable. Mean cooperation at the time of mask application is also comparable in both groups

DISCUSSION

We selected children in the age group of 2-10 years with both sexes equally distributed in both the groups, because this age group is most susceptible to the separation anxiety, since their understanding is limited. Most of the preschool children suffer from severe anxiety and apprehension before operation. This can largely affect the smooth conductance and emergence from anaesthesia. This can lead to development of maladaptive behavioral responses in later part of life.¹²

Benzodiazepines in current time has emerged as an ideal premedicant having all the desirable properties in this regard, of them midazolam is an ideal premedicant drug. More than 88% of anesthesiologists prescribe midazolam for premedication.

Midazolam is a benzodiazepine. It is highly lipid soluble in vivo. Its lipid solubility is pH dependent, being more in alkaline pH. It acts by binding to GABA receptors. It is metabolized by cytochrome P450 3A4. It has anxiolytic, amnestic, sedative, hypnotic, anticonvulsant & spinally mediated muscle relaxant property. It has been used by several routes such as oral, intranasal, parenteral and per rectal for premedication. Each has its own advantage and disadvantage. Intranasal midazolam use has been reported since 1988.¹⁴ The intranasal route is desirable because it obviates the need for IV access, avoids the pain of IM administration, and is easily accessible. Due to the rich vascular plexus of the nasal cavity and the communication to the subarachnoid space via the olfactory nerve and sheath, adequate cerebrospinal fluid levels can be achieved rapidly.

In this study we compared the acceptability and efficacy of intranasal midazolam and oral midazolam as premedicant in children who are posted for surgeries like hydrocele, hernia, laceration repair, lymph node biopsy etc. under general anesthesia.

Our study we found that oral midazolam acceptance rate was high because ease of administration, palatability. Nasal route acceptance rate was low. This could be due to - discomfort and nasopharyngeal irritation, watering of eyes, majority of children cried after nasal spray, bad taste, educating the child to take a deep breath when sprayed which is cumbersome, expulsion of drug due to sneezing because of irritation.

The initial acceptance in our study was limited by crying, but most of the children later accepted it after persuasion. Sometimes the children accepted when their

mother administered it. In our study, the acceptance rate was also low. Similar findings reported by other authors.^{7,9,14} There are several reports of satisfactory acceptance of nasal route.^{14,15}

Time of onset of action is quicker with intranasal midazolam (7.61+1.42 mins) when compared to oral midazolam (16.11+1.29 mins), which is significant (p value < 0.0001). These findings are similar to study conducted by PradiptaBhakta et al,⁹ Narendra P.L. et al,¹⁷ Khatavkaret al.¹⁸ Mean sedation score (Wilson grading) was compared in both the groups i.e. intranasal midazolam (3.48+0.96 grade), oral midazolam (3.52+1.00 grade) which is statistically not significant (p value= 0.8863). Mean cooperation at the time of separation from parents was compared, they were almost same in both the groups i.e. intranasal (1.72 +0.68), oral midazolam (1.68 +0.96) which is statistically not significant (p value= 0.8372). Our findings are comparable to other studies.^{9,18}

Mean cooperation at the time of mask application was compared in both the groups, almost equal i.e. intranasal (3.56+0.96), oral midazolam (3.96+0.91) which is statistically not significant (p value =0.8807).

Vital parameters such as heart rate, respiratory rate, SpO₂ were compared in both the groups without any significant changes compared to base line values (p values not significant in different time intervals). Similar findings reported by other authors.^{9,18}

CONCLUSION

From present study comparing oral and nasal midazolam for premedication in children Following conclusions are made:

- Oral and intranasal routes of midazolam as premedicant in children are equally effective and provide adequate sedation and that they ease separation of the child from parent, and all vital signs were stable throughout the procedures
- Oral midazolam is more readily acceptable. Acceptability of intranasal midazolam is poor many children had nasal discomfort and nasopharyngeal irritation, watering of eyes majority of children cried after nasal spray.

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