Original Research Article

Indian Journal of Anesthesia and Analgesia
May – June 2020; 7(3): 743–749
DOI: http://dx.doi.org/10.21088/ijaa.2349.8471.7320.14

An Observational Study To Compare The Efficacy of Oral and Intranasal Midazolam as Premedication in Children

Garima Gupta[1], Malini Mehta[2]

[1]3rd Year PG student, [2]Professor, Department of Anesthesiology, Smt. B.K. Shah Medical Institute & Research Centre, Sumandeep Vidyapeeth, Piparia, Waghodia, Vadodara, Gujarat 391760, India.

Abstract

Context: Preoperative period exposes to anxiety and stress to children and their parents resulting in emotional and psychological disturbances. To alleviate this midazolam has been found to be effective premedication. The purpose of this study is to compare the efficacy of oral versus nasal route and acceptance by children. *Aims:* To compare efficacy of oral and intranasal midazolam as premedication in children. *Settings and Design:* comparartive study, observational study in tertiary health care set up. *Methods and Material:* Fifty patients of age 2-5years of either gender of ASA I and II were assigned to two groups of 25 each undergoing elective surgeries of 1.5-2 hours under general anaesthesia. In Oral group - midazolam formulation 0.5 mg/ kg (preservative free plus sweetener) and in intranasal group - midazolam nasal spray as 0.2 mg/kg with half the dose in each nostril was administered 30minutes prior to surgery and were assessed for acceptance of drug, level of sedation 30minutes after premedication, behaviour at time of separation from parents and behaviour during mask acceptance at the time of induction which was by a standard intravenous technique. Intraoperatively children were monitored for heart rate and SpO_2. *Statistical analysis used:* unpaired student t test and p value < 0.05 is significant, Statistical Package for the Social Sciences SPSS Statistics for Windows, Version 20.0 software (IBM, Bengaluru, India), Microsoft word and excel have been used to generate graphs and tables. Mean, median and standard deviation have also been used. *Results:* Two routes were statistically insignificant regarding acceptance of drug, sedation after 30min and behavior during parental separation, though oral was slightly better than nasal clinically. Mask acceptance of oral midazolam was better than nasal and significant. *Conclusions:* Both are safe with oral is better than nasal route for premedication in children due to significant mask acceptance.

Keywords: Intranasal spray, midazolam, oral syrup

How to cite this article:
Garima Gupta, Malini Mehta. An Observational Study to Compare The Efficacy of Oral and Intranasal Midazolam as Premedication in Children. Indian J Anesth Analg. 2020;7(3):743–749.

Introduction

The preoperative period can be a stressful time for children and their parent.[1] It has been found that preoperative anxiety of parental separation, overall environment of the hospital and fear of experiencing pain predisposes children to behavioural changes, eating disorder, enuresis, nightmares and sleep disturbances postoperatively.Midazolam is the most common premedication in children and is reportedly safe and effective both at separation and induction of anaesthesia.[2] In children, intravenous (IV) and (intramuscular) i.m. route causes anxiety, therefore, oral or intranasal administration of a sedative agent is preferred for premedication

Corresponding Author: **Malini Mehta**, Professor, Department of Anesthesiology, Smt. B.K. Shah Medical Institute & Research Centre, Sumandeep Vidyapeeth, Piparia, Waghodia, Vadodara, Gujarat 391760, India.
E-mail: ggarima1192@gmail.com
Received on 13.01.2020, **Accepted on** 29.02.2020

Formulas

This Calculator Uses the following Formulas to Compute Sample Size and Power,respectively

$$n_A = kn_B \text{ and } n_B = \left(\frac{p_A(1-p_A)}{k} + p_B(1-p_B)\right)\left(\frac{z_{1-\alpha/2} + z_{1-\beta}}{p_A - p_B}\right)^2$$

$$1-\beta = \Phi\left(z - z_{1-\alpha/2}\right) + \Phi\left(-z - z_{1-\alpha/2}\right), \quad z = \frac{pA - pB}{\sqrt{\frac{p_A(1-p_A)}{n_A} \quad \frac{p_B(1-p_B)}{n_B}}}$$

where

K=nA/nB is the Matching Ratio
Φ is the Standard Normal Distribution Function
Φ^{-1} is the Standard Normal quantile Function
α is Type I error
β is Type II error Meaning 1 - β is Power

Materials and Methods

After obtaining approval of the institutional ethical committee, fifty patients were enrolled who underwent elective surgeries under general anesthesia. Informed and written consent was taken from parents. The sample size was determined by above formula.

They were divided into 2 groups.

Group PO (Per oral) was given oral midazolam formulation (parenteral midazolam 5mg/ml preservative free plus sweetener) in the dose of 0.5 mg/kg.

Group IN (Intranasal) was given midazolam intranasal spray in the total dose of 0.2 mg/kg with half the dose administered in each nostril (through metered doses inhaler delivering 1.25mg per spray and containing total 16 metered doses).

Patients below 2 years and above 5 years, with ASA III or more, with known allergy, sensitivity or any other form of reaction to benzodiazepines, taking other sedatives,with upper respiratory tract infections and with nasal pathology, on anticonvulsant therapy, scheduled for neurosurgical procedures and with mental retardation were excluded from the study.

After detailed pre-anaesthetic check-up of all the children posted for planned surgery, they were kept nil by mouth for about 6 hours before surgery and clear fluids were permitted up to 3hrs prior to the procedure. The children were kept in a silent, undisturbed area along with the parent. Pulse rate and oxygen saturation were monitored and recorded.

The anesthesiologist administered the study drug to the child orally to 25 children and intranasaly to 25 children 30 minutes prior to surgery.

The Following parameters were assessed to find the efficacy of premedication

1. Acceptance of drug
2. Level of sedation 30minutes after premedication.
3. Behaviour at the time of separation from parents.
4. Behaviour during mask acceptance

Acceptance of the drug was assessed by using the compliance score by Parnis et al.[3]

1. Poor – Refuses to accept medicine
2. Moderate – accepts medicine with (persuasion) difficulty
3. Good – accepted medicine without complaint

Level of sedation was assessed at 30 minutes after the administration of study drug by four point sedation score by Filos et al.[4]

1. spontaneous eye opening (awake and alert)
2. Drowsy, responsive to verbal stimuli
3. Drowsy, arousable to physical stimuli
4. Unresponsive

The behaviour at the time of separation from parents was assessed when the child was separated from parents to shift to operating room using the separation score by Pandit et al.[5]

1. Excellent - happily separated
2. Good - separated without crying
3. Fair - separated with crying

4. Poor - need for restraint

After shifting to operation theatre, they were premedicated with inj. glycopyrrolate 0.004mg/kg IV and inj. ondansetron 0.1 mg/kg IV. Child was preoxygenated with face mask with 100% oxygen for 3 minutes.

Acceptance of face mask was graded on a four point score[6]

1. Poor – afraid, combative, crying
2. Fair – moderate fear of mask, not easily calmed
3. Good – slight fear of mask, easily calmed
4. Excellent – unafraid, cooperative, accepts mask easily

Anesthesia was induced by a standard technique of intravenous induction. Endotracheal intubation with appropriate endotracheal tube was done after giving inj. succinylcholine (2mg/kg) IV and was maintained on O_2, N_2O, sevoflurane and atracurium. Intraoperatively children were monitored for heart rate, SpO_2 every 15 minutes till end of surgery. At the end of surgery neuromuscular blockade was reversed with inj. Neostigmine (0.05mg/kg) and inj. Glycopyrolate (0.008mg/kg) IV. Extubated was done after fulfilling the recovery criteria and child was shifted to recovery room. Postoperatively they were watched upto 6 hours for any complication.

Data collected was analysed using unpaired student t test, p value < 0.05 is significant, Statistical Package for the Social Sciences SPSS Statistics for Windows, Version 20.0 software (IBM, Bengaluru, India). Microsoft word and excel have been used to generate graphs and tables. Mean, median and standard deviation have also been used.

Results

Demographically the distribution of patients with respect to gender, age, weight, height and ASA grading was comparable amongst both the groups. (p value > 0.05) (Table 1).

The overall difference between the groups was statistically insignificant. (p = 0.865) 3 children who spitted drug in oral route were not included in study (Table 6).

Table 1. Gender distribution between the groups

Gender	Oral	Nasal	Total
	Number of patients (%)	Number of patients (%)	
Male	17(68%)	15(60%)	32
Female	8(32%)	10(40%)	18
Total	25(100%)	25(100%)	50

Table 2. Age distribution between the groups

Group	Mean Age	Sd
Oral	3.92	1.28
Nasal	3.90	1.25

Table 3. Weight distribution between the groups

Group	Median Weight (kg)	Mean Weight	SD	p value
Oral	8.00	9.08	1.79	0.835
Nasal	9.00	8.25	2.12	

Table 4. Height distribution between the groups

Group	Mean Height (Cm)	SD	p value
Oral	109.89	6.98	0.985
Nasal	110.54	8.54	

Table 5. American Society of Anaesthesiologists (ASA) grade distribution between the groups

Group	ASA I	ASA II
Oral	17.00	19.00
Nasal	8.00	6.00
Total	25.00	25.00

Table 6. Compliance scores between the groupsTable 6

Score 1	Oral Group	Nasal Group	P value
	Number of patients (%)	Number of patients (%)	
Poor	0 (0%)	0(0%)	-
Moderate	18(72%)	19(76%)	0.869
Good	7(28%)	6(24%)	0.781
Total	25(100%)	25(100%)	0.865

Sixteen percent (16%) in nasal group as compared to only 8% in oral group were awake and alert, therefore oral group was clinically better although statistically not significant (p > 0.05) (Table 7).

Table 7. Level of sedation scores (four point sedation score by Filos et al) between the groups

Score 2	Oral Group	Nasal Group	p value
	Number of patients (%)	Number of patients (%)	
1 (awake & alert)	2(8%)	4(16%)	0.414
2 (respond to verbal stimuli)	3(12%)	3(12%)	1.0
3 (respond to physical stimuli)	17(68%)	16(64%)	0.862
4 (unresponsive)	3(12%)	2(8%)	0.655
Total	25(100%)	25(100%)	0.537

Table 8. Separation score between the groups

Score 3	Oral Group	Nasal Group	*p* value
	Number of patients (%)	Number of patients (%)	
1 (excellent)	6(24%)	3(12%)	0.317
2 (good)	14(56%)	13(52%)	0.847
3 (fair)	5(20%)	9(36%)	0.285
4 (poor)	0	0	-
Total	25(100%)	25(100%)	0.336

None of the patients were required to be restrained (score 4). The overall difference between the groups was statistically not significant (p =0.336) (Table 8).

Table 9. Behaviour during mask acceptance between the groups (Four Point Score)

Score 4	Group		*p* value
	Number of patients in Oral (%)	Number of patients in Nasal (%)	
1 (poor)	1(4%)	7(28%)	0.034
2 (fair)	5(20%)	9(36%)	0.285
3 (good)	17(68%)	9(36%)	0.117
4 (excellent)	2(8%)	1(4%)	0.564
Total	25(100%)	25(100%)	0.038

Good to excellent mask acceptance score was observed in 76% children in oral group as compared to only 40% in nasal group. The overall difference between the groups was statistically significant (p= 0.038) (Table 9).

Discussion

Children are at risk of various behavioural problems like nightmares, emotional stress due to hospitalization, while undergoing surgical operations and during anaesthesia induction[7] therefore, adequate premedication is required for successful management of anaesthesia in the children. An ideal premedication calms children down, decreases their fear, makes induction for anaesthesia smooth and even rapid recovery.

Midazolam which is a water soluble benzodiazepine has emerged as a widely used pre medication due its fast onset of action and short elimination half life.[8] Some studies suggest effective route for premedication with midazolam to be intramuscular (Taylor et al., 1986), rectal (Maurice et al., 1986), intranasal (Hartgraves and Primosch 1994) and oral (Cox et al., 2006). Kogan et al. (2002) and Yildririum et al. (2006)[9] found no difference between oral and intranasal route. Hence, we have used oral and intransal route in this study.

We have selected pediatric patients of age group 2-5 years because they face maximum risk of separation anxiety as they are not able to understand things around them.[7]

Mac Milan et al. also studied the efficacy of different doses of oral midazolam on 80 children of age 1-6 years and concluded that 0.5mg/kg dose is safe and effective with no additional benefits provided by 0.75mg/kg and 1mg/kg, in fact they may cause more side effects like loss of balance, head control, blurred visions and dysphoric reactions.[10]

Hence, in our study we have used oral midazolam in the dose of 0.5mg/kg given with a sweetener as the drug is bitter in taste. Maximum 5ml was given as it is less than residual gastric volume limit.[8]

Davis PJ et al.[11] (1995) conducted a study on 88 children of 10-36 months and found that both the doses of 0.2 mg/kg and 0.3mg/kg of intranasal midazolam are similar in sedation, parental separation and induction. Pradipta Bhakta et al.[12] (2007) found that 0.2mg/kg of intranasal midazolam produce effective sedation and no added advantage is provided by 0.3mg/kg.

Hence we have selected 0.2mg/kg dose of intranasal midazolam spray in our study.

In our study we found that the compliance score (drug acceptability) was similar for both the groups (p value 0.865). R K Verma et al.[13] (2012) and Raval and Gunga[14] (2014) also found drug acceptance in oral route to be comparable with nasal ($p > 0.05$).

Nainegali et al.[15] (2016) found drug acceptance to be significantly better in oral group 90.9% than nasal 12.1% ($p < 0.001$) and Devulapalli et al.[16] (2015) concluded that acceptability of drug was much better in oral route compared to nasal route (92% Versus 60%) ($p = 0.021$).

Better acceptability of oral route could be due to the ease of administration and palatability of midazolam syrup as it is cumbersome to educate the child regarding a deep breath and sniffing position when sprayed in nose and also due to nasopharyngeal irritation.

Nasopharyngeal irritation was seen in 8% patients in the form of sneezing in our study. Deshmukh et al.[17] (2006) found 40%, Bhakta P et al.[12] (2007) observed 45%, Ramesh Koppal et al.[18] (2011) found 10% and R Abhishek et al.[19] (2015) found 10% patients having nasal irritation in the form of rubbing, sneezing, watering and lacrimation with no redness or ulcer. having nasal irritation. Raval and Gunga[14] (2014) also reported 20% patients with nasal irritation and sneezing in nasal group and

attribute it to acidic preparation of midazolam (pH = 3.34). 3 patients spitted the drug out and were not included in the study.

Kamar et al.[9] (2014) and Jayshree and Milin[8] (2017) observed excellent sedation at 30 minutes after premedication with midazolam. Therefore we have also compared sedation score at 30 minutes after its administration.

Our study showed that sedation score was comparable amongst the two groups (p = 0.537). Only 8% were awake and alert in oral as compared to 16% in nasal, making oral midazolam syrup better sedative agent clinically than nasal spray in the present study.

A study by Lee-kim et al. (2004) demonstrated that there is no statistical difference between the oral and intra nasal midazolam group for overall behaviour however intra nasal subjects showed more movements and decreased sleep, therefore less sedation.[9] Sunny Alex et al.[20] (2008), Verma RK et al.[13] (2012) found 53.33% in nasal versus 43.3% in oral, R Abhishek et al[19] (2015) and P V Deshmukh et al.[17] in 2016 also reported sedation score to be similar between the two groups at 30 min. Devulapalli et al.[16] (2015) evaluated both the groups for sedation and found mean sedation score (Wilson grading) higher in oral than nasal but statistically not significant.

Ramesh Koppal et al.[18] (2011) observed sedation was better through trans nasal route at 30 min with p = 0.003 which could be due to the higher dose of 0.5mg/kg intranasaly. Raval and Gunga[14] (2014) evaluated oral and trans nasal midazolam and concluded that sedation was higher in trans nasal group. Nainegali et al.[15] (2016) reported sedation better through trans nasal route (p <0.001) at 20 minutes which may have been due to the higher dose (0.4 mg/kg) and with the use of an atomizer for delivering the drug. Mehdi et al.[21] (2019) also reported sedation score to be significantly higher in intranasal group as compared to oral they confer this to high bioavailability (55-83%) and better and rapid absorption through nasal mucosa (p < 0.001).

Drug gets absorbed nasally better due to high vascularity of nasal mucosa as compared orally due to low bioavailability.[7] This rapid absorption avoids the high first-pass metabolism of midazolam. But there can be problem with volume retention in nasal cavity and effective dose availability which is removed by using concentrated nasal spray[22].

Since midazolam is a benzodiapene, it binds to $GABA_A$ receptor triggering chloride channel and hyperpolarization of cells thus causing resistance to excitation of neuron, hence producing sedation.

In the present study *parental separation* score was good to excellent 80% of children in oral group as compared to 64% in nasal group. The overall difference was statistically insignificant. (p = 0.336)

Sunny Alex et al.[20] (2008), Raval and Gunga[14] (2014), Devulapalli et al.[16] (2015) and P V Deshmukh et al.[17] found separation from parents at 30min to be comparable between the two groups (p>0.05). Ramesh Koppal et al.[18] (2011) found equally effective parental separation by both the routes (weakly significant p value of 0.03). R Abhishek et al.[19] (2015) found satisfactory parental separation score in nasal group more than oral group (86% versus 83%) (p = 0.616). Nainegali et al.[15] (2016) also reported good parental separation in nasal group (93.9%) but statistically insignificant.

Kamar et al.[9] found parental separation statistically significantly better in oral group as compared to nasal group (p = 0.046).

In the operation theatre the acceptance of mask (four point score) was good to excellent in 76% patients in oral group as compared to only 40% in nasal group. The overall difference was statistically significant (p value = 0.038).

Mehdi et al.[21] (2019) also found ease of induction higher in oral group in contrast to nasal group (p < 0.001).

Sunny Alex et al.[20] (2008), Devulapalli et al.[16] (2015) and R Abhishek et al.[19] (2015) found the mask acceptance to be similar between two groups (p value > 0.05). R K Verma et al.[13] (2012) reported ease of induction score higher in nasal group compared to oral group (80% vs 43.3%) (p < 0.05). PV Deshmukh et al.[17] (2016) found 87% patients in intranasal group with satisfactory mask acceptance as compared to 77% in oral group (p > 0.05).

Lower scores in nasal route could be due to difficulty in positioning while spraying in nostrils and also due to hydrophilic vehicle and acidic pH as better absorption may occur with more concentration of midazolam in a lipophilic vehicle and non-acidic neutral pH.[13]

In most studies, the undiluted, commercially available parenteral fluid containing 5 mg/ml midazolam has been used intranasaly which has accounted for lacrimation, burning and general discomfort but this is not the case with intranasal midazolam spray, which we have used in this study.

Heart rate and SpO_2 were comparable between

the groups at any time intervals during the entire study period. No complications like nausea, vomiting, bradycardia and respiratory depression were recorded during the study in any patients as also observed in the studies compared.

Oral route is better to nasal route for premedication with midazolam in children between ages of 2-5 years as it produces satisfactory ease of induction by successful mask acceptance.

Limitations of our study included small sample size, drug administration facilitated by parent and not able to monitor the onset of sedation which could have some effect on efficacy.

Conclusion

From the present study it is concluded that oral midazolam formulation (0.5mg/kg) and commercially available intranasal spray (0.2mg/kg) are relatively safe as premedication in the pediatric age group of 2-5 years. Oral midazolam is clinically better in terms of drug acceptance, sedation and parental separations but statistically not significant and mask acceptance is statistically significantly better with oral midazolam thereby, making oral midazolam formulation more effective premedication than intranasal spray.

Financial support: Nil

Conflicts of interest: Nil

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