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Effects of intranasal midazolam as premedication in paediatric anaesthesia. A clinical study

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Key points

Midazolam is a short acting, water soluble benzodiazepine which allays anxiety and is particularly useful in children who suffer considerable emotional stress in the operative environment. The nasal route is convenient, non painful and has good absorption rate.

Abstract

Introduction

Operation theatre environment, surgery and anaesthesia cause stress and anxiety. This can cause psychological disturbances, especially in children. Sedative and anxiolytic premedication have been used to prevent such outcomes. Intranasal route is least traumatic and easily accepted. Intranasal midazolam has been used for premedication in children.

Objectives

This study was undertaken to evaluate the efficacy of intranasal midazolam as premedication with regard to degree of sedation, ease of parental separation, response to venepuncture, response to induction, post anaesthesia recovery characteristics and side effects if any.

Materials and Methods

Sixty patients, ASA grade I and II, between 3-6 years of age group of either sex posted for elective surgery under general anaesthesia, randomly divided into 2 groups of 30 patients each were studied. The response to parental separation, venepuncture and mask placement, post anaesthesia recovery characteristics and side effects were recorded. ECG, NIBP, HR, SpO2 were monitored.

Results

In midazolam group, 80% of the children were satisfactorily sedated at 5 min after administration of the drug whereas in normal saline group only 50% were satisfactorily sedated. In midazolam group, at 10 mins, parental separation in 90% children was much easier compared to 13.3% in NS group. Response to venepuncture was more satisfactory in midazolam group than normal saline. Response to mask placement was also good in midazolam group. There was no undue prolongation of recovery time in both the groups.

Conclusions

The study shows that intranasal midazolam 0.2 mg/kg administered 15 min prior to induction in children of 3-6 years of age produces satisfactory level of sedation, ease of separation from parents, decreased discomfort associated with venepuncture with better mask acceptance. No significant hemodynamic changes occurred throughout the procedure.

Keywords: Paediatric Anaesthesia, Intranasal Premedication, Midazolam.

Introduction

Surgery and Anaesthesia induce considerable emotional stress upon children.[1] Age, parental anxiety level, previous hospital experiences and type of surgery are factors that can influence a child's anxiety level and psychological well being.[2] Preoperative anxiety stimulates sympathetic, parasympathetic and endocrine system leading to an increase in heart rate, blood pressure and cardiac excitability. Children aged two to five years are especially vulnerable to this problem, since their understanding is limited.[3] Preoperative anxiety in children can lead to post operative maladaptive behaviours in the form of eating problems, bad dreams, enuresis, increased fear of doctors and hospitals. Preoperative anxiety in unpremedicated children is two fold.[4,5] Hence all paediatric patients need to be premedicated in order to decrease preoperative anxiety.

The non-pharmacological means in the form of friendly visit by the anaesthesiologist to establish rapport with the child, parental presence inside the operation theatre help to minimize the child's anxiety, but may not be fully effective. Pharmacological agents as sedative premedication is more effective.[6]

The premedicant should be pleasant, acceptable, rapid and reliable in onset with little adverse effects. The commonly used premedicants in children are benzodiazepines like Midazolam, Opioids like Fentanyl and sufentanil, phencyclidine derivative like Ketamine, short acting barbiturate Pentobarbital and alpha 2 adrenoreceptor agonist like Clonidine , each with points in favour and against. Opioid premedication can result in unpleasant dysphoria, increased incidence of preoperative and postoperative vomiting and significant respiratory depression. Midazolam is a potent imidazobenzodiazepine which possesses typical benzodiazepine properties namely hypnotic, amnestic, anticonvulsant, anxiolytic activity and is a near ideal sedative premedicant lacking analgesic property. It is rapidly absorbed and short acting, having an elimination half-life of about 2 hours. It can be administered by oral, rectal, intravenous, intramuscular and sublingual routes but each route has disadvantages. The intramuscular route is painful and children dislike the needle most. The rectal administration is associated with unpredictable absorption and discomfort to the child. Oral route has got low bioavailabilty due to high first pass metabolism and also bitter taste which is a limiting factor and it is a cause for rejection. In sublingual route, the drug must be held under the tongue for at least thirty seconds but co-operation is difficult to achieve in children. Owing to its high mucosal vascularity, pre-anaesthetic medication administered nasally has rapid and reliable onset of action. Avoidance of painful injection, ease of administration has made it a convenient way to pre-medicate children.

This study was designed to evaluate the efficacy of intranasal Midazolam in children as premedication.

Materials and Methods

After ethical committee clearance and obtaining informed consent from the parents, a total of 60 patients aged between 3-6 years, of either sex belonging to ASA Grade I and II, posted for elective surgeries were selected randomly and prospective study was done by dividing them into 2 groups of thirty patients each (Table 1a, 1b). The study was conducted during a period starting from 1st May 2013 to 30th April 2014. Drugs were divided into two aliquots and given in both the nostrils using a 2 ml syringe from which the needle has been removed. With the children sitting on the parents' lap, premedicant was administered 15 min prior to induction.

Group S: Children received 0.04 ml/kg of Normal Saline. Group M: Children received 0.2 mg/kg of intranasal midazolam preservative free injectable preparation and the concentration of the drug was 5 mg/ml.

Patients with rhino pharyngitis, nasal pathology, h/o allergy to the study drug, on treatment with theophylline, H2 receptor antagonists, history of prematurity or chronic illness, h/o developmental delay, cardio-respiratory disorders, hepatic and renal disease, ASA Grade III and above were excluded from the study. A thorough general physical examination was done and potential intra-

venous cannulation sites were noted. All routine investigations were done. Parents were also instructed to keep the children fasting for 4-6 hours depending on the age.

All the resuscitation and monitoring equipments were kept ready before administration of pre-medication, for management of any adverse reactions.

On the morning of surgery, Baseline Heart Rate (HR), Respiratory Rate (RR), Oxygen Saturation (SpO2), Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) were recorded using Dragger mutipara monitor before administration of the drug (Table 2). With the children sitting on the parents' lap, the saline/ drug was administered drop by drop by the anaesthesiologist with the help of a 2ml syringe to avoid wastage through anterior and posterior nostril. Parenteral preparation was used and the concentration was 5mg/ml.

At 5 mins after administration of the drug/Saline the degree of sedation (Table 3) was noted and HR, RR, SpO2, NIBP were noted (Table 2a) every 5 min till the completion of surgery. At 10 min, children were separated from the parents and shifted to the operation theatre. Reaction to separation from parents was assessed (Table 4). IV canulation attempted and reaction to Venepuncture recorded (Table 5) and appropriate monitors were connected (precordial stethoscope, electrocardiogram, NIBP, pulse oximeter).

At 15 min, general anaesthesia was induced using N2O, oxygen, halothane and response to mask placement assessed and recorded (Table 6). The inspired halothane concentration was adjusted to the patient's clinical needs. IV fluids calculated and administered based on the NPO period and degree of surgical trauma. Patients requiring intubation were intubated with succinylcholine 1.5mg/kg IV and maintained with O2, N2O, Halothane and Inj. Vecuronium 0.08mg/kg IV and IPPV. Patients with spontaneous respiration were maintained with O2, N2O and Halothane on face mask andInj. Fentanyl 1.5 mcg/kg IV was administered for analgesia.

At the end of surgery depending on the technique (mask/IPPV) all the inhalational anaesthetic agents were discontinued and O2 administered through face mask and children allowed to awaken. Patients in whom relaxants were used, residual effect of relaxants were reversed with Neostigmine 50 mcg/kg and glycopyrrolate 10 mcg/kg IV, extubation done after thorough suctioning of the oral cavity and return of protective reflexes. Children shifted to PACU after confirmation of adequate clinical recovery. Closed observation was done for respiratory depression.

Postoperative recovery score was assessed at 10, 20, 30 min on a ten point scale using the following parameters-colour, airway, respiration, level of consciousness and movement of all the 4 limbs (Table 7) and were followed up for 24 hours for side effects such as Watering of eyes, bad taste, nasal congestion/nasopharyngeal irritation, blurred vision and nausea and vomiting if any were noted.

The observed data was subjected to statistical analysis using Chi-Square test and Student t test (independent) using software namely SPSS 16.0 and WINKS SDA 6.

Results

In midazolam group, minimum HR was 104 and in Saline group, minimum HR was 124 and maximum was 156 in both the groups with no significant changes in the SBP and DBP in both the groups. The SpO2 in midazolam group was slightly decreased after 5 min but was within acceptable range and it was 100% after induction while there were no significant changes in the NS group. It was observed that in midazolam group, at 5 min there was a decrease in respiratory rate from 30 to 22/min over 15 min. (Table 2b). The sedation level at 5 min was better in midazolam group with majority 25 (83.3%) of the children adequately sedated (ie.alert, calm, drowsy, asleep) as compared to that in normal saline group, where majority 15 (50%) of the children remain agitated ($p < 0.05$). Separation from parents was much easier in Midazolam group where 27 (90%) children were separated easily from parents (grading being

excellent and good) as compared to normal saline group where 26 (86.6%) children separation was not satisfactory (grading being fairand poor) needed further convincing and persuation ($p < 0.05$).

In Midazolam group, 21 (70%) children responded satisfactorily to venepuncture whereas in Normal Saline group, only 7 (23.3%) children responded satisfactorily ($p < 0.05$). Majority of the children in midazolam group 13(43.3%) appeared calm at the time of mask placement while majority of children 15(50.0%) in normal saline group appeared agitated ($p<0.05$). At 10 min, the minimum and maximum score in midazolam and normal saline group was 7 and 9 respectively. At 20 min, the minimum score in midazolam group was 8 and in normal saline group was 9, whereas maximum score was 10 in both the groups. At 30 min, the minimum and maximum score in midazolam and normal saline group was 10.

The mean duration of surgery in midazolam group was 63.50 min and in normal saline was 58.33 min ($p >0.05$).

In midazolam group, only 4 children had developed side effects like nasopharyngeal irritation, congestion and bad taste. In Saline group, none had any side effects.

	N	Mean Age±SD	p value	Male	Female	p value	Mean Wt±SD	p value
Midazolam	30	5.33±.959		21 (70%)	9(30%)		15.17±3.715	
Normal Saline	30	4.93±.980	0.116	17(56.7%)	13 (43.3%)	0.284	14.77±4.023	0.691
Total	60	5.13±.982		38(63.3%)	22 (36.7%)			

Table 1. Distribution of age, gender and weight in both the group

ASA Grading	Groups	
	Midazolam	Normal Saline
I	23	28
	76.66%	93.33%
II	7	2
	23.33%	26.66%
Total	30	30
	100%	100%

Table 1b. Distribution of ASA physical status

	HR / min		SBP (mmHg)		DBP (mmHg)		SpO2 (%)	
Time in min	M	NS	M	NS	M	NS	M	NS
0	156	152	94	100	70	70	100	100
5	144	156	94	100	64	72	98	99
10	146	156	90	94	60	66	97	100
15	136	140	90	96	60	60	98	100
20	140	144	84	94	66	56	99	100
25	146	152	80	80	56	60	100	100
30	136	150	80	84	60	52	100	100
35	124	142	84	80	70	66	100	100
40	136	140	80	84	56	60	100	100
45	120	144	84	84	50	60	100	100
60	124	144	84	90	60	64	100	100
75	114	124	80	94	56	60	100	100
90	104	124	80	90	52	60	100	100

Table 2a. Changes in Hr, SBP, DBP, and SpO_2 after premedication

Time in min	Respiratory Rate/min	
	Midazolam	Normal Saline
0	30	28
5	26	28
10	22	26
15	24	30

Table 2b. Changes in respiratory rate after premedication

Sedation (before surgery)	Group	
	Midazolam	Normal Saline
Agitated	5	15
	16.7%	50.0%
Alert	12	12
	40.0%	40.0%
Calm	10	3
	33.3%	10.0%
Drowsy	2	0
	6.7%	0.0%
Asleep	1	0
	3.3%	0.0%
Total	30	30
	100.0%	100.0%

Table 3. Sedation level at 5 min. after premedication

Separation From Parents	Group		Total
	Midazolam	Normal Saline	
Excellent	12	0	12
	40.0%	.0%	20.0%
Good	15	4	19
	50.0%	13.3%	31.7%
Fair	2	16	18
	6.7%	53.3%	30.0%
Poor	1	10	11
	3.3%	33.3%	18.3%
Total	30	30	60
	100.0%	100.0%	100.0%

Table 4. Response to separation from parents (at 10 min.)

Reaction to venepuncture	Group		Total
	Midazolam	Normal Saline	
Satisfactory	21	7	28
	70.0%	23.3%	46.7%
Unsatisfactory	9	23	32
	30.0%	76.7%	53.3%
Total	30	30	60
	100.0%	100.0%	100.0%

Table 5. Response to venipuncture

Response to Mask Placement	Group		p value
	Midazolam	Normal Saline	
Agitated	0	15	<0.001
	.0%	50.0%	
Alert	11	10	
	36.7%	33.3%	
Calm	13	4	
	43.3%	13.3%	
Drowsy	3	0	
	10.0%	0.0%	
Asleep	3	1	
	10.0%	3.3%	
Total	30	30	
	100.0%	100.0%	

Table 6. Response to mask placement (at 15 min.)

Time in min	Group	Scores				
		6	7	8	9	10
10 min	Midazolam	0	16	12	2	0
	Normal saline	0	5	22	3	0
20 min	Midazolam	0	0	10	12	8
	Normal saline	0	0	0	12	18
30 min	Midazolam	0	0	0	0	30
	Normal saline	0	0	0	0	30

Table 7. Post anesthesia recovery score at 10, 20 and 30 min.

Discussion

Preoperative anxiety is operationally defined as subjective feeling of tension, apprehension, nervousness, worry and vigilance associated with increased autonomic nervous system activity. Midazolam is a water soluble benzodiazepine with a more rapid onset and shorter duration of action. The various modes of administration are intranasal, oral, rectal, intravenous or intramuscular route. Intranasal route appears to be better because of high mucosal vascularity and offers rapid and complete absorption within 1 to 2 hours into the systemic circulation.The demographic parameters of the children in this study were comparable. There were no statistical difference ($p>0.05$) among the groups in age, gender, weight and ASA physical status. In the present study, at the end of 5 min after premedication it was observed that in Group M, majority of the children 25 (83.3%) had satisfactory level of sedation (sedation level -2 ,3 ,4 ,5) and only 5 (16.7%) were agitated whereas in NS group 15(50%) were agitated, and the remaining 15 (50%) had lower level of sedation (sedation level 2 ,3 ,4 ,5) ($p<0.05$). Results of the present study are consistent with the studies of Manjushree Roy et al,[7] Weber et al[8]and Wilton et al[9]with regard to satisfactory level of sedation at 5 min after intranasal Midazolam. At 10 minutes after administration of the drug, behaviour of the children to parental separation was good to excellent in 27(90%) in midazolam group whereas in the NS group only 4 (13.3%) children, were good and the rest 26 (86.6%) were poor to fair ($p<0.05$). Similar results were obtained by Karl et al, [10] Wilton et al, [9] Alderson et al, [11] Manju Shree Roy et al[7] and Helen Karl et al.[10,12] The response to vene puncture was satisfactory in Midazolam group 21 (70%) whereas in NS group 7 (23.3%) children showed satisfactory response,the remaining 23 (76.7%) showed unsatisfactory response, ($p < 0.05$). This study concurs with that of Wilton et al,[9] Manjushree Roy et al,[7] Asif Pervez kazemi et al. [13] and J.M. Malinovsky et al.[14]

At 15mins after premedication, the ease of induction in terms of mask acceptance was satisfactory in Midazolam group 30 (100%), whereas in NS group 15 (50%) were agitated and the remaining 15 (50%) showed satisfactory response to mask placement ($p<0.05$).The results of this study correlates with the studies of Davis et al, [15] Wilton et al, [9] Karl et al,[10] Alderson et al[11] and Manjushree Roy et al.[7] Heart rate, NIBP, SpO2 did not significantly change in both the groups during the study period. ECG in both the groups was within normal limits. There was a decrease in respiratory rate from 30 to 22 per min in the midazolam group over a 15 min period. This decrease is within the normal range observed in children of this age group.[54]After 15 min, anaesthesia was maintained with face mask, assisted ventilation/controlled ventilation after endotracheal intubation, depending on the duration of surgery. After surgery, children were received in PACU, administered oxygen through face mask for an adequate period. NIBP, Spo2 and HR were monitored using Dragger Multichannel monitor. Post anaesthesia recovery characteristics were assessed at 10 mins interval for a period of 30 mins by the following parameters:

1. Colour
2. Airway
3. Level of consciousness
4. Movement of all four limbs
5. Respiration.

Children were considered fit for discharge from PACU, at a score of 10; that is when the children were conscious, colour – pink, no obstruction in the airway, able to breathe deeply and cough freely, able to move 4 limbs freely, Spo2- >98% on room air.

At 10 mins, it was observed that the minimum score was 7 and maximum score was 9 in both the groups. At 20 mins the minimum score was 8 in midazolam and 9 in normal saline, whereas maximum was 10 in both the groups. The minimum score of 8 observed in midazolam group may be attributed to the brief surgical procedures.

At 30 mins all the children in both the groups had a score of 10 and were fit for discharge to the wards. But they were monitored for an additional period and discharged to the ward at the end of 60 mins. No significant changes were observed in NIBP, Heart rate during this period. All the children were followed up for a period of 24 hours. Similar results were obtained by Wilton et al[9] and Manjushree Roy et al.[7] Postoperatively all the children were followed up for 24 hours for side effects and complications. In the present study only 4 children had developed side effects such as nasal congestion, nasopharyngeal irritation and bad taste in midazolam group. No side effects were observed in the saline group. Daniel P. Wermeling[17] had observed similar side effects in his study.

Conclusions

On the basis of the present study it is concluded that administration of preservative free intranasal midazolam in the dose of 0.2 mg/kg as premedication in paediatric patients produces satisfactory sedation.

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