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Research Article

A prospective randomised double-blinded study of intranasal midazolam atomizer spray for procedural sedation in paediatric patients

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ABSTRACT

Background: Premedication prior to anaesthesia in children provides anxiolysis, facilitates parenteral separation and lessens adverse psychological effects on young minds. The present study was designed to study the safety, acceptability and degree of sedation by intranasal midazolam spray in children undergoing short procedures like endoscopy and CT scan.
Methods: Sixty children scheduled for CT scan or endoscopy were randomly divided in to two groups. Thirty patients received intranasal midazolam spray 0.2 mg/kg, 20 minutes prior to procedure (group M) while other thirty patients received intra-nasal 0.9% normal saline spray (group C). Vital parameters such as heart rate (HR), systolic and diastolic blood pressure, respiratory rate (RR), SpO_2, ramsay sedation score (RSS) and anxiety score level was observed and recorded prior to the premedication and then every 5 minutes till the end of the procedure. Parenteral separation and behaviour of the patient while entering the procedure room was also evaluated in both groups.
Results: The mean heart rate, systolic blood pressure, respiratory rate, oxygen saturation were comparable between groups M and C. The mean diastolic blood pressure was significantly lower in group M as compared to group C. RSS and anxiety level score achieved were significantly higher in group M thereby facilitating easy parenteral separation.
Conclusions: We can thereby say that administration of preservative free intranasal midazolam atomizer spray in dose of 0.2mg/kg as premedication in paediatric patients produces satisfactory level of sedation and anxiolysis with minimal adverse effects.

Keywords: Intranasal midazolam, Premedication, Sedation, Anxiolysis

INTRODUCTION

Most of the preschool children suffer from severe anxiety and apprehension when they are separated from their parents before induction of anaesthesia. Thus pre-operative anxiety can largely affect the smoothness of the induction, emergence from anaesthesia and also the psychological and emotional state of children.[1,2]

The rationale use of premedicant drugs may allow the patient to enter the operating room with a minimum degree of apprehension, sedated but arousable and co-operative state without uncomfortable side-effects.[3] In children the issue of premedication is more difficult because intravenous access is frequently absent. Hence in routine practice non-parenteral routes of drug administration are preferred for sedation prior to anaesthesia. Sedative premedication can be administered orally, intramuscularly, intravenously, rectally, sublingually or nasally.[4] Although most of these routes are effective and reliable, each one has certain drawbacks.

Oral or sublingual premedication have a slow onset or may be spit out and drug taste is the main determinant for the success of their administration.[5] Intramusclar medications may hurt and result in sterile abscess. Intravenous medications may be painful during injection or at the start of the infusion. Rectal medications may sometimes make the children feel uncomfortable and they may cause defecation. Nasal medications can be irritating, although their absorption is rapid.[6]

The ideal agent should have a rapid onset, predictable duration and rapid recovery, provide good patient and parent acceptance. In this study we used a new midazolam atomizer spray. In the spray, the drug is delivered in puffs which contain very minute particles that spread over a large surface area. The present study was designed to study the safety, the acceptability and the degree of sedation which was produced by intra-nasal midazolam as a sedative in pediatric patients who were undergoing elective procedures like CT scan and endoscopy.

Midazolam, a water soluble, short acting, 1,4-Benzodiazepine, meets these criteria with its multiple routes of administration (oral, nasal, rectal), onset time of 10-20 minutes, duration of action of approximately 30 minutes and no interference with vital signs in doses less than 0.5mg/kg.[7] Midazolam has got all properties namely sedative, hypnotic and anxiolytic activity. Thus it has become the most popular premedicant. However, good or excellent results are seen in only 60-80% of the cases. The rapid and reliable onset of action, avoidance of painful injections, ease of administration and predictable effects has made the intranasal administration of premedication agents popular.

This study was designed to evaluate the efficacy of intranasal midazolam spray in children as premedication before short procedures like CT scan and endoscopy.

METHODS

After the institutional ethics committee approval, this prospective randomized placebo-controlled study was conducted in 60 ASA I and II patients between age groups of 1 year to 10 years, posted for elective procedures like CT scan and endoscopy. Patients with any nasal pathology, nasal allergy or infection were excluded from the study.

Patients were randomly divided into two groups using computer generated assignment. An informed consent from the patient's parent/ guardian was taken after adequate starvation was ensured, 4 hours for clear liquids and 8 hours for solids.

All these patients received the drug by nasal route by anaesthesiology resident not involved in the study ,in a double blind manner (administered 20 minutes prior to procedure) and divided into following two groups;

- Group M: Received intranasal midazolam spray 0.2mg/kg
- Group C: Received intranasal 0.9% normal saline spray

Midazolam used in the study was preservative free midazolam nasal spray (INSED spray 5 ml). Each puff (100 microliter) contains 0.5 mg of midazolam. Midazolam nasal spray 0.2mg/kg was administered intranasally 20 min before the procedure. Heart rate, systolic and diastolic blood pressure, oxygen saturation, level of anxiety, level of sedation was recorded prior to midazolam spray and at every 5 min interval after administration of midazolam spray.

Anxiety level scoring was given as below

- 1: Clinging to parents and/or crying.
- 2: Awake but not clinging to parents, may whimper but not cry loudly.
- 3: Lying/sitting comfortably with eyes spontaneously open.
- 4: Lying/sitting comfortably with eyes spontaneously closing, responds to minor stimulation.
- 5: Eyes closed, rousable but does not respond to minor stimulation.

Level of sedation was assessed by Ramsay sedation scale. Onset of sedation was defined as change in sedation level by ramsay score 1+. Peak of sedation was defined as ramsay 4.

Ramsay sedation score

- 1: Anxious, agitated, restless.
- 2: Cooperative, tranquil, oriented
- 3: Drowsy, response to verbal commands
- 4: Asleep, brisk response to light glabellar tap and loud auditory stimulus.
- 5: Asleep, sluggish response to light glabellar tap and loud auditory stimulus
- 6: Coma .

Behaviour of the patient while entering the procedure room was assessed and graded as

- 1: Poor- anxious and combative
- 2: Good- anxious and easily assured
- 3: Excellent- sleeping and calm

After taking patient in procedure room, additional sedation or analgesia if required was provided and noted.

Statistical analysis

Data was expressed as mean±standard deviation. Demographic data and complications were analyzed using chi square test and hemodynamic variables were

analyzed using paired "t" test within groups and unpaired "t" test between the groups. The intergroup comparison was analyzed with unpaired t-test and intra group comparison with Paired t-test. P value of <0.05 was considered as significant. P < 0.001 was considered as highly significant.

With reference to the demographic data such as age (p=0.23) and weight (p=0.057), both the groups were comparable using unpaired student's t test. The inter and intra-group comparison of heart rate at different time intervals in midazolam and control groups were comparable by the paired and unpaired t test (Table 1).

RESULTS

Table 1:Comparison of mean heart rate at various time intervals between group M and group C.

Parameter	Study group		Control group		Unpaired T test	P-value
	Mean	S.D.	Mean	S.D.		
HR 0 min	103.23	8.41	104.43	9.17	0.528	0.599
5 min	101.27	8.67	103.40	8.65	0.954	0.344
10 min	97.83	9.31	100.07	10.52	0.871	0.388
15 min	94.77	9.69	96.27	8.50	0.637	0.526
20 min	93.47	9.42	95.53	8.27	0.903	0.370
25 min	91.13	10.67	94.97	8.63	1.530	0.131
HR 30 min	91.63	11.74	95.67	7.18	1.605	0.114

S.D. - Standard deviation, P-Value is not significant

Table 2: Comparison of mean systolic blood pressure at various time intervals between group M and group C.

Parameter	Study group		Control group		Unpaired T test	P value
	Mean	S.D.	Mean	S.D.		
SBP 0 min	99.43	8.50	101.47	6.39	1.047	0.299
5 min	96.07	18.50	109.47	55.70	1.251	0.216
10 min	96.73	8.72	97.40	4.90	0.365	0.716
15 min	95.60	7.45	95.73	5.67	0.078	0.938
20 min	93.83	7.40	96.67	5.49	1.684	0.098
25 min	91.17	8.64	95.53	5.00	2.396	0.020
SBP 30 min	91.60	7.13	94.93	5.53	2.023	0.048

S.D. - Standard deviation, P-Value is not significant.

Table 3: Comparison of mean diastolic blood pressure at various time intervals between group M and group C.

Parameter	Study group		Control group		Unpaired T test	P value
	Mean	S.D.	Mean	S.D.		
DBP 0 min	85.23	120.14	65.93	6.02	0.879	0.383
5 min	61.70	6.71	63.93	5.55	1.405	0.165
10 min	60.07	6.23	64.27	5.35	2.803	0.007*
15 min	59.80	5.05	63.20	4.69	2.704	0.009*
20 min	59.17	4.55	63.03	3.76	3.590	0.001*
25 min	57.50	4.93	62.00	3.19	4.194	0.000*
DBP 30 min	57.77	4.56	62.20	3.61	4.173	0.000*

S.D. Standard Deviation, * P value is significant (<0.05)

The inter and intra group comparison of systolic blood pressure (SBP) at different time intervals in midazolam and control groups showed no statistically significant difference in SBP in midazolam group and control group by the paired and unpaired t test (Table 2).

There was no statistically significant difference found in the baseline diastolic blood pressure (DBP) between two groups. However there was a statistically significantly lower DBP after 10 minutes of starting premedication in midazolam group, 60.07±6.23 mmHg as compared to 64.67±5.35 mmHg in control group (Table 3).

There was no statistically significant difference in the SpO_2 between two groups during and after the completion of procedure and throughout the observation period (P >0.05). The mean ramsay sedation score after 5 minutes premedication in midazolam group was 1.57 (+0.63) as compared to 1.00 in control group. This difference was statistically highly significant. (p <0.001)

using unpaired t test. After 30 minutes of premedication mean ramsay sedation score in midazolam group was 3.77±1.07 as compared to 1.30±0.47 in control group. This difference was statistically very highly significant (p<0.001) (Table 4). The mean anxiety score, 5 minutes after premedication in midazolam group was 1.27 (+0.45) as compared to 1.00 in control group. This difference was statistically not significant. (p ≥0.05). After 10 minutes of premedication mean anxiety score in midazolam group was 2.83±0.75 as compared to 1.00 in control group. This difference was statistically very highly significant (p <0.001). After 30 minutes of premedication mean anxiety score in midazolam group was 3.57±0.95 as compared to 1.25±0.25 in control group. This difference was statistically very highly significant (p <0.001) (Table 5).

Table 4: Comparison of ramsay sedation score between group M and group C.

Parameter	Study group		Control group		Mann-whitney test	P value
	Mean	S.D.	Mean	S.D.		
RSS 5 MIN	1.57	0.63	1.00	0.00	3.326	0.001*
10 min	3.30	1.12	1.10	0.31	6.032	0.000*
15 min	3.67	1.03	1.17	0.38	6.283	0.000*
20 min	3.73	1.05	1.27	0.45	6.195	0.000*
25 min	3.77	1.07	1.33	0.48	6.136	0.000*
RSS 30 MIN	3.77	1.07	1.30	0.47	6.165	0.000*

S.D. Standard deviation , *P value is significant

Table 5: Comparison of anxiety score between group M and group C.

Parameter	Study group		Control group		Mann-whitney test	P value
	Mean	S.D.	Mean	S.D.		
Anxiety S 5 min	1.27	0.45	1.00	0.00	1.774	0.076
10 min	2.83	0.75	1.00	0.00	6.431	0.000*
15 min	3.47	0.94	1.00	0.00	6.431	0.000*
20 min	3.50	0.94	1.03	0.18	6.402	0.000*
25 min	3.57	0.97	1.03	0.18	6.402	0.000*
Anxiety S 30 min	3.57	0.97	1.07	0.25	6.372	0.000*

S.D. Standard deviation , *P value is significant`

On comparing parental separation and behaviour of patients while entering procedure room, four patients in midazolam group showed excellent behavior (Figure 1).

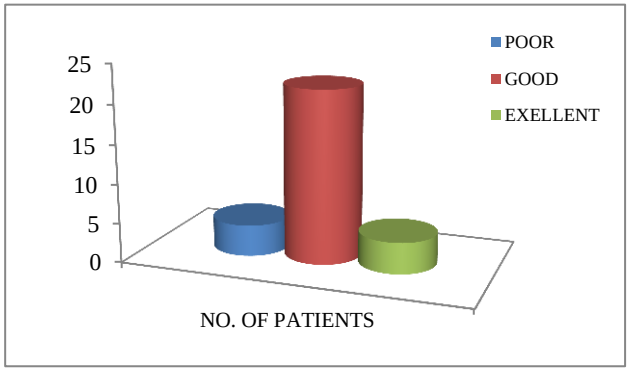

Figure 1: Comparison of parenteral separation and behaviour of patient while entering procedure room between group M and group C.

DISCUSSION

Preoperative anxiety is operationally defined as subjective feeling of tension, apprehension, nervousness, worry and vigilance associated with increased autonomic nervous system activity. Younger children are more concerned about separation from parents and older children are more anxious about the anaesthetic and surgical process. Therefore premedication in addition to allaying the anxieties of surgery, parental separation, and pain allow smoother and safer induction of anaesthesia.

Midazolam, a water soluble, short acting benzodiazepine,is a sedative- hypnotic with anxiolytic activity and hence popular. When given as intra nasal spray instead of drops, its absorption is virtually complete,83%.[8] Moreover, Koppal R et al, conducted a study to evaluated the onset, quality of sedation and separation when midazolam was administered through the oral and trans nasal routes and concluded that the trans nasal group achieved a faster sedation score and gave better separation scores.[9]

The heart rate in both groups were comparable which is similar to study by Nial et al where they observed that heart rate and respiratory rate did not vary significantly.[10] The diastolic blood pressure decreased after ten minutes of intra-nasal midazolam and co-related with the patients sedation and lowered anxiety. At the end of 5 minutes significant number of patients were sedated as per ramsay sedation score with 0.2 mg/kg intranasal midazolam

group and after 10 minutes had achieved good anxiolysis as per the anxiety score. In study by Bhakta et al, it was concluded that intranasal midazolam in a dose of 0.2 $mgkg^{-1}$ is an effective pre-medication for producing effective sedation and anxiolysis in paediatric patients without any untoward side effect.[1] No added advantage was found in 0.3 $mgkg^{-1}$ dose. Similarly Niall et al also recommended using the lower dose of 0.2 mg/kg midazolam for adequate anxiolysis and sedation.[10] More over a higher dose of midazolam requires large volume, resulting in seepage of some volume in oral cavity through posterior nasal opening and expulsion of the drug by sneezing or dribbling from anterior nostril resulting in delayed effect in higher dose.

In the present study, parental separation was not only easier but their behavior was also excellent in most children in midazolam group. Our finding is similar to that by Fishbein et al, who found that premedication with intranasal midazolam is effectively reduces negative behavior during parenteral separation while maintaining sedation during the endoscopic procedure.[11] Davis PJ et al also demonstrated that intranasal midazolam effectively produced easier parent separation and smoother anaesthesia induction.[12]

We did not have any major adverse effects except for two children who had nasopharyngeal irritation which subsided by post –procedure saline nebulization.

CONCLUSION

We can thereby say that administration of preservative free intranasal midazolam atomizer spray in dose of 0.2 mg/kg as premedication in paediatric patients produces satisfactory level of sedation and anxiolysis with minimal adverse effects.

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