

COMPARATIVE EVALUATION OF INTRANASAL DEXMEDITOMIDINE AND INTRANASAL MIDAZOLAM FOR PRE MEDICATION IN CHILDREN: A RANDOMISED DOUBLE BLIND STUDY

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Received : 09/09/2023
Received in revised form : 05/10/2023
Accepted : 16/10/2023

Keywords:
Intranasal Dexmedetomidine,
Midazolam, Sedation, Behaviour,
Children.

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DOI: 10.47009/jamp.2023.5.5.219

Source of Support: Nil,
Conflict of Interest: None declared

Int J Acad Med Pharm
2023; 5 (5); 1119-1123



Abstract

Background: Our primary objective was to compare intranasal administration of midazolam and dexmedetomidine as premedication in paediatric patient and to assess level of anxiety at parent separation assessed by Observer Assessment of Alertness and Sedation Scale sedation score and behaviour at venepuncture assessed by behaviour score. As a secondary outcome occurrence of any adverse events like bradycardia and desaturation were also assessed. **Materials and Methods:** This randomised double-blind study was conducted in the department of Anaesthesiology, IGIMS, and Patna from January 2016 to December 2017. Seventy-four (74) paediatric patients of ASA grade I, aged between 3 to 6 years after approval from Institutional Ethical Committee (IEC/1357/ACAD dated 12.10.2017). In this study a total of 74 patients were enrolled of which 14 patients were excluded for not meeting inclusion criteria (n=8) and patient refusal (n=6). Thus 60 patients were taken for randomisation (n= 30 in each group). Patients age between 3 to 6 years of ASA physical status I posted for elective surgeries under general anaesthesia were included in study. Patients with nasal infection or nasal pathology for intranasal drug, pre-existing pulmonary and cardiovascular diseases and known allergy to any of the test drugs, were excluded from study. The children were randomly divided into two groups according to the computer-generated randomisation table. Group M received 0.2 mg/kg intranasal Midazolam using 1ml insulin syringe. Group D received 1µg /kg intranasal Dexmedetomidine using 1ml insulin syringe. Data were recorded in Microsoft Excel and analysed using the Statistical Package for Social Sciences (SPSS Inc.; Version 18.0, Chicago, IL, USA). **Result:** The demographic characteristics of the patients in the two groups, group D and group M, were comparable with respect to age, weight and sex with no significant difference (p>0.05). In Group D the baseline behaviour score was 2.61±0.66 as compared to 2.71±0.43 in Group M (p>0.05). At 60 minutes Group D's behaviour score was 1.54±0.72 as compared to 2.27±0.45 in Group M (p<0.05). **Conclusion:** We conclude that intranasal dexmedetomidine 1µg/kg is an effective and safe alternative for premedication in children.

INTRODUCTION

Children scheduled for surgical procedures might experience significant anxiety and distress during the pre-operative period. They remain uncooperative, fearful, anxious or physically resistant particularly during times of parent separation, mask application and venepuncture.^[1] Pre-operative anxiety can have negative psychological and physiological effects on a child.^[2] Various interventions used to allay the anxiety of a child during the peri-operative period are pre-operative preparation programs, parental

presence during induction and sedative premedication.^[3]

The use of sedative premedication may help to reduce anxiety, minimize the emotional trauma and facilitate a smooth induction of anaesthesia. Benzodiazepines have been most commonly for premedication. Midazolam is a water-soluble, short-acting gamma-amino-butyric acid receptor inhibitor which is used by multiple routes of administration via oral, nasal and rectal. Administered nasally it has a faster onset of action. Thus it gained popularity as a premedication agent in children.^[4] It provides

effective sedation, anxiolysis and varying degrees of anterograde amnesia.^[5]

However adverse effects such as post-operative behavioural changes, hiccups and paradoxical hyperactive reactions have been observed.^[5] Dexmedetomidine, which is a highly selective alpha-2 agonist, has a faster onset of action with analgesic, sedative properties and devoid of respiratory depressive action which has been used as a premedication.^[6,7]

Intranasal application is a relatively non-invasive, convenient and easy route of administration, not requiring much of patient co-operation as would be the case for swallowing the medication or retaining it sublingually. The rich vascular plexus of the nasal cavity provides a direct route into the blood-stream leading to the fast onset of action.^[8]

Hence in this study, our primary objective was to compare intranasal administration of midazolam and dexmedetomidine as premedication in paediatric patient and to assess level of anxiety at parent separation assessed by Observer Assessment of Alertness and Sedation Scale sedation score and behaviour at venepuncture assessed by behaviour score. As a secondary outcome occurrence of any adverse events like bradycardia and desaturation were also assessed.^[9]

MATERIALS AND METHODS

This randomised double-blind study was conducted in the department of Anaesthesiology, IGIMS, and Patna from January 2016 to December 2017. Seventy-Four (74) paediatric patients of ASA grade I, aged between 3 to 6 years after approval from Institutional Ethical Committee (IEC/1357/ACAD dated 12.10.2017). In this study a total of 74 patients were enrolled of which 14 patients were excluded for not meeting inclusion criteria (n=8) and patient refusal (n=6). Thus 60 patients were taken for randomisation (n= 30 in each group). Patients age between 3 to 6 years of ASA physical status I posted for elective surgeries under general anaesthesia were included in study. Patients with nasal infection or nasal pathology for intranasal drug, pre-existing pulmonary and cardiovascular diseases and known allergy to any of the test drugs, were excluded from study.

The children were randomly divided into two groups according to the computer-generated randomisation table. Group M received 0.2 mg/kg intranasal Midazolam using 1ml insulin syringe. Group D received 1µg /kg intranasal Dexmedetomidine using 1ml insulin syringe.

For intranasal route dexmedetomidine (100 µg per ml parenteral preparation) was taken in a 1ml syringe with normal saline to make a final volume of 1 ml. Midazolam was prepared in such a manner so that the final concentration of the drug was 5 mg/ml.

To avoid bias, drugs were administered by a blinded investigator. Observers and attending

anaesthesiologist were blinded for study drug given. All the children were premeditated in pre-operative holding area in the presence of parent 50 minutes prior to induction. Drugs were administered while keeping the child in lap of parent (preferably mother) in resting position in a drop-by-drop method by syringe. Base line heart rate (HR), oxygen saturation (SpO₂) was noted and monitored every 5min after administration of drug until the patient was shifted to operating room.

The parental separation anxiety was assessed while shifting the patient to operating room through 6-point sedation scale⁶ and patient's behaviour in the operating room was assessed by the attending anaesthesiologist through 4-point behaviour scale⁷, who was blinded to the drug given.

1. Does not respond to mild prodding or shaking.
2. Responds only to mild prodding or shaking.
3. Responds only after the name is called loudly or repeatedly
4. Lethargic response to name spoken in normal tone
5. Appears asleep but responds readily when name spoken in normal tone
6. Appears alert and awake, responds to name in normal tone

A Sedation Score of 1 to 4 were classified as satisfactory in terms of acceptable separation from parent, score of 5 or 6 were considered unsatisfactory as difficult separation. In case of difficult separation or failed sedation (sedation score ≥ 5) patient was taken for mask induction and number of such patients was recorded.

The subject's behaviour in operating room was measured using 4 point Behaviour Scale.

1. Calm and cooperative.
2. Anxious but reassurable.
3. Anxious but not reassurable
4. Crying or resisting

Subjects with score of 1 or 2 are considered as satisfactory, scores of 3 or 4 are considered unsatisfactory. In case of unsatisfactory behaviour score (behaviour score ≥ 3) patient was taken for mask induction and number of such patients were also recorded. After transferring of the patient to operating room, monitors were attached and heart rates (HR) and oxygen saturation (SpO₂) were recorded. An intravenous line was secured after the patient arrived in the operating room. At the time of venipuncture children were assessed for response to venipuncture using the behaviour scale. Intravenous fluid was started according to weight of the child. Induction was done by using IV anaesthetic agents or mask induction which ever was required. The vital parameters and adverse events if any were noted till the end of procedure.

Keeping in view our primary outcome and on the basis of results of previous study, the mean values of sedation score in the dexmedetomidine group and midazolam group were 2.94 and 3.99 respectively⁸. Their standard deviations were 1.37 and 1.58 respectively. With assumed power of 95%,

considering type - 1(alpha) error as 0.05 and type-2 (beta) error as 0.2, sample size came to be 28 in each group. To further authenticate the study and minimize any error, we chose to select a sample size of 30 per group.

Statistical analysis: Data were recorded in Microsoft Excel and analysed using the Statistical Package for Social Sciences (SPSS Inc.; Version 18.0, Chicago, IL, USA). Quantitative data were expressed as mean and standard deviation, whereas qualitative data were expressed as numbers and percentages (%). Student's t-test was used to test the significance of difference for the quantitative variables and Chi-square was used to test the significance of difference for qualitative variables. One-way repeated measure analysis of variance (ANOVA) was used to determine the significance of difference across time points.

RESULTS

In this study a total of 74 patients were enrolled of which 14 patients were excluded for not meeting inclusion criteria (n=8) and patient refusal (n=6). Thus 60 patients were taken for randomisation (n= 30 in each group) [Figure 1]. The demographic characteristics of the patients in the two groups, group D and group M, were comparable with respect to age, weight and sex with no significant difference (p>0.05) [Table 1]. Group D's mean sedation score

was 2.46±1.28 as compared to 4.28±0.42 in Group M (p<0.05), as shown in [Table 2].

Behaviour at venepuncture was assessed with a 4 point behaviour scale. In Group D the baseline behaviour score was 2.61±0.66 as compared to 2.71±0.43 in Group M (p>0.05). At 60 minutes Group D's behaviour score was 1.54±0.72 as compared to 2.27±0.45 in Group M (p<0.05) as shown in [Table 3].

The difference in the behaviour scores between two groups was evaluated at each time point for statistical significance. It was evident that up to 10 min, the difference in behavioural scores between both the groups was not statistically significant, but gradually the scores in Group D were significantly lower than that of Group M (p < 0.05).

Hemodynamic parameters i.e. heart rate and oxygen saturation was observed in both the groups at an interval of 5 minutes, after premedication till 50 minutes or till arrival in operation theatre which ever was first. The baseline values were comparable in both the groups and remained so after premedication with test drug.

Initially the sedation score of patients were ≥ 5 but after 20 minutes the sedation score in both the groups gradually decreased to ≤ 5. So, at the time of parental separation no patient had failed sedation. Similarly, the behaviour score of none of the patient was ≥ 3 at the time of venepuncture. None of the patient required mask induction for failed sedation or unsatisfactory behaviour.

Table 1: Demographic characteristics of patients receiving dexmedetomidine and midazolam SD: Standard Deviation

Variables	Dexmedetomidine (n=30)	Midazolam (n=30)	p value
Gender, n (%)			
Male	23(77)	25(83)	0.757
Female	7(24)	5(17)	
Age (years), mean±SD	5.6±2.7	5.8±2.7	0.497
Weight (kg), mean±SD	15.4±7.4	16.1±6.8	0.855

Table 2: Comparison of Sedation scale in both the study groups at different time points.

Time(mins)	Sedation scale (Dexmedetomidine)	sedation scale (Midazolam)	p value*
	Mean ± SD	Mean ± SD	
0	6.00 ± 0.00	6.00 ± 0.00	-
10	5.31 ± 0.52	6.00 ± 0.00	<0.0001
20	3.36 ± 1.51	5.50 ± 0.00	<0.0001
30	3.10 ± 1.40	4.51 ± 0.49	<0.0001
40	2.11 ± 1.28	4.10 ± 0.00	<0.0001
50	2.16 ± 1.44	3.38 ± 0.50	0.0001
60	2.46 ± 1.28	4.28 ± 0.42	<0.0001

*Analyses done by student t test

Table 3: Comparison of Behaviour scale in both the study groups at different time points.

Time (mins)	Behaviour Scale (Dexmedetomidine)	Behaviour scale (midazolam)	p value*
	Mean ± SD	Mean ± SD	
0	2.61 ± 0.66	2.71 ± 0.43	0.3354
10	2.59 ± 0.64	2.48 ± 0.50	0.5523
20	1.59 ± 0.62	1.87 ± 0.35	0.0266
30	1.57 ± 0.62	2.08 ± 0.73	0.0221
40	1.48 ± 0.63	2.11 ± 0.62	0.0002
50	1.54 ± 0.72	2.28 ± 0.46	<0.0001
60	1.54 ± 0.72	2.27 ± 0.45	<0.0001

SD: Standard Deviation. *Analyses done by student t test

DISCUSSION

The pre-procedure period in paediatric patients can be made fearless either by psychological methods or by pharmacological methods. Premedication is required to allay anxiety and fear, allow smooth separation from parents and easy acceptance of needle prick before induction of anaesthesia. Additional advantages are analgesic, amnesic, antiemetic, anti-sialagogue and vagolytic effects. In the current study, intranasal route for drug administration was chosen as a quick and simple method with benefits over other routes that also requires relatively more patient cooperation.

Four routes of administration of midazolam in young children were compared and sedation was comparable in all four routes but intranasal route offered faster onset of action.^[9] Onset of action with intranasal midazolam was 7.7 ± 2.4 min as compared to 12.5 ± 4.9 min with oral or 16.3 ± 4.2 min with rectal routes.^[10]

Intranasal midazolam has been used in various doses (0.01 mg kg⁻¹ to 0.5 mg kg⁻¹) as pre medication. A dose-finding study of intranasal midazolam showed that percentage of satisfactory separation (91% vs. 90%) and induction scores (60% vs. 80%) was comparable in case of 0.2 mg kg⁻¹ and 0.3 mg kg⁻¹ dose.^[11] A statistically significant difference was observed in the level of sedation at 5 min with 0.2 mg kg⁻¹ and at 10 min in 0.3 mg kg⁻¹.^[12] In this study dose of 0.2 mg kg⁻¹ had a faster onset of action and no major advantage with the higher dose. Therefore we decided to administer 0.2 mg kg⁻¹ midazolam as premedication by the intranasal route.

Intranasal preparation for dexmedetomidine is not available and hence intravenous preparation was used intranasally in many studies. Intranasal dexmedetomidine has been used in doses ranging from 0.5 µg/kg to 1.5 µg/kg. 75% of the children in dexmedetomidine 1 µg/kg group had satisfactory sedation when compared to 59.4% in 0.5 µg/kg group.^[13]

The sedation rate was 82.5% and 84% for atomiser and drops respectively when compared in 279 children.^[14] They also concluded that in either mode of administration, dexmedetomidine was equally effective. Hence in our study, we used drops and administered the drug intranasally using an insulin syringe.

Parental separation anxiety has been assessed by different scales by different authors. Mostafa et al used 4 point scale at 30 min and Ghali et al used a 3 point scale for parental separation anxiety.^[15] In our study, we decided to assess parental separation anxiety through 6 point sedation scale. We considered it as successful when the sedation score was between 1 and 4, and unsatisfactory or not successful if the sedation score was between 5 and 6. In our study, it was observed that the level of satisfactory sedation dexmedetomidine group was achieved within 20 minutes whereas in midazolam

group it was achieved at 30 min. The mean sedation score at separation from parents was 2.47 in dexmedetomidine group and 4.27 in midazolam group. The difference in sedation at parental separation was statistically significant, ($p < 0.05$), which was similar to study done by Sheta et al who compared 72 children and found that in children in dexmedetomidine group were significantly more sedated than midazolam group when they were separated from their parents (77.8% vs. 44.4%, respectively).^[16]

Akin et al. conducted a study comparing intranasal dexmedetomidine and midazolam on children, aged between 2 and 9, undergoing elective adenotonsillectomy. Doses similar to that utilized in our study were utilized and administered approximately 45–60 min before the induction of anaesthesia. They reported that there was no evidence of a difference between the groups in either sedation score or anxiety score upon separation from parents.^[17]

Authors have done a double-blind study in 51 children, aged 1–6 years, scheduled to undergo computed tomography imaging under sedation were randomized to receive either 0.5 mg/kg oral midazolam or 2.5 µg/kg intranasal dexmedetomidine to allay their anxiety and prevent motion artefacts and stress of intravenous cannulation. They concluded that intranasal dexmedetomidine was found to be superior to oral midazolam for producing satisfactory sedation.^[18]

A study was done in 72 children undergoing complete dental rehabilitation for sedation status, mask acceptance, and hemodynamic parameters in an age of 3–6 years between intranasal midazolam 0.2 mg/kg, intranasal dexmedetomidine 1 µg/kg. In their study, dexmedetomidine is an effective and safe alternative for premedication in children compared to midazolam.^[19]

The prospective randomised double-blinded trial was done Kumar L et al to compare the effects of premedication with 0.5 mg/kg oral midazolam versus 1 µg/kg intranasal dexmedetomidine in children between 2 and 12 years undergoing abdominal surgery. The sedation scores at separation and induction were the primary outcome measures. Behaviour scores and hemodynamic changes were secondary outcomes. The sedation scores were superior in dexmedetomidine than midazolam at separation and induction ($p < 0.001$).^[20]

Study done on sixty children 3–6 years old of congenital heart disease undergoing cardiac catheterization comparing the intranasal dexmedetomidine 0.1 µg/kg and intranasal midazolam 0.2 mg/kg 30 min before induction. The sedation score, anxiety score, and child-parent separation score were recorded until the child taken to the operating room. The premedication of children with intranasal dexmedetomidine attained satisfactory and significant sedation and lower anxiety level with better parental separation than those who received intranasal midazolam.^[21,22]

Hemodynamic disturbances such as bradycardia and severe hypotension were not observed in the children in our study who received intranasal dexmedetomidine or intranasal midazolam. There was no evidence of oxygen de-saturation, respiratory depression or apnoea in our study. During the entire study, we did not come across any significant side effects like nausea and vomiting.

CONCLUSION

We conclude that intranasal dexmedetomidine 1µg/kg is an effective and safe alternative for premedication in children and provides more successful parental separation, better sedation level at the time of induction of anaesthesia, better pre-procedural and intra-procedural hemodynamic stability when compared to intranasal midazolam 0.2mg/kg as premedication with negligible side effects or postoperative complications.

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