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ORIGINAL ARTICLE

COMPARISON OF INTRANASAL DEXMEDETOMIDINE AND MIDAZOLAM AS PREMEDICATION IN CHILDREN UNDERGOING CARDIAC SURGERIES AND PROCEDURES

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Abstract. Aims and Objectives. *To compare premedication with intranasal dexmedetomidine and intranasal midazolam for their sedative effects and ease of parental separation in children undergoing cardiac surgeries.* ***Materials and Methods.*** *This prospective, interventional study was conducted on 40 children aged 1-10 years undergoing cardiac procedures, who were randomized into two groups of 20 each. Group D received 2 mcg/kg intranasal dexmedetomidine, and Group M received 0.2 mg/kg intranasal midazolam 30 minutes before the surgery. The sedation levels were assessed by the Ramsay Sedation Scale (RSS), and ease of separation from parents by Child-Parent Separation Score (CPSS) in both groups.* ***Results.*** *The CPSS score was significantly lower with group D as compared to group M (scores 1 vs 2, p = 0.0002 prior to shifting of children to OT). Ramsay Sedation Scale value was significantly higher in group D compared to group M after 15, 25 and 30 minutes (scores 3 vs 2, p < 0.0001).* ***Conclusion.*** *Intranasal dexmedetomidine achieved significant as well as satisfactory sedation, lower levels of anxiety, and better parent separation than intranasal midazolam in pediatric patients undergoing cardiac surgeries.*

Key words: *intranasal, premedication, dexmedetomidine, midazolam, cardiac surgery, paediatric anaesthesia, parental separation, ramsay sedation scale*

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INTRODUCTION

In the pediatric age group, cardiac surgeries are mainly performed for the repair of congenital heart defects (CHD). As per the Indian Academy of Pediatrics, the birth prevalence of CHD is reported to be 8-12/1000 live births [1, 2]. Over 200,000 children are estimated to be born with congenital heart disease in India every year. About one-fifth of these suffer from critical heart disease requiring early intervention [3]. Coarctation of the aorta repair, arterial switch operation, ventricular septal defect repair, Norwood procedure, Glenn/Hemi-Fontan procedure, Fontan procedure, truncus repair, complete atrioventricular canal repair, and tetralogy of Fallot repair are most common and standardized surgical repairs performed in children according to the Society of Thoracic Surgeons (STS) [4].

Anxiety and fear of parental separation resulting in inconsolable crying have always been a major hurdle to smooth induction of anesthesia in the pediatric

population [5, 6]. Children aged 2 to 5 years are especially vulnerable to this problem since their understanding is limited. Anxiety and psychological trauma due to maternal deprivation are major challenges in pediatric anesthesia. Preoperative anxiety stimulates the autonomic nervous system and endocrine system, leading to an increase in the heart rate, blood pressure and cardiac excitability. Children with cardiac lesions are at an exaggerated risk of decompensation due to hemodynamic changes with inconsolable crying [7].

Several drugs and various routes of administration have been tested in children to find a safe and effective premedication drug via a non-invasive route. Intranasal administration of sedative drugs is relatively easy and non-invasive, with a rapid onset of action, and it guarantees good bioavailability due to the high vascularity of nasal mucosa. Furthermore, it has the advantage of being well tolerated, without any pungency or an unpleasant taste [8].

Dexmedetomidine is a strong and fast-acting alpha-2 adrenergic receptor agonist that is used as premedication due to its sedative and anxiolytic effects and stable hemodynamics. Unlike many other sedatives, dexmedetomidine is compatible with intranasal administration, and it rarely causes any respiratory depression [7-9]. Another sedative and anxiolytic premedication commonly used is midazolam, which is a short-acting benzodiazepine and also possesses anterograde amnesic effects. It has been used via various routes, including intravenous, intramuscular, oral and intranasal [10].

The present study was conducted to compare intranasal dexmedetomidine and midazolam for their sedative effects and ease of parental separation in the pediatric population posted for cardiac surgeries.

MATERIALS AND METHODS

After institutional ethical committee clearance and informed written consent from parents, 40 consecutive children aged 1 to 10 years of either sex and meeting the inclusion criteria (American Society of Anaesthesiologists (ASA) physical status classes II and III), scheduled for cardiac surgeries were enrolled in this prospective randomized, interventional study. Children with known allergies to dexmedetomidine and midazolam anticipated difficult airway and hemodynamic instability were excluded from the study.

All patients were examined a day prior to the procedure with a detailed history from the parent(s), complete general physical examination, and detailed airway assessment and laboratory investigations. Parents were instructed to keep the children fasting as per standard guidelines (6 hours for solids, 4 hours for liquids and 2 hours for clear fluids) prior to the procedure. All patients were randomized in a series of blocks of ten. Ten randomly generated treatment allocations within sealed opaque envelopes were prepared, assigning A and B in 5 envelopes each, where label A represented Group D and label B represented Group M.

Group D children received 2 µg/kg intranasal dexmedetomidine, and Group M children received 0.2 mg/kg intranasal midazolam in the preoperative room 30 minutes before taking them into operation theatre (OT). The intranasal drug was dripped into both nostrils using a 1 ml syringe, with the patient in the recumbent position, using an intranasal spray device (LMA/MAD NasalR – Teleflex Intranasal Mucosal Atomization Device). After administering the intranasal drug, heart rate, non-invasive blood pressure and oxygen saturation were recorded every 5 minutes (at baseline, 5 minutes, 10 minutes, 15 minutes, 20 minutes, 25 minutes and 30 minutes). The child's sedation level was also assessed by a blinded observer at baseline and just prior to shifting to OT, using the Ramsay Sedation Scale (RSS) [11]. The score was rated from 1-5 (Table 1), and a higher score meant that the level of sedation was higher. Child-Parent Separation Score (CPSS) was recorded just prior to the shifting of children for the procedure [12]. It was evaluated with a 3-point scale as:

1 = Patient unafraid, cooperative, or asleep

2 = Patient slightly crying and/or fearful, quieted with reassurance

3 = Patient crying and fearful, not quieted with reassurance

A lower score meant that the child-parent separation anxiety was decreased, and the child was calm and cooperative.

Table 1. Ramsay Sedation Scale [11]

Sedation score	Description
1	Awake; Anxious and agitated, or restless or both
2	Awake; Cooperative, oriented and tranquil
3	Awake; Responding to commands only
4	Asleep; Brisk response to light glabellar tap or loud auditory stimulus
5	Asleep; Sluggish response to light glabellar tap or loud auditory stimulus
6	Asleep; No response

The primary outcome of our study was to compare sedation levels by RSS and ease of separation from parents by CPSS in the two intervention groups. The secondary outcome was to compare hemodynamic stability (heart rate, non-invasive blood pressure) and oxygen saturation in the two intervention groups. All outcome measures were taken by an anaesthesiologist who was blinded to the drug used in the study.

The sample size was calculated based on a study by Messeha et al., who observed that the sedation score at 20 minutes after drug administration and CPSS in the dexmedetomidine group was 4 ± 0.9 and 1.21 ± 0.4, respectively, whereas in the midazolam group, it was 2.9 ± 1.0 and 2.09 ± 0.51, respectively [7]. Taking these values as a reference, the minimum required sample size with 99% power of study and 5% level of significance is 28 patients in each study group. Unfortunately, due to the COVID-19 pandemic, the number of elective cardiac surgeries was reduced in the study period, consequently allowing a sample size of only 20 patients per group. The comparison of the variables that were quantitative and not normally distributed in nature was analyzed using the Mann-Whitney Test (for two groups), and an independent t-test was used for comparison between two groups of normally distributed data. The comparison of the variables, which were qualitative in nature, was analyzed using the Chi-Square test. Statistical analysis was done using the Statistical Package for Social Sciences (SPSS) software, developed by IBM in Chicago, USA, version 21.0. For statistical significance, p value of less than 0.05 was considered significant.

RESULTS

A total of 40 pediatric patients were included in the study, 20 each in Group D and Group M. Table 2 shows the demographic profile of patients in both study groups, which was comparable. The mean age of patients in the study was 5.94 ± 2.99 years, which was comparable between the two groups (6.22 ± 2.99 in Group D and 5.65 ± 3.04 in Group M, p = 0.511). The distribution of cardiac procedures in the two groups is outlined in Table 3. Table 4 elaborates a comparison of vital parameters (heart rate, systolic blood pressure and oxygen saturation) at baseline and every 5 minutes after intranasal premedication till 30 minutes between group D and group M. As can be inferred from the table, at no time was any vital parameter significantly different between the groups (p > 0.05 in all subgroups).

When CPSS was compared between the study groups, no significant difference was seen in the distribution of scores or their mean and median values at baseline (Table 5). However, during the second evaluation (just prior to shifting to OT), more children had lower scores in group D as compared to group M (p = 0.0004). The mean and median values of CPSS were also significantly lower in dexmedetomidine premedication than midazolam (p = 0.0002). Table 5 also compares RSS scores between the two study groups. No significant difference was seen in mean and median scores, as well as their distribution at baseline between groups D and M. However, when evaluated just prior to shifting to OT, the mean and median RSS scores were significantly higher in group D than in group M (p < 0.0001). Similarly, the proportion of patients exhibiting higher sedation scores was

Table 2. Comparison of demographic profile of patients in the two intervention groups, showing no significant difference

Socio-demographic characteristics	Group D (n = 20)	Group M (n = 20)	Total	p-value
Age (years)				
≤ 5	9 (45%)	11 (55%)	20 (50%)	0.527
> 5	11 (55%)	9 (45%)	20 (50%)	
Mean ± SD	6.22 ± 2.99	5.65 ± 3.04	5.94 ± 2.99	0.511
Median (25th – 75th percentile)	6.5 (3.875-9.25)	4 (3-9)	5 (3-9)	
Gender				
Female	11 (55%)	10 (50%)	21 (52.50%)	0.752
Male	9 (45%)	10 (50%)	19 (47.50%)	
Weight (kg)				
Mean ± SD	19.68 ± 6.82	20.25 ± 7.4	19.96 ± 7.03	0.978
Median (25th – 75th percentile)	17.5(14.75-22.5)	18.5(13-27.5)	18(14-26.25)	

Table 3. Distribution of cardiac interventions in the two study groups

Cardiac Procedures	Group D (n = 20)	Group M (n = 20)
Cardiac Cath Study	6	8
ASD repair	4	3
VSD repair	4	2
TOF repair	3	4
TGA repair	2	1
TAPVC repair	1	2

Table 4. Comparison of SpO2 (%), Systolic Blood Pressure (mmHg) and Heart Rate (beats per minute) values between groups D and M at baseline and every minute till 30 minutes after giving intranasal premedication drug

	SpO_2		Systolic BP		Heart Rate	
	Group D (n = 20)	Group M (n = 20)	Group D (n = 20)	Group M (n = 20)	Group D (n = 20)	Group M (n = 20)
At baseline						
Mean ± SD	97 ± 8.59	99.35 ± 1.84	108.45 ± 9.74	104.4 ± 11.45	102.25 ± 16.1	103.75 ± 18.92
Median (25th – 75th percentile)	100 (98.75-100)	100 (100-100)	106 (100-115.75)	100 (98-111.25)	99 (92.25-112.5)	109.5 (98-118.5)
p-value	0.271 ^		0.236*		0.789*	
At 5 minutes after drug administration						
Mean ± SD	97.7 ± 6.52	99.5 ± 1.79	103.75 ± 11.75	104.85 ± 16.55	107.55 ± 12.91	105.85 ± 15.16
Median (25th – 75th percentile)	100 (99.75-100)	100 (100-100)	101 (96.5-110.25)	100 (92-110)	108.5 (98-118)	112.5 (97.5-116.5)
p-value	0.383 ^		0.810*		0.705*	
At 10 minutes after drug administration						
Mean ± SD	98.25 ± 3.97	99.45 ± 1.82	103.25 ± 11.52	102.6 ± 12.12	104 ± 11.72	105.6 ± 15.11
Median (25th – 75th percentile)	100 (99.5-100)	100 (100-100)	101 (98-110)	101 (95-110.5)	102 (97.5-110.5)	110 (97.5-116)
p-value	0.363 ^		0.863*		0.710*	
At 15 minutes after drug administration						
Mean ± SD	98.4 ± 3.28	99.4 ± 1.85	103.75 ± 11.9	104.3 ± 13.29	103.95 ± 12.2	102.95 ± 14.14
Median (25th – 75th percentile)	100 (98-100)	100 (100-100)	101 (97-107.5)	101 (94-114)	102 (96-114.25)	102 (96.75-114)
p-value	0.243 ^		0.891*		0.812*	
At 20 minutes after drug administration						
Mean ± SD	98.5 ± 3.2	99.45 ± 1.82	103.45 ± 13.07	102.25 ± 13.53	104.45 ± 12.56	103.95 ± 14.57
Median (25th – 75th percentile)	100 (99-100)	100 (100-100)	100(97-103)	100(93-102)	101(97.5-112.25)	101(98-116.5)
p-value	0.251 ^		0.777*		0.908*	
At 25 minutes after drug administration						
Mean ± SD	98.65 ± 3.18	99.5 ± 1.79	102.5 ± 12.47	103.6 ± 15.54	104.35 ± 13.2	105.6 ± 15.94
Median (25th – 75th percentile)	100(100-100)	100(100-100)	102 (96-111.75)	101 (90-117.25)	100 (98-116.5)	106 (98-118.5)
p-value	0.595 ^		0.806*		0.789*	
At 30 minutes after drug administration						
Mean ± SD	98.5 ± 2.84	99.45 ± 1.61	102.1 ± 10.59	103.25 ± 12.66	103.2 ± 13.57	104.2 ± 16.18
Median (25th – 75th percentile)	100 (98-100)	100 (100-100)	100(98.5-107)	101(90-110)	100.5(95.25-114.25)	100(97.5-120)
p-value	0.228 ^		0.757*		0.833*	

^ – Mann Whitney Test; * – Independent t test

Table 5. Comparison of CPSS and RSS scores between groups D and M at baseline (without premedication) and just prior to shifting to OT (at least 30 minutes after premedication)

CHILD-PARENT SEPARATION SCORE				RAMSAY SEDATION SCORE			
	Group D (n = 20)	Group M (n = 20)	p-value		Group D (n = 20)	Group M (n = 20)	p-value
At baseline							
Score 1	0 (0%)	0 (0%)		Score 2	19 (95%)	20 (100%)	
Score 2	3 (15%)	0 (0%)	0.231^	Score 3	1 (5%)	0 (0%)	1.0†
Score 3	17 (85%)	20 (100%)		Score 4	0 (0%)	0 (0%)	
Mean ± SD	2.85 ± 0.37	3 ± 0		Mean ± SD	1.05 ± 0.22	1 ± 0	
Median (25th-75th percentile)	3 (3-3)	3 (3-3)	0.075†	Median (25th-75th percentile)	1 (1-1)	1 (1-1)	0.317^
Just prior to shifting to OT							
Score 1	16 (80%)	4 (20%)		Score 2	2 (10%)	16 (80%)	
Score 2	4 (20%)	16 (80%)	0.0004^	Score 3	17 (85%)	4 (20%)	< 0.0001†
Score 3	0 (0%)	0 (0%)		Score 4	1 (5%)	0 (0%)	
Mean ± SD	1.2 ± 0.41	1.8 ± 0.41		Mean ± SD	2.95 ± 0.39	2.2 ± 0.41	
Median (25th-75th percentile)	1 (1-1)	2 (2-2)	0.0002†	Median (25th-75th percentile)	3 (3-3)	2 (2-2)	< 0.0001^

† – Fischer's exact test; ^ – Mann Whitney Test

higher in the dexmedetomidine group than in the midazolam group. This difference was highly significant statistically ($p < 0.0001$).

DISCUSSION

Tackling parental separation anxiety in children in the preoperative period and choice of premedication has always been a challenge for pediatric anesthetists and has been studied and discussed innumerable times. Ideal premedication agents should be fast-acting, rapidly metabolized, non-toxic and should provide stable hemodynamics. With the introduction of safer and shorter-acting agents administered through non-invasive routes, sedative premedication has resulted in a more tranquil induction of anesthesia in children. Two such agents included in our study are midazolam and dexmedetomidine, administered via the intranasal route. The advantage of the intranasal route is that it is relatively non-invasive, and the absorption and bioavailability rates are similar to those of drugs administered intravenously [8].

Dexmedetomidine is a highly selective α-2 adrenergic receptor agonist that is commonly used as a premedication due to its sedative, anxiolytic and sympatholytic activity. Another advantage of dexmedetomidine is its compatibility with intranasal administration [7, 8]. The site of action of this drug is locus coeruleus, where it causes electroencephalographic (EEG) activity similar to normal sleep. Dexmedetomidine results in "arousable sedation" or "cooperative sedation," which indicates that the sedated patient can still interact with healthcare professionals [9]. Midazolam, on the other hand, is a short-acting benzodiazepine drug that stimulates gamma-aminobutyric acid (GABA) receptors in the cerebral cortex by increasing the conductance of chloride ions and hyperpolarization that inhibits the normal function of neurons producing sedation. Like all benzodiazepines, it possesses sedative, anxiolytic, amnestic, hypnotic, and anticonvulsant properties [10].

Sheta et al. conducted a prospective, randomized, double-blind study to evaluate intranasal dexmedetomidine (1 μg/kg) and intranasal midazolam (0.2 mg/kg) as premedication agents in 72 paediatric patients undergoing dental rehabilitation [13]. Outcome measures included were level of sedation, mask acceptance, and hemodynamic parameters after administration of premedication. The authors also recorded recovery conditions, postoperative pain and agitation. It was observed that the onset of sedation was shorter in the midazolam group, but the level of sedation was higher in the dexmedetomidine group when children were separated from their parents. Thirteen children in group M showed signs of nasal irritation and tearing, compared to none in group D. Mask acceptance was 80.6% in group D compared to 58.3% in

group M (p = 0.035). The incidence of postoperative shivering and agitation was significantly lower with dexmedetomidine premedication compared to midazolam. There were no incidences of bradycardia or hypotension in either of the study groups. These findings are similar to those of our study, where dexmedetomidine provided better sedation and lower anxiety than midazolam. Our study also showed no hemodynamic changes using either premedication agent. A similar study comparing intranasal dexmedetomidine (0.1 μg/kg) and midazolam (0.2 mg/kg) as premedication was conducted by Messeha et al. in 60 children undergoing cardiac surgeries [8]. They included similar outcome measures to our study, which were hemodynamic parameters, oxygen saturation, RSS and CPSS scores. An extra anxiety score was also used for evaluation (1 = cooperative and calm, 2 = anxious but could be reassured, 3 = anxious and could not be reassured, and 4 = resisting or crying). They found a significant decrease in mean arterial pressure and heart rate in the dexmedetomidine group, as compared to the midazolam group after administration of both drugs. This was in contrast to our study, which showed no change in heart rate and blood pressure in either of the groups. Oxygen saturation levels were maintained in both groups, which was similar to our study. The authors reported significantly higher sedation and lower anxiety scores with the use of dexmedetomidine than midazolam 15 and 20 minutes after administration of drugs, respectively. Dexmedetomidine also resulted in a significantly lower separation score than midazolam (1.21 vs. 2.09, $p < 0.05$), although the agitation score was comparable between the two groups (1.13 vs. 1.33, $p > 0.05$). These findings are comparable to those of our study, where dexmedetomidine showed better sedation and lower separation anxiety than midazolam.

A related and more recent study by Diwan et al. on 60 pediatric surgical patients also showed similar results [14]. The authors reported higher sedation, lower anxiety levels, and easier parental separation at the time of transferring patients to the OR in children who received intranasal dexmedetomidine (1 μg/kg) than those who received intranasal midazolam (0.2 mg/kg). No hemodynamic changes were observed in either of the groups. These results are comparable to our study. Fu et al. published a meta-analysis of studies comparing intranasal midazolam with intranasal α2 adrenergic agonists dexmedetomidine and clonidine as premedication agents [15]. They concluded that dexmedetomidine was the preferred intranasal premedication for paediatric patients since it provides better sedation and lower anxiety than midazolam. However, there was insufficient evidence advocating the use of intranasal clonidine as sedative premedication over midazolam.

Our study had a few limitations. Firstly, being a single-center hospital-based study, its results cannot be generalized to all pediatric populations. More studies with a larger study population are required to confirm our test results. Secondly, although randomization ensured comparable baseline characteristics of patients in both groups, we could not provide proper blinding of the doctor recording the vital parameters and sedation scores. Lastly, as our study was conducted during the COVID-19 pandemic, the study population was relatively small.

There were a few strong points in our study. Firstly, there is a paucity of literature from the Indian subcontinent comparing intranasal dexmedetomidine and midazolam as premedication in pediatric patients undergoing cardiac procedures. The present study can act as a stepping zone for further studies by recruiting a large number of patients to ascertain the efficacy of the study drugs given intranasally as premedication. Secondly, our results corroborate with the work of many other authors, thus adding to the already existing knowledge about premedication in children. Our study provides a comprehensive comparison of the hemodynamic parameters and oxygen saturation, as well as sedation and separation scores between intranasal dexmedetomidine and intranasal midazolam, which are used as premedication agents.

CONCLUSION

To conclude, when compared with 0.2 mg/kg intranasal midazolam, premedication with 2 μg/kg intranasal dexmedetomidine achieved a higher level of sedation and lower parental separation anxiety among children undergoing various cardiac procedures. No significant variations in hemodynamic parameters or oxygen saturation were observed with the use of either drug. The present findings suggest intranasal dexmedetomidine to be the preferred choice of premedication over midazolam in paediatric patients undergoing cardiac procedures.

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