

Efficacy of Intranasal Dexmedetomidine Vs Intranasal Midazolam as Premedication in Children.



Anaesthesiology

KEYWORDS: dexmedetomidine; midazolam; intranasal; minor surgical procedures; premedication.

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ABSTRACT

Background: A prospective, randomized, double-blind study was designed to evaluate the effects of intranasally administered dexmedetomidine vs. intranasal midazolam as a premedication in children undergoing minor surgical procedures.

Methods: 100 children of 2-8 years of age with ASA-1 physical status posted for minor surgical procedures were divided in to two groups. Group D received intranasal dexmedetomidine 1 µg/kg and group M received intranasal midazolam 0.2 mg/kg. The patient's vital data and sedation status, behavioural and child parent separation scores were recorded every 10 minutes for 30 minute before induction of anaesthesia. Post anaesthesia recovery conditions were also assessed by paws score.

Results: The sedation scores before induction were significantly lower in group D (2.9±0.36) than group M (4.84± 0.37). The behavioural scores also significantly lower in group D than group M (1.04 ± 0.28 vs. 2.54± 0.50). Compared with the children in group M, those in group D were significantly more sedated when they were separated from their parents (2.1 ± 0.30 vs. 1.00 ± 0.00, respectively). 18 children (36%) in group M, showed signs of nasal irritation and none of these signs was seen in the children in group D. The PAWS score of group D is 1.04±0.19 which is lower than group M 1.98±0.25 and it is statistically significant. There were no incidences of bradycardia, hypotension, in either of the groups during study observation.

Conclusions: Intranasal dexmedetomidine is more effective than intranasal midazolam as premedicant in view of lower sedation score easier child parent separation and better postoperative recovery without any adverse side effects.

INTRODUCTION-

Children are more anxious and in significant distress during the peri operative period. They are fearful and uncooperative for any procedure and especially during parental separation before getting them in to operation theatre¹.

Midazolam is a water soluble benzodiazepine with dose dependent anxiolytic effect and with anterograde amnesia which helps to reduce psychological trauma of anaesthesia and surgery². Although midazolam is the most commonly used premedication in children, it is still not devoid of adverse effects, such as postoperative behavioural changes, cognitive impairment, paradoxical reactions, and respiratory depression^{3,4}.

Dexmedetomidine is a potent, highly selective, and specific α₂ adrenoreceptor agonist that has both sedative and analgesic effects. Unlike traditional gabaminergic sedative drugs, such as midazolam, the primary site of action of dexmedetomidine is the locus ceruleus rather than the cerebral cortex. Therefore, its induced sedation is characterized by an easy and quick arousal from sedation resembling natural sleep⁵.

Dexmedetomidine is odourless and does not cause mucosal stimulation, making it suitable for intranasal administration in paediatric patients^{6,7}. The drug via intranasal route is absorbed directly into the systemic circulation without first pass metabolism and is less painful route of administration⁸.

The objective of this study was to compare the effect of dexmedetomidine versus midazolam for intranasal premedication in children posted for elective surgery on preoperative anxiety, sedation, and ease of child-parent separation as well as any postoperative side effects.

METHODOLOGY-

In this prospective, randomized, double-blind study, the study protocol was approved by the Ethical Committee and informed consent was obtained for each patient from parent/legal guardian.

In this study 100 patients of ASA Grade 1 and Grade 2, of either sex aged between 2-8 years posted for elective minor surgical procedures

were included. The children with previous history of allergy to anaesthetic medication, History of CNS disorder, Congenital Heart Disease, Mental retardation were excluded from study. All patients were evaluated for fitness and fasted 6 h for solids and 2 h for clear liquids.

In the pre-operative room, baseline heart rate, blood pressure and oxygen saturation of the subject were noted before the commencement of the trial.

The children were randomly divided by computer generated table into Group D or Group M of 50 patients each supposed to receive intranasal dexmedetomidine 1 µg/kg and intranasal midazolam 0.2 mg/kg respectively. All drugs were prepared by an anaesthetist who is not involved in the study and each drug was administered by the observer was completely blind to the study and to the group allocation of the child. The subjects were placed in recumbent position and the respective doses of intranasal drug were dripped into both the nostrils using a nasal dropper.

Post-anaesthetic vitals were recorded every 10 minutes. Children were evaluated for adequacy of sedation, behaviour and response to child-parent separation by sedation score, behaviour score and separation score respectively at 10, 20 and 30 minutes after drug administration. Children were observed for any signs of upper airway obstruction, respiratory depression, apnoea and oxygen desaturation. Following surgery recovery of child is assessed by post-anaesthetic wake-up score.

EVALUATION SCALE-

Sedation score:

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

Behaviour score:

- 1- Calm and co-operative.
- 2- Anxious but reassuring.

- 3- Anxious but not reassuring.
- 4- Crying or resisting.

Separation score:

- 1- Patient unafraid co-operative asleep.
- 2- Slight fear or crying quite with reassurance.
- 3- Moderate fear or crying not quite with reassurance.
- 4- Crying need for restraint.

Post- anaesthesia wake-up score:

- 1- Calm and co-operative.
- 2- Not calm but could be easily calmed.
- 3- Not easily calmed, moderate agitation and restless.
- 4- Combative, excited and disoriented.

STATISTICAL ANALYSIS-

Data were analysed using SPSS® version 16 (Statistical Packages for the Social Sciences, Chicago, IL, USA). Results were expressed as mean ± standard deviation (SD) or numbers (percentages). Quantitative data were compared using one-way analysis of variance (ANOVA) and unpaired t-test; qualitative data were analysed using a chi-square test. A p-value of < 0.05 was considered statistically significant.

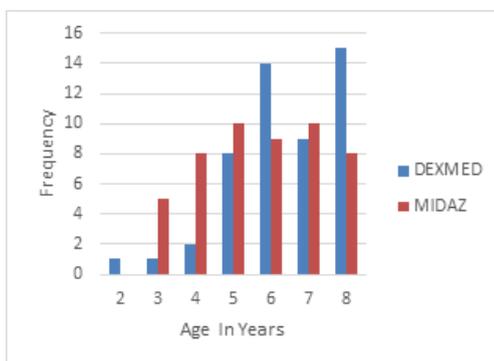
RESULTS-

In present study, children in the two study groups were in the age group of 2-8 years with mean age of 6.4±1.44 in Group D and 5.9±1.56 in Group M, mean weight of 19.92±3.31 in Group D and 18.62±3.36 in Group M and with almost equal male and female population. The two groups were comparable with respect to age, weight (Table-1). No child complained of pain or discomfort with intranasal drug administration. There were no statistical differences in the demographic parameters (Graph-1). Pre sedation vitals heart rate, SBP, DBP, SPO₂, between group D and group M were comparable and there is no statistical difference (Graph-2).

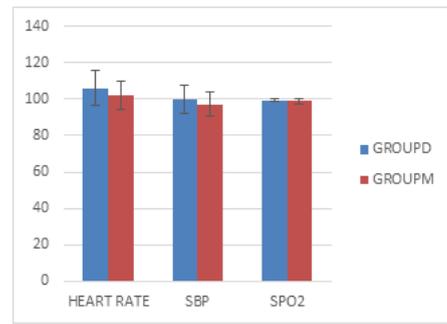
Table-1: Demographic Data and Pre Sedation Vitals.

	Group-D	Group-M	T Value	P Value	Significance
Demographic data					
Age (yrs)	6.4± 1.44	5.9± 1.56	1.67	0.09	Not Significant
Weight(kg)	19.92± 3.31	18.62± 3.36	1.95	0.06	Not Significant
Pre sedation vitals					
HR(Per Minute)	106.14± 9.84	102.88± 7.91	1.83	0.07	Not significant
SBP(mm Hg)	99.96± 8.01	97.08± 6.62	1.90	0.06	Not significant
DBP(mm Hg)	66.4± 5.63	65.2± 6.14	1.02	0.31	Not significant
SPO ₂ (%)	99.3 ± 0.84	99.04 ± 1.53	1.06	0.29	Not significant

Graph-1: Age Distribution.



Graph-2: Pre sedation Vitals.

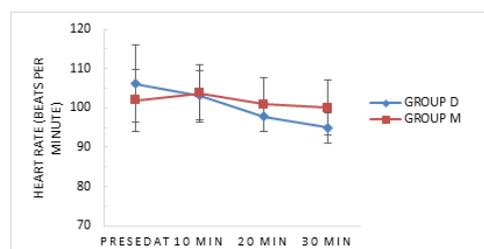


Both the heart rate and Systolic blood pressures were decreased in group D after premedication. The Mean heart rate at 30 minutes after premedication in group D is 95.04± 3.86 and group M is 100± 7.01 which is statistically highly significant (p<0.0001). The SBP at 30 min after pre medication in group D is 94.76±6.54 and group M is 100.4±5.69 which is statistically highly significant (p<0.0001). There is no incidence of bradycardia and hypotension were noted in both the groups. In Group D, SPO₂ changed from baseline value of 99.3±0.84 to 98.8±1.27 at 30 minutes whereas in Group M it changed from baseline value of 99.04 ± 1.53 to 99.06±1.24. Statistically there is no difference between the groups (Table-2), (Graph-3,4).

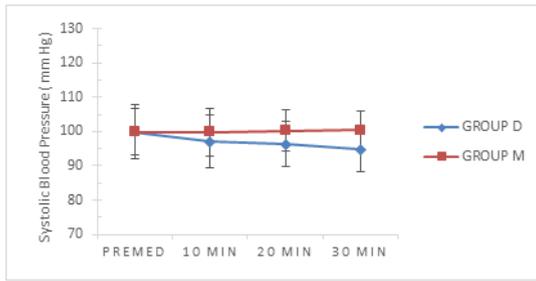
Table-2: vital data at 10 minute intervals after premedication.

Post Sedation Vitals	Group-D	Group-M	T Value	P Value	Significance
Heart Rate					
10 Min	103.16± 6.25	103.72± 7.20	0.42	0.68	Not Significant
20 Min	97.8± 3.90	100.92± 6.87	2.79	0.006	Significant
30 Min	95.04± 3.86	100± 7.01	4.38	0.0001	Highly Significant
Systolic Blood Pressure(Mm Hg)					
10 Min	97.04± 7.71	99.84±6.85	1.92	0.06	Not Significant
20 Min	96.36±6.71	100.28±6.03	3.0719	0.003	Significant
30 Min	94.76±6.54	100.4±5.69	4.59	0.0001	Highly Significant
Diastolic Blood Pressure(Mm Hg)					
10 Min	66.8±4.71	64.4± 7.60	1.89	0.06	Not Significant
20 Min	67± 4.63	64.2 ±7.58	2.23	0.02	Significant
30 Min	66.8± 4.71	64± 7.82	2.17	0.03	Significant
Spo₂ (%)					
10 Min	99.14±0.98	99.18± 1.26	0.1768	0.86	Not Significant
20 Min	98.96±1.01	99.1±1.19	0.6315	0.529	Not Significant
30 Min	98.8±1.27	99.06±1.24	1.0343	0.303	Not Significant

Graph-3: Comparison of Heart Rate during the Time Course.



Graph-4: Comparison of SBP during the Time Course.

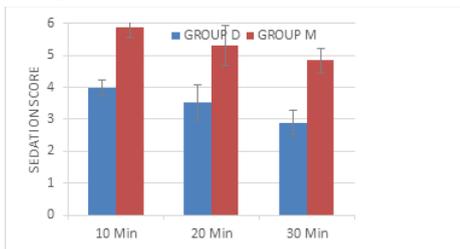


The sedation scores, behavioural score and parental separation scores were low in group D when compared to group M from the beginning of premedication. There is a significant difference in sedation score, behavioural score and parental separation scores after premedication at 10, 20, 30minutes between the two groups (P<0.0001). This is statistically highly significant. (Table-3),(Graph-5,6,7).

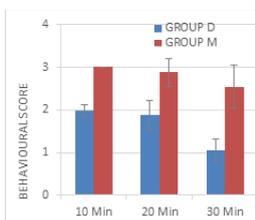
Table-3: Sedation, Behavioural and Parental Separation scores at 10 minute intervals after premedication.

	Group-D	Group-M	T Value	P Value	Significance
Sedation Scores					
10 Min	3.98± 0.25	5.88 ± 0.33	32.72	0.0001	HighlySignificant
20 Min	3.52± 0.54	5.3 ± 0.61	15.34	0.0001	HighlySignificant
30 Min	2.9±0.36	4.84± 0.37	26.41	0.0001	HighlySignificant
Behavioural Scores					
10 Min	1.98 ± 0.14	3.01 ± 0.00	51.00	0.0001	HighlySignificant
20 Min	1.88 ± 0.34	2.88 ± 0.33	13.89	0.0001	HighlySignificant
30 Min	1.04 ± 0.28	2.54± 0.50	18.37	0.0001	HighlySignificant
Parental Separation Scores					
10 Min	2.02 ± 0.14	3.00 ± 0.00	49.00	0.0001	Highly Significant
20 Min	1.9± 0.30	2.84 ± 0.37	13.89	0.0001	Highly Significant
30 Min	1.00 ± 0.00	2.1 ± 0.30	25.67	0.0001	Highly Significant

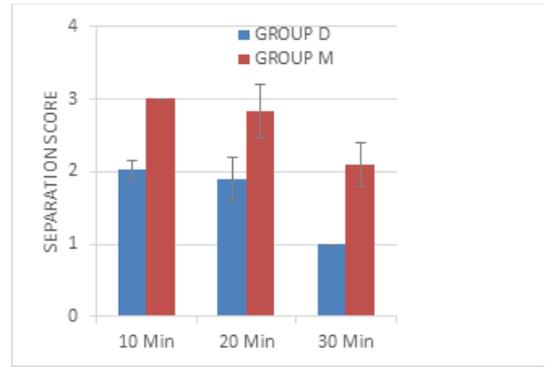
Graph-5: Comparison of sedation scores During the Time Course after pre medication.



Graph-6: Comparison of behavioural scores During the Time Course after pre medication.



Graph-7: Comparison of parental separation scores During the Time Course after pre medication.



In group D 48 out of 50 (96%) study population had the score of 1, where as in group M 2 out of 50 study population (4%) had post anaesthesia wake up score of 1(Table-4), (Graph-8).The PAWS score of group D is 1.04±0.19 which is lower than group M 1.98±0.25 and it is statistically significant (p<0.0001) (Table-5), (Graph-9).

Table-4: Distribution of Frequency of PAWS scores in both groups after pre medication.

PAWS Score	Group-D		Group-M	
	Frequency	Percent	Frequency	Percent
1	48	96	2	4
2	2	4	47	94
3	0	0	1	2
4	0	0	0	0
Total	50	100	50	100

Graph-8: Distribution of Frequency of PAWS scores in both groups after pre medication.

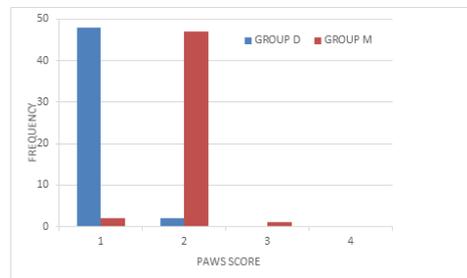
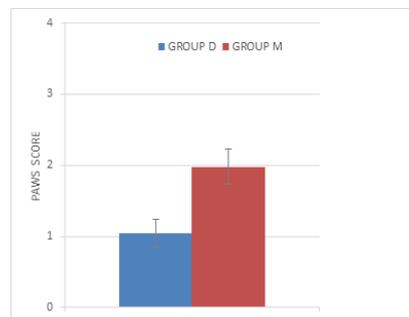


Table-5: Comparison of PAWS scores between the groups.

POST SEDATION VITALS	Mean & SD		Unpaired T Test		
	Group-D	Group-M	T Value	P Value	Significance
PAWS SCORE	1.04±0.19	1.98±0.25	21.190	0.0001	Highly significant

Graph-9: Comparison of PAWS scores between the groups.



DISCUSSION-

Premedication helps to alleviate the stress and fear of treatment as well as to ease child-parent separation and promote a smooth

induction of anaesthesia^{9,10}. The ideal premedication drug and the most appropriate route of its administration are still debatable. Intranasal administration of a sedative should be effective, safe, and yield a rapid onset of sedation. More importantly, compliance with nasal sedation is easier to achieve than with oral sedation in young children¹¹.

Midazolam has many desirable properties of premedicant for children especially undergoing day care surgery. It produces sedation by stimulating GABA receptors in the cerebral cortex. It exerts a reliable dose dependent anxiolytic effect without over sedation and produces minimum cardiovascular and respiratory effects. Also anterograde amnesia produced by midazolam should help to reduce the physiological trauma of anaesthesia and surgery. However intranasal midazolam is associated with an unpleasant burning sensation in the nasal cavity and respiratory depression, postoperative shivering. Therefore the nasal administration of midazolam is not favoured in practice.

Dexmedetomidine produces sedation by stimulating α_2 adrenergic receptors and the locus ceruleus, stimulation of α_2 adrenergic receptors at this site reduces central sympathetic output resulting in increased firing of inhibitory neurons. Dexmedetomidine GABA receptor therefore it causes sedation and analgesia without causing respiratory depression. It produces "cooperative sedation" which means that though the patient is sedated the patient can still interact with healthcare professionals.

Alpha 2-Agonists produce a modest reduction in Blood Pressure and Heart Rate. In a recent study comparing midazolam, clonidine, and dexmedetomidine for premedication in children, both clonidine and dexmedetomidine were shown to reduce mean BP and HR before and during surgery¹². In our study on inter group comparison there was significant decrease in pulse rate at 20 minutes onwards in Group D as compared to Group M.

In Group D heart rate decreased from baseline 106.14±9.84 to 95.04±3.86 (p value < 0.0001) which was both statistically and clinically significant whereas in Group M, there is no significant change in heart rate from baseline of 102.88±7.91 to 100±7.01. These results were similar in comparison with the study of AL Meenakshi Sundaram *et al*¹³.

In Group D systolic blood pressure decreased from baseline 99.96±8.01 to 94.76±6.54 which was both statistically and clinically significant whereas in Group M, there is no significant change in systolic blood pressure.

There was no statistically significant difference oxygen saturation in any of these groups. The post sedation changes within the groups and between two study groups were statistically insignificant and mean SPO2 never dropped below 95%. These results were similar to the study conducted by Darshna D. Patel *et al*¹⁴.

The dose of intranasal dexmedetomidine of 1 µg/kilogram has been shown to have a time of sedation onset of approximately 25 minutes and median duration of approximately 85 minutes¹⁵. In our study both midazolam and dexmedetomidine were administered intranasally and children were observed for 30 minutes before the induction of anaesthesia.

Therefore the sedation score, behavioural score was significantly less at 30 minutes after intranasal dexmedetomidine. This also resulted in easier child-parent separation.

The mean sedation score in Group D at 30 minutes was 2.9±0.36 and in Group M, it was 4.84±0.37 (p<0.000) inferring statistically that at 30 minutes after administration of sedative premedication children in Group D achieved adequate sedation than compared to those in Group M.

The mean behaviour score in Group D at 30 minutes was 1.04 ± 0.28 and in Group M, it was 2.54± 0.50 (p<0.000) implying that Group D achieved better anxiolysis than Group M. The results were similar to the study conducted by A.L.Meenakshi Sundaram *et al*¹³.

The mean separation score in Group D at 30 minutes was 1.00±0.00 and in Group M, it was 2.10±0.30 (p<0.000) implying that subjects Group D showed easy child-parent separation than those in Group M. The results were comparable to that of study conducted by Ashraf M. Ghali *et al*⁷ where in subjects who received intranasal dexmedetomidine easier child-parent separation than those who received oral midazolam.

Post anaesthesia recovery was assessed by post anaesthesia wake-up score. In Group D, 100% of subjects had satisfactory post anaesthesia wake-up score whereas in Group M the same was 98%. The results were comparable to that of study conducted by Saad A. Sheta *et al*¹⁶.

The only side effect seen with intranasal midazolam group is 21 out of 50 children were crying due to irritation and burning sensation of nasal mucosa following administration of drug.

Thus in our study that premedication intranasal dexmedetomidine of 1µg/kg was found to be better in terms adequacy of sedation, anxiolysis and child parent separation compared to intranasal midazolam of 0.2mg/kg. There were no major side effects observed except for burning sensation of nasal mucosa in minority of Patients with intranasal midazolam.

CONCLUSION-

Intranasal dexmedetomidine compared to intranasal midazolam was associated with lower sedation score easier child parent separation and better postoperative recovery without any adverse side effects. Thus it can be concluded that intranasal dexmedetomidine can be used effectively and safely as pre-anaesthetic medication in children undergoing minor surgical procedures under general anaesthesia.

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