How to Cite:
Ali, M. M., George, J., & Deepak, S. (2022). Comparison of intranasal dexmedetomidine and midazolam as premedication on haemodynamic stability: A teaching hospital based study in Kerala. *International Journal of Health Sciences*, *6*(S2), 13018–13027. https://doi.org/10.53730/ijhs.v6nS2.8426

Comparison of intranasal dexmedetomidine and midazolam as premedication on haemodynamic stability: A teaching hospital based study in Kerala

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***Abstract*---**Background: Premedication in pediatric population helps to produce a relaxed state with reduced anxiety and increased. These pre-medications, midazolam and dexmedetomidine are effectively used as sedatives. The present study was planned to compare intranasal dexmedetomidine with intranasal midazolam as a pre-anesthetic medication in children. Fear of unpleasant and painful procedures, separation from parents and unwillingness to breathe through an anaesthesia face mask may produce stormy anaesthetic induction in unpremeditated patients. Because of this premedication should be an integral part of paediatric anaesthetic practice. Aims and Objectives: To evaluate the Intranasal administration of Midazolam and Dexmedetomidine as Premedication on Haemodynamic Stability among Paediatric Patients. Material & Methods: This Comparative study was carried out at Department of Anaesthesiology, P K DAS Institute of Medical Sciences, Vaniamkulam, Ottapalam Kerala, India . A total of 70 Paediatric Patients of both sex age group between 1- 5 year from the routine surgical list of our Hospital were included in the study. The children were divided into two groups i.e. 35 in each based on the premedication received and by random allotted numbers. Out of the selected 70 subjects 35 were allotted into each group based on the random numbers which was generated by computer and

respective premedication were given to the children. In the children belonging to GROUP-M Premedication was given in form of intranasal midazolam spray 0.5mg/kg body weight. In the GROUP-D Premedication was intranasal dexmedetomedine instillation 1mcg/kg body weight. In the preanaesthetic room, vital parameters, dosing time and acceptance of premedicant were noted. The Vital parameters like. pulse rate, respiratory rate, blood pressure, oxygen saturation (SpO2) was noted before the preanasthetic medication, 1 min, 5 min, 15 min, 30 min, 45 min after Premidication were noted. Results and Observations: Comparison in two groups with regards to demographic data. There was no significant statistical difference in age,weight,sex, duration of surgery and type of surgery between the two groups. The Blood Pressure, Pulse and Respirator rate was found to differ between group after 30 min of drug administration. Spo2 was found to constant in both the groups. Conclusion: Our study concluded that Intranasal dexmedetomidine causes some degree of cardiovascular depression in paediatric patients but it is better than Midazolam, however, they do impart cardiovascular stability to patients undergoing the stress of surgery.

***Keywords*---**stress surgery, intranasal midazolam, intranasal dexmedetomidine, intranasal, haemodynamic, premedication, cardiovascular stability, paediatric patients.

Introduction

The primary outcome was determined with correlation to preoperative sedation, response of child to parental separation, mask induction, and the incidence and severity of postoperative agitation. Secondary outcomes studied hemodynamic stability of both drugs. Premedication in pediatric population helps to produce a relaxed state with reduced anxiety and increased compliance as well as to ease separation from parent and allowing the patient to tolerate and co-operate with the necessary procedure.[1-4] Intranasal administration has been shown to be very effective, easy, non-invasive route with high bioavailability and rapid onset of action due to the high vascularization of the nasal mucosa .The American editor Anaesthetist, Frank Hoffer McMechan in 1920 used the word "PREMEDICATION".Sington[5] and Hewer[6] in their first edition of "Recent advances in anaesthesia" also used the word Premedication. The pre-anaesthetic medication forms an eternal part of any kind of anaesthetic management for all types of surgery. Few types of premedication are almost universally administered before induction of anaesthesia. In ancient days both wine and opium were given to lessen the fear of surgery. Many anesthetic pre-medications are used to relieve this stress response. Of these pre-medications, midazolam and dexmedetomidine are effectively used as sedatives. Our study was planned to compare intranasal dexmedetomidine with intranasal midazolam as a pre-anesthetic medication in children. 70 children aged 1–5 years, of either sex, with American Society of Anesthesiologists (ASA) physical status and undergoing elective adenotonsillectomy surgery were enrolled in this comparative prospective, double blinded, randomized clinical Anaesthetic management begins with the

preoperative psychological preparation of the patient and administration of a drug or combination of selected drugs to produce specific pharmacological responses before to the induction of anaesthesia. Traditionally this initial psychological and pharmacological component of anaesthetic management is referred to as preoperative medication. The objectives of premedication are:[7,8].

A.To lessen preoperative anxiety and fear. B. To assist anaesthesia, enhance the quality of induction, maintenance and recovery from anaesthesia. C. To prevent autonomic reflexes. D. To prevent undesirable side effects. Fear of unpleasant and painful procedures, separation from parents and an unwillingness to breathe through an anaesthesia face mask may produce stormy anaesthetic induction in unpremedicated patients.[7,8,9] Because of this premedication should be an integral part of paediatric anaesthetic practice. Preanaesthetic medication Plays a crucial role in the children who are given anaesthesia. Preparing a child for the elective surgery should be facilitated byvarious booklets with pictorial presentation slide show s or through few movie scenes and then by the reinforcement of the information by the anaesthesiologist. Among children there are few drugs which are used as preanasthetic medication. One such type of drugs is Diazepam which has a very good anxiolytic property with poor antiemetic effect but doesn't have analgesic or antisialogogue effect. Similarly, trimeprazine also provide good sedation and had a mild antisialogogue effect but it is associated with more chances of postoperative restlessness. Use of intranasal midazolam spray as premedication has come into practice from early nineties.[10,11]. Owing to high mucosal vascularity, intranasal route offers rapid and virtually complete absorption within one-two hours into systemic circulation. As midazolam has high hepatic clearance, avoidance of hepatic first pass metabolism offers greater systemic bioavailability[10,12]. It has faster onset than oral or rectal route.[13] New drugs such as the α2- agonists have emerged as alternatives for premedication in pediatric anaesthesia. A highly selective α2 – agonist Dexmedetomedine which has both sedative and analgesic properties and is devoid of respiratory depressant effect. These properties render it potentially useful for anaesthesia premedication.[14] In our present study we used Midazolam intranasal and Dexmedetomidine Intranasal. A γ-amino-butyric acid (GABA) receptor inhibitor, Midazolam is the most widely employed sedative drug in children as a premedication. It is known to provide effective sedation, anxiolytic effect, and of antero-grade amnesia of varying degrees. [15,16] A recent clinical study shows that a dose of 0.2 mg/kg midazolam is effective in reducing both induction anxiety and separation from parent, with no effect on recovery time. [17,18]

Materials and Methods

This study was carried out at Department of Anaesthesiology P K DAS Institute of Medical Sciences, Vaniamkulam, Ottapalam Kerala, India. A total of 70 Pediatric Patients of of both sex age group between 1- 5 year from the routine surgical list of our Hospital were included in the study. The children were divided into two groups i.e. 35 in each based on the premedication received and by random allotted numbers. Out of the selected 70 subjects 35 were allotted into each group based on the random numbers which was generated by computer and respective premedication were given to the children. In the children belonging to GROUP-M

Premedication was given in form of intranasal midazolam spray 0.5mg/kg body weight. In the GROUP-D Premedication was intranasal dexmedetomedine instillation 1mcg/kg body weight. In the preanaesthetic room, vital parameters, dosing time and acceptance of premedicant were noted. The Vital parameters like. pulse rate, respiratory rate, blood pressure, oxygen saturation (SpO2) was noted before the preanasthetic medication, 1 min, 5 min, 15 min, 30 min, 45 min after Premedication were noted.

Results and Observations

The two groups were comparable with regards to demographic data. There was no significant statistical difference between the two groups with regards to distribution of sex, weight, age, type of surgery and duration of anaesthesia.

Table 1: Demographic Data of the study groups

Demography	Group-M Mean	SD	Group-D Mean	SD	P-value	Significance
Age	3.03	1.54	3.16	1.23	0.71	NS
Weight	12.43	4.90	13.63	4.33	0.31	NS
Duration of Surgery	71.83	11.17	69.33	10.23	0.36	NS

In group M numbers of Male and Female patients were 30 and 5 respectively with a male: female ratio was 6:1. In group D numbers of Male and Female patients were 29 and 6 respectively with a male: female ratio was 5:1, As in Figure 1.

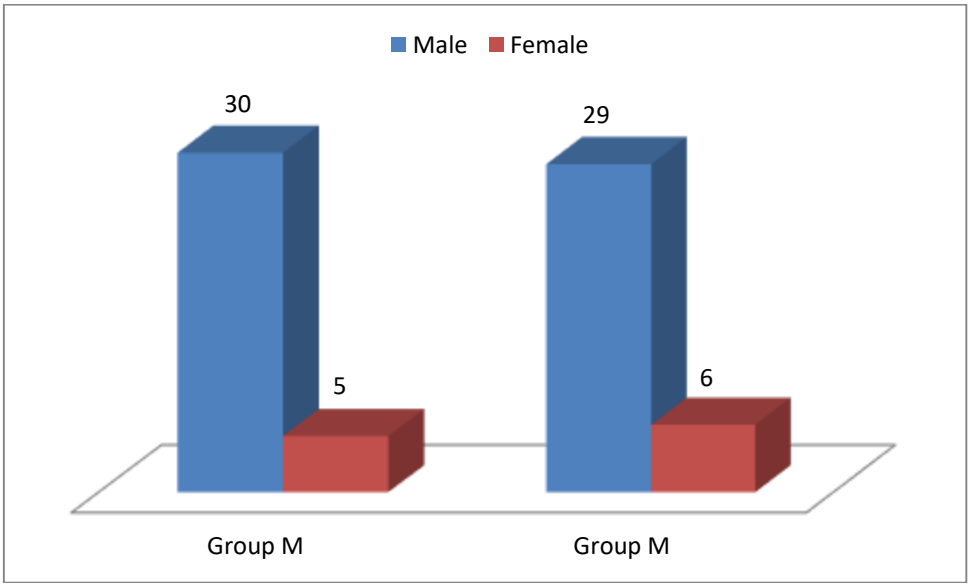

Figure 1: Sex Distribution

Table 2: Mean Blood Pressure changes in Both Group

Time		Group-M	Group-D	P-value	Significance
Before Premedication	Mean	73.66	74.02	0.56	NS
	SD	2.43	2.40		
1minute after Premedication	Mean	73.75	74.13	0.56	NS
	SD	2.52	2.35		
5minutes after Premedication	Mean	73.15	73.48	0.57	NS
	SD	2.30	2.26		
15minutes after Premedication	Mean	71.73	71.35	0.525	NS
	SD	2.77	1.72		
30minutes after Premedication	Mean	71.93	69.44	0.0001	S
	SD	2.71	1.64		
45minutes after Premedication	Mean	71.91	69.13	<0.0001	HS
	SD	2.70	1.69		

In the above table the Blood Pressure changes (Mean) in both the groups M and D was recorded before the administration of Premedication and after 1, 5,15,30 and 45 Minutes of Premedication. The Blood pressure between the groups was found to be statistically significant only at the 30 min and highly significant at 45 minutes after the administration of premedication. Blood Pressure Before and after the premedication at 1,5 and 15 minutes was not statistically significant.

Table 3: Mean Respiratory Rate changes in Both Groups

Time		Group-M	Group-D	P-value	Significance
Before Premedication	Mean	22.34	21.53	0.20	NS
	SD	2.60	2.31		
1minute after Premedication	Mean	21.76	21.2	0.27	NS
	SD	2.16	1.84		
5minutes after Premedication	Mean	21.06	21.2	0.79	NS
	SD	2.18	1.84		
15minutes after Premedication	Mean	19.96	21.2	0.02	S

	SD	2.26	1.84		
30minutes after Premedication	Mean	19.66	21.03	0.01	S
	SD	2.26	1.73		
45minutes after Premedication	Mean	19.36	20.93	0.003	S
	SD	2.32	1.61		

From the analysis of data, it is evident that the mean respiratory rate was comparable in both groups. Also the mean respiratory rate did not change significantly till 15 after premedication. But it is evident that there was change in respiratory rate at 15 min, 30 min and 45 min in group as compared to group and thus was statistically significant

Table 4: Mean Pulse Rate changes in Both Group

Time		Group-M	Group-D	P-value	Significance
Before Premedication	Mean	113.5	113.3	0.93	NS
	SD	9.42	9.048		
1minute after Premedication	Mean	112.96	111.26	0.49	NS
	SD	9.76	9.50		
5minutes after Premedication	Mean	111.1	110.06	0.67	NS
	SD	10.41	8.44		
15minutes after Premedication	Mean	108.96	105.66	0.15	NS
	SD	10.26	7.35		
30minutes after Premedication	Mean	107.63	100.13	0.005	S
	SD	10.30	6.68		
45minutes after Premedication	Mean	105.96	98	0.0005	S
	SD	10.6	5.43		

It is evident that mean pulse rate was comparable in both groups at it was found to statistically significant at 30 and 45 min after premedication's only. Mean pulse rate did not change significantly up to 15 min after premedication. At 15min and 45min in both group M and group patients became calm and sedated. Pulse rate was better controlled in group D as compared to patients in group M, so significant difference was seen at 15 and 45min.

Table 5: Mean changes in oxygen saturation (%) by pulse oximeter (SpO2) in Both Groups

Time		Group-M	Group-D	P-value	Significance
Before Premedication	Mean	98.5	98.33	0.18	NS
	SD	0.508	0.47		
1minute after Premedication	Mean	98.53	98.33	0.12	NS
	SD	0.507	0.47		
5minutes after Premedication	Mean	98.23	98.06	0.13	NS
	SD	0.43	0.44		
15minutes after Premedication	Mean	98.13	98.13	1.00	NS
	SD	0.34	0.34		
30minutes after Premedication	Mean	98.03	98.03	0.28	S
	SD	0.18	0.305		
45minutes after Premedication	Mean	98.03	98.03	1.00	HS
	SD	0.18	0.18		

There was no drop in the oxygen saturation among the study subjects in both the groups. The association of oxygen saturation was found to be statistically not significant between the groups.

Discussion

A newer alpha 2-agonist, Dexmedetomidine has more selective action on the alpha 2-adrenoceptor and has a short half-life. Its bioavailability is around 80% when given via the nasal mucosa. Dexmedetomidine usage in paediatric population as preanesthetic is increasing because of its huge safety profile. We hypothesized that dexmedetomidine can be used as an alternative to midazolam for intranasal premedication in children. Midazolam is the most commonly used anxiolytic premedication in children. It facilitates gamma amino butyric acid (GABA) receptor-mediated chloride conductance, which has an inhibitory effect on neurons in the cerebral cortex. It has been successfully used through various routes, e.g. intravenous, intramuscular, oral and intranasal. Premedication is necessary to make the patient calm and to lessen the anxiety related to surgery and anesthesia Anesthesiologists responsibility in premedicating a patient before induction of anaesthesia is of vital importance. There is universal agreement on the need for some premedication. It forms an integral part of anaesthetic management. Preanaesthetic medication may reduce the risks of adverse psychological[19,20] and physiological[21,22] sequel of induction of anaesthesia in

a distressed child. Anaesthetic management begins with the preoperative preparation of the patient and administration of a drug or combination of drugs selected to produce specific pharmacological responses prior to induction of anaesthesia. Physiological and psychological makeup of a child differs from adults and this affects him as a subject for anaesthesia. He is much upset emotionally from being snatched away from his parents. Physiologically child is unstable than adults; so there is marked fluctuation of pulse, blood pressure, respiration and secretion during anaesthesia, if dose is altered slightly . The mean pulse rate was comparable in two groups. As per the statistical analysis, it appears that dexmedetomedine group showed decrease in heart rate and mean arterial pressure with time when compared to group midazolam. But to rule out any cardiovascular depression that might not be evident from the monitoring of pulse rate only, we decided to measure the mean blood pressure. Hence measurement of blood pressure was recorded on the preoperative assessment and then only immediately after premedication and then at 5min15 min, 30 min and 45 min after premedication. There was significant decrease in heart rate and decrease in systolic blood pressure after 30 min in group D as compared to group M. The findings of our study was comparable and similar to the study findings of Vivian M et al[23] who concluded that heart rate and systolic blood pressure significantly decreased with time in dexmedetomedine group than midazolam group. In another study done by Ghali AM et al[24] concluded that Thus, dexmedetomedine causes cardiovascular depression in pediatric patients when administered by the intranasal route as compared to midazolam. The Respiratory Effects of the Premedication in our study was similar to the study findings of the Naqash et al[25], Lee-Kim, S.J., S. Fadavi, et al. [26]and Vivian M Yuen et al 15.All the mentioned studies concluded that there was Oxygen Saturation was maintained by both the groups throughout the operation time. The study findings of Malinovsky was little contrast to our study findings where a case of respiratory depression was noted. We found that there were no clear differences among both the groups with relevance to adverse effects, emergence from anaesthesia, or follow-up. The foremost limitation seen in this trail is that the timing of the drug administration, since peak onset of both the drug varied. So, fixing premedication time of both groups is also the reason for the difference and dose of midazolam could also be inadequate.

Limitations

1. The three- or four-point scales used in this study is invalidated still, which again is considered as a limitation.
2. There were some difficulties we encountered in evaluating paediatric patients while using these scales, For instance, if the child was crying but not combative, we found it hard to make a decision what rating to provide on the mask induction scale.
3. More valid scales are to be used.

Conclusion

Both Dexmedetomidine and Midazolam are effective drugs which can be given as preanesthetic medication. However Dexmedetomidine produces better parental separation and mask acceptance scores as compared to Midazolam. We concluded

that intranasal dexmedetomidine 1 mcg/kg as instillation is an effective premedicant as compared to intranasal midazolam. inpediatric patients undergoing surgical procedure. Intranasal dexmedetomidine causes some degree of cardiovascular depression in pediatric patients when administered by intranasal midazolam; however, they do impart cardiovascular stability to patients undergoing the stress of surgery, by ameliorating the psychological and physiological aspect of anxiety. There is no significant respiratory depression and fall in arterial saturation seen in both groups. Intranasal dexmedetomidine provides better postoperative recovery than intranasal midazolam.

Sources of Support: None Declared
Conflict of Interests: None Declared

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