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Intranasal Dexmedetomidine Vs Intranasal Midazolam as Premedication in Children Undergoing Tonsillectomy

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Abstract **Original Research Article**

Background: The pre-operative period is a very stressful event for most of the individuals undergoing surgery especially the pediatric patients. So, relieving their pre-operative anxiety becomes an important concern for an anesthesiologist. Many anesthetic pre-medications are used to relieve this stress response. Of 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. A total of 100 children aged 6–12 years, of either sex, weighing 18–32 kg, with American Society of Anesthesiologists (ASA) physical status 1 and undergoing elective adenotonsillectomy surgery were enrolled in this comparative prospective, double blinded, randomized clinical study. The children were divided into 2 groups: group D and group M, of 24 each. Sixty minutes before induction of anesthesia, group D (n = 50) received intranasal dexmedetomidine at a dose of 1 µg/kg and group M (n = 50) received intranasal midazolam of 0.2 mg/kg. ***Results*:** Children who were pre-medicated with dexmedetomidine had lower sedation scores, lower anxiety levels, easier child-parent separation, better mask acceptance than those who received midazolam. The incidence of emergence agitation was decreased in both groups with no significant difference. ***Conclusion:*** Intranasal dexmedetomidine seems to have more advantages compared with midazolam. Thus, it can be used safely as a pre-anesthetic medication in children undergoing any surgical procedures under general anesthesia.

Keywords: Premedication, Midazolam, Dexmedetomidine, Intranasal, tonsillectomy.

INTRODUCTION

Preanaesthetic medication in paediatric patients is well known to be a challenge for anaesthesiologists. A distressed child is at risk for potentially hazardous psychological and physiologic sequel. The age of the child, as well as family characteristics, illness and hospital all contribute to the degree of distress.

A peaceful separation of the parent and the child is the definition of successful premedication. Premedication helps to alleviate the stress and fear of treatment as well as to ease child-parent separation and promote a smooth induction of anesthesia [1-3]. Adenotonsillectomy is one of the most common surgical procedures performed on pediatric patients. The preoperative period can be stressful for children and their parents. The goals of preanesthetic medication for children include allaying patient anxiety and facilitating the induction of anesthesia and preventing postoperative psychological sequelae.

Midazolam, a γ-amino-butyric acid (GABA) receptor inhibitor is the most commonly used sedative drug for premedication in children. It provides effective sedation, anxiolysis,and varying degrees of antero-grade amnesia; however adverse effects such as post-operative behavioural changes, hiccups and paradoxical hyperactive reactions have been observed [4, 5]. A recent evidence-based clinical update has shown that

intranasal midazolam 0.2 mg/kg is effective in reducing both separation and induction anxiety in children, with minimal effect on recovery time.

Dexmedetomidine is a newer alpha 2-agonist with a more selective action on the alpha 2-adrenoceptor and a shorter half-life [6, 7]. its bioavailability is 81.8% (72.6-92.1%) when administered via the nasal mucosa. Therefore, we sought to compare the effects of intranasal dexmedetomidine [8]. on mask acceptance and preoperative sedation in pediatric patients with the effects of midazolam administered via the same route. The primary end point was satisfactory mask induction, and the secondary end points included satisfactory sedation upon separation from parents, hemodynamic changes, postoperative analgesia, and agitation score at emergence

AIMS AND OBJECTIVES

This study is conducted to evaluate whether intranasal dexmedetomidine is as effective as intranasal midazolam for premedication in children posted for adenotonsillectomy.

- To compare satisfactory sedation level.
- To compare the co-operation for mask induction.
- To compare the alleviation of anxiety level

MATERIALS AND METHODS

SOURCE OF DATA

After getting approval from institutional ethical committee, this double-blind randomized controlled study was conducted in the department of anaesthesiology at sree mookambika institute of medical sciences between July 2019 to April 2020 in patients undergoing elective tonsillectomy(with or without adenoidectomy) under general anaesthesia.

Inclusion Criteria

- ASA Physical status I
- 6-12 years of age

Exclusion Criteria

- Recent upper respiratory tract infection/ lower respiratory tract infection
- Known allergy or hypersensitivity reaction to dexmedetomidine or midazolam.
- Renal & Hepatic failure
- Leukaemia
- Cardiac arrthymias
- Congenital diseases

*Congenital cardiac defect
*Pierre-Robin, Down's syndrome

- Developmental delay
- Neurological disorders

***SAMPLE SIZE**

Considering P_1(82.2%) in group M (midazolam) and P_2(60%) in group D(dexmedetomidine) based on previous study with power 80% and α-5%, the sample size selected for the present study is 100(50 in each group).

Procedure

Pre anesthetic evaluation was done, appropriate investigation were done. All patients were reviewed on previous day of surgery both patients and parents were explained in detail about the procedure ,informed & written consent was taken and advised nil per oral 6hours for solids and 2hours for clear liquids. The children were randomly allocated to one of two groups by a computer generated tables of random numbers. In the premedication room routine monitors (NIBP, ECG, SPO2) were connected and baseline parameters were recorded. All of the children had EMLA cream application on dorsum of hand and received intranasal medication 60 min before induction of anaesthesia.

Patient in group M (50) received 0.2mg/kg of midazolam intranasally as nasal drop (5mg/ml IV preparation) in 1ml syringe and group D(50) received 1µg/kg of dexmedetomidine intranasally as nasal drops using 1ml insulin syringe.

The drug mixture was prepared by an independent investigator who was not involved in the observation or administration of the anesthesia. The observers and attending anesthesiologists were blinded to the drug being administered. Sedation status and anxiety level was assessed by a blinded observer every 10 min with a six- point sedation scale and four – point scale. After 60 min children were shifted to operating room and separation from parents was also evaluated using the anxiety scale.

After shifting to operating room all baseline monitoring continued, preoxygention was done with 100% oxygen, under aseptic precaution, another anaesthesiologist secured IV cannula using 20-22G in EMLA cream applied hand. A three-point scale used to assess the degree of mask acceptance by an anesthetist who was blinded to the type of premedication used. All patients were premedicated with inj glycopyrolate 0.005 mg/kg IV and inj fentanyl 1-2 µg/kg and induced with inj propofol 2 mg/kg and inj atracurium 0.5 mg/kg. Patients intubated with appropriate size oral RAE tube. Maintenance of anaesthesia was with oxygen and nitrous oxide in the ratio of 1:2 and Sevoflurane 1-1.5%. At end of the surgery patients were reversed with inj neostigmine 50 µg/kg and inj. Glycopyrolate 5µg/kg. After adequate suctioning patients extubated. Patients shifted in left lateral position to PACU. Heart rate, SpO2, SBP, and DBP during and after anesthesia were recorded. The level of postoperative sedation and anxiety scores as well as adverse effects on emergence or in the PACU (hypoxemia, bradycardia, nausea,

vomiting, shivering, and hypotension) was also recorded.

DATA COLLECTION TOOL

Modified observers assessment of Alertness/sedation score

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

Anxiety was evaluated every 10 min with a four-point scale.

Anxiolysis Score

1. Calm and cooperative;
2. Anxious but could be reassured;
3. Anxious and could not be reassured
4. Crying or resisting

Mask Induction Score

1. Calm, cooperative or asleep
2. Moderate fear of the mask, cooperative with reassurance
3. Combative, crying.

Score >3 unsatisfactory,
Score 1 or 2 successful response

Postoperative agitation score

After extubation in PACU (postanesthesia care unit) a blinded anesthetist assessed the child's level of agitation according to a three-point scale.

1. Calm, easily arousable, follows commands
2. Restless or crying but calms to verbal instructions
3. Combative, disoriented, thrashing.

STATISTICAL ANALYSIS

1. The quantitative data were presented as mean and standard deviation (SD). Comparison of quantitative variables between the two study groups was done by using independent t test when the data were normally distributed and Mann-Whitney test in non-parametric data. Qualitative data were presented as number and percentage and the differences between the two groups were compared using the chi-square ($\chi 2$) test and/or Fisher exact test when the expected count in any cell found less than 5. The confidence interval was set to 95% and the margin of error accepted was set to 5%. $p < 0.05$ was considered statistically significant (S).

RESULTS

Table 1: Patients' demographic data

Characteristics	Midazolam group (n = 50)	Dexmedetomidine group (n= 50)	p value
Age mean ± SD	8.98 + 2.18	9.00 + 2.11	0.962
Weight mean ± SD	26.32 + 6.13	26.14 + 6.85	0.890
Gender			
Male	30	26	
Female	20	24	
Duration of surgery (min) mean ± SD	34.58 + 3.32	34.24 + 3.52	0.620
Duration of Anesthesia (min) mean ± SD	47.04 + 4.50	47.44 + 3.69	0.628
Extubation time (min) mean ± SD	8.00 + 1.41	8.10 + 1.52	0.733

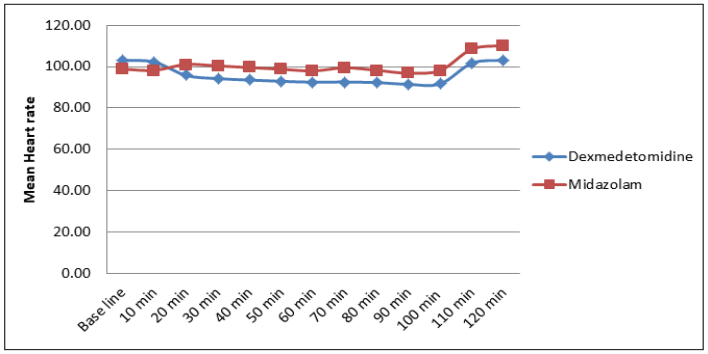


Fig 1: Mean Heart Rate

In our study there was significant reduction in heart rate in dexmedetomidine group when compared to midazolam group from the 20th minute continuously intraoperatively. There was no significant difference in group during the 10th minute after pre medication.

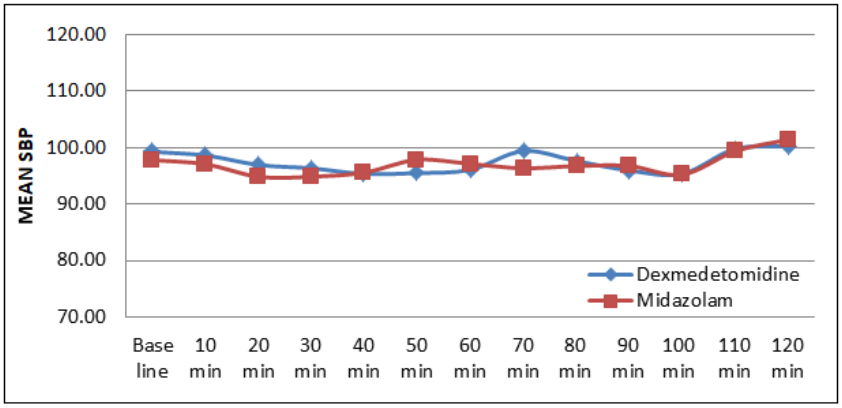
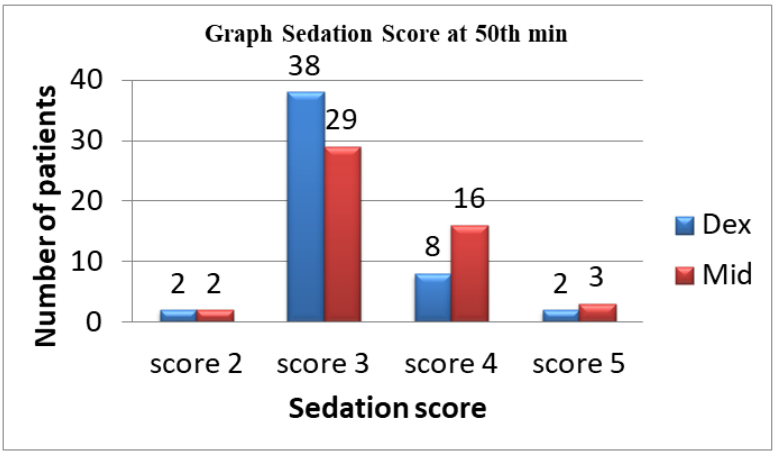
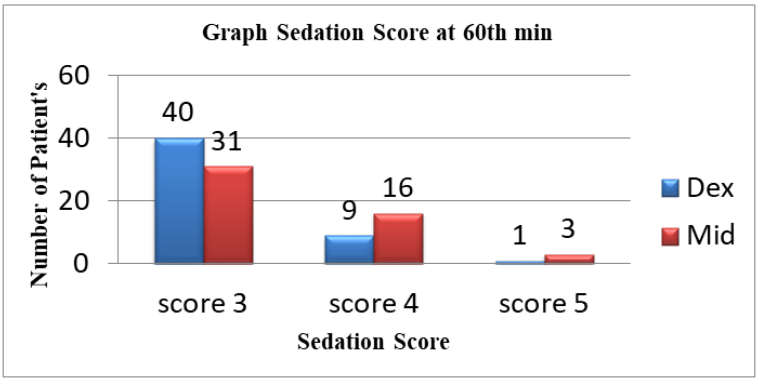


Fig 2: Mean systolic blood pressure

There was no statistical significance in between groups both during preoperative and intraoperative period.

Score	**Drugs**		**P values**
Separation from parents (Anxiolysis Score)	Dexmedetomidine n(%)	Midazolam n(%)	
Calm, cooperative	43 (86)	34 (68)	0.03
Anxious but could be Reassurable.	5 (10)	10 (20)	0.16
Anxious and could not be Reassurable.	1 (2)	4 (8)	0.16
Crying, or resisting	1 (2)	2 (4)	0.56
Quality of mask acceptance			
Calm, cooperative or asleep	42 (84)	35 (70)	0.09
Moderate fear of the mask, cooperative with reassurance	4 (8)	10 (20)	0.08
Combative, crying.	4 (8)	5 (10)	0.72
Postoperative agitation score			
Calm, easily arousable, follows commands	35 (70)	30 (60)	0.30
Restless pr crying but calms to verbal commands	14 (28)	18 (36)	0.39
Combative, disoriented, thrashing	1 (2)	2 (4)	0.56





DISCUSSION

Premedication refers to administration of a drug or combination of drugs before surgery that serves to either complement or improve the quality of anaesthesia. The main goals of premedication are to relieve anxiety, provide amnesia, provide adequate analgesia, prevent aspiration and to suppress the hemodynamic response to intubation and surgical stimulus. Premedication can be administrated through various routes oral, Intramuscular Intravenous, rectal, intranasal etc. Advantages of Intranasal administration is easy to administer, painless ,rapid absorption of drugs, better bioavailability, higher brain concentration is achieved compared to other routes

In our study, we compared effects of intranasal dexmedetomidine vs intranasal midazolam on mask acceptance and satisfactory sedation upon separation from parents in children undergoing tonsillectomy with or without adenoidectomy and found that premedication with 1µg/kg of intranasal dexmedetomidine was superior to 0.2 mg/kg of intranasal midazolam in decreasing anxiety at parenteral separation. However both are equally effective in terms of satisfactory sedation and mask acceptance. An ideal preanesthetic medication should ease separation from parents and facilitate the patients acceptance of the face mask during the induction of anaesthesia. Midazolam is the most commonly used agent for premedication. The major problem in everyday practice when using intranasal midazolam is associated with an unpleasant burning sensation in the nasal cavity. Therefore, the nasal administration of midazolam is not favoured in practice. However, there are also studies that report that intranasal administration of midazolam is better tolerated by infants than its oral administration [13].

Walbergh *et al*., [9] conducted study comparing the plasma concentration in children following intranasal and intravenous midazolam and concluded intranasal midazolam rapidly achieved sedative plasma concentration.

Malinovsky *et al*., [10] studied the effect of intranasal, rectal and oral route on plasma miadazolam concentration after premedication in children and observe that adequate sedation occurred 10 min with intranasal midazolam.

Dexmedetomidine's site of action in the central nervous system is primarily in the locus ceruleus where it induces electroencephalogram activity similar to natural sleep. As dexmedetomidine poses anxiolytic, sedation analgesic and sympatholytic properties, it is a useful adjunct for premedication, especially for patients susceptible to periopertive stress.

Yuen *et al*., [11] studied the sedative and analgesic effect of intranasal dexmedetomidine and concluded that intranasal route is effective, well tolerated and convenient for the administration of dexmedetomidine and reported in their comparison of 0.5 and 1 µg.kg intranasal doses that 1 µg/kg of dexmedetomidine is more effective. Talon *et al*., preferred high doses of intranasal dexmedetomidine (such as 2 µg/kg) for preoperative premedication in children with burns.

Talon *et al*., [12] preferred higher doses as their patient group was also experiencing the pain and stress associated with burns. We chose to use 1 µg/kg intranasal dose of dexmedetomidine. Davis *et al*., reported that there is no difference between 0.2 and 0.3 mg/kg intranasal midazolam. Many other studies have used an intranasal dose of midazolam of 0.2 mg/kg. The dose in our study was determined in light of these studies. We may have noted the greatest sedative effect in the intranasal midazolam group if we had used higher doses of 0.3mg/kg.

There are no data available regarding the optimum timing of parental separation after the administration of intranasal dexmedetomidine. Yuen *et al*., [11] reported that the sedative effect of intranasal dexmedetomidine is observed after 45–60 min and that the greatest sedative effect occurs at 90–105 min in healthy volunteers.

In a study of pediatric patients by the same authors, this duration was accepted approximately 60 min depending on the conditions in the operating theater. Intranasal midazolam offers the significant advantage of being a fast-acting drug. Satisfactory

separation from the parents for intranasal midazolam has been found between 25 to 30 min. As the timing of the onset of the effect of both agents used in our study differed, we determined the preoperative sedation time to be 60 min. In this investigation, we have shown that 86% of children in dexmedetomidine group attained a satisfactory sedative compared to 68% in midazolam group. Moreover 84% of these sedated patients had mask acceptance during induction without signs of distress and awakening.

In our study reduction in Systolic Blood Pressure and Heart Rate with intranasal dexmedetomidine was 13.19% and 13.14% respectively. These levels with intranasal midazolam were 10.46% and 7.56%. In study conducted by yuen *et al*., also showed there was decrease in SBP & HR after 1μg/kg of dexmedetomidine was 14.1% and 16.4% respectively.

In our study there was significant reduction in heart rate in dexmedetomidine group when compared to midazolam group from the 20th minute continuously intraoperatively. There was no significant difference in group during the 10th minute after pre medication. The reduction in HR and BP were expected because dexmedetomidine decreases sympathetic outflow and circulating catecholamine levels and increases cardiac vagal activity (Lester *et al*., 2018) [13]. Similarly, Abdelmoneim *et al*., [14]. had found that mean BP and HR decreased significantly at 30 min after intranasal dexmedetomidine of 1 μg/kg, compared with that in children who received intranasal midazolam of 0.5 mg/kg. Also, a study by Singla *et al*., [15] has found that dexmedetomidine of 1 μg/kg reduces both HR and BP in pre-operative period significantly. The oxygen saturation in both the groups was found to be comparable at all time intervals

Postoperative agitation score, both the groups had better score and there is no statistical significance. There were no differences between the groups with regard to the adverse effects of the drugs in question during the premedication period, emergence from anesthesia, or follow-up in the PACU. There was no difference in the incidence of postoperative nausea and vomiting and discharge time between the dexmedetomidine and midazolam study groups. Emergence agitation (EA) is related to multiple factors: pre-operative anxiety, pain, certain surgical procedures (ophthalmological and otorhinolaryngology), personality traits, pre-school age, too rapid emergence and type of inhalational anesthetics (high incidence with sevoflurane). Not a sole factor can lead to EA, Silva *et al*., [16]. In spite of the fact that pain is a major cause of EA, its adequate management may not prevent EA from occurring. So, giving pre-anesthetic medication to ameliorate pre-operative anxiety has been tried, hoping that it might decrease the incidence of EA, Özcengiz *et al*., [17].

The major limitation of this study is the timing of the drug administration, Since peak onset of both the drug varied. So fixing premedication time of both groups may be reason for the difference and dose of midazolam may be inadequate. The other limitation of this study is the use of unvalidated three- or four-point scales. When using these scales, we encountered some difficulties in the evaluation of children. For example, if the child was crying but not combative, we found it hard to decide what rating to give on the mask acceptance scale. It may be necessary to use more valid scales.

CONCLUSION

We concluded that Intranasal dexmedetomidine seems to have more advantages compared with intranasal midazolam in terms of lower sedation scores, lower anxiety levels, easier child-parent separation, better mask acceptance. Thus, it can be used safely as a pre-anesthetic medication in children undergoing any surgical procedures under general anesthesia.

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