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A Prospective, Randomized, Double-blinded Control Study on Comparison of Oral Midazolam and Dexmedetomidine as Premedication in Children

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Abstract

Context: Oral premedication is commonly used in pediatric anesthesia to provide preoperative anxiolytics and to ensure smooth induction. Midazolam is currently the most commonly used premedication, but newer drugs such as dexmedetomidine have emerged as alternatives for premedication in the pediatric population. *Aims:* The aim of the study is to compare the clinical effects of oral dexmedetomidine and oral midazolam on preoperative sedation and postoperative recovery profile in children. *Materials and Methods:* We performed a prospective, randomized, double-blinded controlled study in 106 children, 2–10 years of age undergoing elective surgeries under general anesthesia. Patients were randomly assigned to receive either oral dexmedetomidine 4 mcg/kg (Group D, n = 53) or oral midazolam 0.5 mg/kg (Group D, n = 53) 40 minutes prior to mask induction. Preoperative sedation and anxiolytics, the response of the child during separation from the parent, quality of mask acceptance and recovery profile were compared for the two groups. *Statistical Analysis:* Results were analyzed using an unpaired Student's *t*-test and Chi-squared test. $p < 0.05$ was considered statistically significant. *Results:* The level of preoperative sedation at the end of 40 minutes was significantly higher in the dexmedetomidine group (3.74 ± 0.07) than the midazolam group (3.17 ± 0.10). Response to parental separation and quality of mask acceptance was significantly better in group dexmedetomidine compared to group midazolam ($p > 0.05$). Intraoperative Heart rate and Mean Arterial Pressure (MAP) was lower in the dexmedetomidine group compared to midazolam group. The incidence of postoperative agitation was significantly less in the dexmedetomidine group ($p < 0.05$). *Conclusion:* In this study, we concluded that the premedication with oral dexmedetomidine produced better preoperative sedation and recovery from anesthesia in pediatric population compared to premedication with oral midazolam.

Keywords: Propofol; Dexmedetomidine; Intraoperative Sedation; Procedural Sedation; Spinal Anesthesia.

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Introduction

Premedication in children is an important criterion to determine the smooth induction and recovery from the surgery. Most of the pediatric population coming for surgery shows signs of significant preoperative anxiety and fear. To reduce the psychological and physiological effects of preoperative anxiety and fear, most of the anesthesiologists used sedative premedication, parental presence in anesthesiology (PPIA-allowing parents in the premedication room) and behavioral preparation methods.[1] Of these methods, sedative premedication is routinely followed in many centers. Behavioral preparation methods and PPIA are not commonly practiced in busy hospitals.[2] Recent studies have proven that the presence of parents in the operating room does not produce any benefit to the child but gives them satisfaction. Premedication helps in decreasing this anxiety and fear to facilitate a smooth induction of anesthesia and thereby reducing the risk of adverse reactions such as physiological and pharmacological effects of anesthesia induction in a distressed child.[3,4] There are various disadvantages and undesired effects seen in the child coming for surgery without the administration of premedication which include increased secretions in the oral cavity which may lead to increased risk of laryngospasm at the time of induction and extubation, increased possibilty of heart rate fluctuation during the perioperative periodand increased chance of emergence delirium.[5]

Commonly administered routes of premedication are oral, nasal, sublingual, rectal, Intramuscular (IM) and Intravenous (IV). Each one of these routes has advantages and disadvantages of its own. Due to these issues, in routine clinical practice, the anesthesiologist prefers the use of oral administration of sedative agents for premedication purposes before induction of anesthesia. The Disadvantage of oral administration of premedication is that most of the drugs used for premedication have a bitter taste and the possibility of a child spitting the drug when given orally is high. To avoid this, premedication drugs need to be mixed with sweetening agents before administration.

Commonly used premedication drugs include triclofos sodium, ketamine, Midazolam, Clonidine, Fentanyl and dexmedetomidine. Currently, the routinely used sedative drug for premedication in the pediatric population is oral midazolam.[6] Midazolam is a short-acting benzodiazepine. Use of midazolam has been attributed to several advantages like amnesia, rapid onset and offset of action and anxiolytics.[7-10] The disadvantages include respiratory depression, restlessness[5] and its bitter taste requires a sweetening agent to be mixed to make it acceptable for the child. Recently Dexmedetomidine, a selective alpha 2- agonist, have been emerged as an efficient alternative for the use as pediatric premedication.[11–13] Dexmedetomidine has anxiolytic as well as sedative property and it is not known to cause respiratory depression. Few preliminary studies show that dexmedetomidine can be used as a premedication in children coming for elective surgeries to reduce anxiety and to reduce the occurrence and severity of emergence delirium.[14–16] Since, there are only very few studies on oral dexmedetomidine as pediatric premedication, we conducted a randomized double-blinded study on comparing oral midazolam and oral dexmedetomidine as pediatric premedication.

Materials and Methods

This study was registered in the Clinical Trial Registry-India (CTRI) (Trial Number: CTRI/2017/12/010874). After obtaining approval of the institutional Ethical Committee, this study was performed as a prospective, randomized, double-blinded, controlled study in 106 children, aged 2–10 years undergoing elective surgery under general anesthesia at our institution. An informed and written consent was obtained from the parents or legal guardian during the preanesthetic check-up. Intavenous access with appropriate size IV cannula was obtained in the admitting ward on the morning of surgery. Patients were allocated in a randomized manner by computer-generated random envelope method into Two Groups: Group D-(dexmedetomidine n = 53) and Group M-(midazolam, n = 53). They were assigned to receive either oral midazolam 0.50 mg/kg or oral dexmedetomidine 4 mcg/kg 40 minutes before induction of anesthesia in the preoperative holding area. An injectable preservative-free 5 mg/ml preparation of midazolam was used in Group M and the IV formulation of dexmedetomidine (100 mcg/ml) was used in Group D. Both drugs are mixed with freshly prepared pulp-free apple juice to prepare a final volume of 5 ml. Preoperative sedation, the response of the child at parental separation, the response of the child during mask ventilation and recovery profile was compared between the two groups. Sedation status was assessed before the drug administration and thereafter, every 10 minutes for a maximum of 40 minutes after premedication.

Children aged from 2–10 years of ASA Grade I-II undergoing elective surgeries lasting between 30 minutes and two hours were included in the study. Those Children with developmental delay or mental retardation, with a history of emergence delirium in the previous surgery, with known allergies to the study drugs and child spitting out the premedication drug were excluded from the study.

The first anesthesiologist opened the envelope and prepared the drug according to the group generated. The first anesthesiologist did not take any further part in the study. Once the child comes into the premedication room, Electrocardiogram (ECG), pulse-oximeter (SpO_2) and Noninvasive Blood Pressure (NIBP) monitors are attached and the baseline values are noted. Second anesthesiologist, who was blinded to the group involved, administered the drug to the child. Heart rate, blood pressure, and saturation are continuously monitored and recorded every 15 minutes from the time of administration of the drug. The level of sedation was assessed every 10 minutes and recorded from the time of administration of drug till 40 minutes.

The level of sedation was assessed by using a 4-point scale:[20]

1 = anxious, depressed/agitated/crying;

2 = awake, calm, quiet;

3 = drowsy, responds to verbal commands/ gentle stimulation;

4 = asleep.

The child was transferred to the induction room at the end of 40 minutes. The response of the child at parental separation was recorded. It was graded using a 4-point scale[20] as:

1 = crying, cannot be reassured;

2 = awake, anxious, can be easily reassured;

3 = good separation, awake, calm;

4 = asleep.

Once the child comes into the operating theatre, ECG, pulse-oximeter, and NIBP were attached. The facemask was kept on the child with 100 percent oxygen and sevoflurane. Mask acceptance was assessed using a 5-points scale:[20]

1 = combative, crying;

2 = moderate fear of mask, not easily calmed;

3 = cooperative with reassurance;

4 = calm, cooperative;

5 = asleep, steal induction.

Mask induction Scores of 1 and 2 were considered unsatisfactory while a Score of 3–5 was regarded as a successful response to premedication. Injection glycopyrrolate 10 mcg/kg IV was given. Injection fentanyl 2 mcg/kg IV given for analgesic requirement. Anesthesia was induced with sevoflurane. Anesthesia was maintained with nitrousoxide with oxygen (N_2O:O_2) ratio of 2:1. IV fluids were administered according to the holiday Segar formula. In the intraoperative period, continuous monitoring of heart rate, blood pressure, and saturation was done and recorded every 15 minutes. Atracurium was used as a muscle relaxant in patients who required Endotracheal Tube (ETT) insertion and it was avoided in patients who required a Laryngeal Mask Airway (LMA). Use of endotracheal intubation or use of LMA was decided according to the need for the surgery.

At the end of the procedure, the child was reversed from anesthesia. As soon as the child was able to maintain a patent airway, the child was shifted to the recovery room. ECG, pulse oximeter and NIBP monitors attached. The child was let there to wake up naturally in the recovery room. In the recovery room, recovery profile was assessed using a 3 point scale:[20]

1 = Agitated, crying;

2 = Crying but easily consoled;

3 = Calm, asleep.

The child was kept in the recovery room for two hours, at the end of two hours; the child was shifted to the respective wards. The child was followed up in the ward until 12 hours from the time of administration of the drug. Heart rate, blood pressure, and saturation were recorded every two hours.

Statistical Analysis

All values were reported as mean ± Standard Error of the Mean (SEM). Data analysis for numerical data was performed using unpaired Student's *t*-test and for categorical data was performed by Chi-square. A p - value of < 0.05 was considered statistically significant and a p - value of < 0.001 was considered statistically very significant.

Results

One hundred-six children were enrolled in the study and assigned into Group M (n = 53) and Group D (n = 53). There was no statistical difference

between the groups with respect to demographic characteristics, ASA status, and duration of surgery, Table 1. Hemodynamic parameters including heart rate, MAP and saturation were compared between the two groups, a statistically significant reduction of heart rate was noted in Group D at 75th minute of administration of the drug till 120th minute, but no interventions made since, it does not fall below the 20% of the preoperative values. The remaining values were comparable.

Table 1: Demographics, ASA status and duration of surgery

	Group D	Group M	*p* - value
Age (years)	5.92 + 0.36	5.94 + 0.36	0.970
Sex (%) Male/Female	27/26	26/27	0.500
Weight (kgs)	20.43 = 0.81	20.47 + 0.81	0.974
ASA Status ASA 1/ASA 2	49/4	50/3	0.6942
Duration of Surgery (minutes)	76.60 + 3.25	79.23 + 3.04	0.557

The sedation score was compared between the two groups and it was significantly more at 40 minutes in the dexmedetomidine group (3.74 ± 0.07) compared to the midazolam group (3.17 ± 0.10). *p*- value < 0.001, Table 2. Parental separation was compared between the two groups. *p* - value was found to be < 0.001 which is statistically highly significant, Table 3. Mask acceptance was compared between two groups and *p* - value was found to be < 0.001 which is statistically highly significant, Table 4. The recovery profile was compared between the two groups. *p* - value was found to be 0.0001 which is statistically highly significant, (Table 5).

Table 2: Sedation score

Timing	Dexmedetomidine	Midazolam	*t*-test	*p* - value
0 min	1.00 ± 0.00	1.00 ± 0.00	–	–
10 min	1.06 ± 0.04	1.15 ± 0.05	–1.453	0.149*
20 min	2.09 ± 0.06	1.94 ± 0.06	1.801	0.075*
30 min	2.47 ± 0.08	2.43 ± 0.09	0.320	0.749*
40 min	3.74 ± 0.07	3.17 ± 0.10	4.712	0.0001‡

Table 3: Comparison of parental separation

Group	Parental separation			Chi-square	*p* - value
	2	3	4		
Dexmedetomidine	0	14	39	25.81	0.0001‡
Midazolam	14	23	16		

Table 4: Mask acceptance

Group	Mask acceptance			Chi-square	*p* - value
	3	4	5		
Dexmedetomidine	2	30	21	45.196	0.0001‡
Midazolam	34	7	12		

Table 5: Recovery profile

Group	Recovery profile		Chi-square	*p* - value
	2	3		
Dexmedetomidine	6	47	12.425	0.0001‡
Midazolam	22	31		

Discussion

Premedication is required in pediatric population coming for surgery to decrease the adverse psychological effects of hospitalization, operative procedure, emergence delirium, and parental separation. An ideal premedication should provide adequate anxiolysis and sedation to allow a smooth induction of anesthesia. It should be free from side-effects such as hemodynamic disturbances and emergence delirium and respiratory depression. Oral midazolam is one of the routinely used drugs in pediatric anesthesia as premedication and has shown to be more effective in allaying the child's anxiety and fear than the parental presence. Midazolam has both anxiolytic as well as sedative property which is believed to produce a calming effect. This characteristic feature of midazolam makes the children less anxious when they are separated from their parents and during mask placement during the induction of anesthesia. It facilitates gamma-aminobutyric acid receptor-mediated chloride conductance, which has an inhibitory effect on neurons in the cerebral cortex. The dose of 0.50 mg/kg of injectable midazolam given orally as premedication is acceptable, effective and safe. Recently, α_2-receptor agonists such as clonidine[24] and dexmedetomidine have also been found to be useful for premedication in children. These drugs act on central α_2-receptors located at the locus ceruleus causing inhibition of release of noradrenaline and create electroencephalogram activity similar to normal sleep. This results in anxiolytic effects, analgesia, and sedation without respiratory depression.[17–20]

Heart rate was monitored continuously from the administration of the drug and was recorded every 15 minutes till two hours and then recorded every two hours for 12 hours. It was found that there was a significant difference in the heart rate between the two groups at 75 minutes, 90 minutes, 105 minutes and 2 hours. It is concluded that children under Group D had a statistically significant reduction in heart rate after 75 minutes of administration of drugs till two hours of administration of drug compared to children under Group M. Though there was a decrease in heart rate none of the children required intervention because it was not clinically significant. Pant et al.[23] conducted a study on sublingual midazolam and sublingual dexmedetomidine as pediatric premedication and in the study, he found that the heart rate was significantly lower throughout the perioperative period ($p < 0.001$) in the dexmedetomidine group. Their study result was similar to our result.

Blood pressure was continuously monitored from the administration of the drug and the MAP was recorded every 15 minutes till two hours and then recorded every two hours for 12 hours. It was found that there was a significant difference in the MAP at 60 minutes, 75 minutes, 90 minutes, 105 minutes and two hours between two groups. In the remaining times, the MAP between the two groups were comparable. It is concluded that children under Group D had a statistically significant reduction in MAP after 60 minutes of administration of drugs till two hours of administration of drug compared to children under Group M. Though there was a decrease in MAP none of the children required intervention because it was not clinically significant. Oxygen Saturation was comparable between the two groups and there was no significant difference between the two groups in terms of saturation throughout the study.

The sedation score was analyzed just before administration of the drug and then for every 10 minutes till 40 minutes. The sedation score was compared between the two groups and there were no significant differences between the two groups for the first 30 minutes. However, at the end of 40 minutes, there is a significant difference in the sedation score between the two groups. It was concluded that dexmedetomidine produces better sedation over midazolam at the end of 40 minutes. Yuen et al.[25] conducted a study on comparison of oral midazolam and intranasal dexmedetomidine and found similar results in terms of sedation score. In that study, the median sedation score was assessed by the modified Observer Assessment of Alertness and Sedation Scale (OASS) in 6 patients receiving 0.5 mg/kg midazolam compared to median score of 3 in children who received intranasal dexmedetomidine 0.5 mcg/kg. In that study, they concluded that intranasal dexmedetomidine was better than oral midazolam in preoperative sedation.

Parental separation was compared between the two groups and the p - value was found to be 0.0001 which is statistically highly significant. In Group D, 14 children were assessed to have a parental separation score of three and 39 children were assessed to have a parental separation score of four. In Group M, 14 children were assessed to have a parental separation score of two, 23 children were assessed to have a parental separation score of three and 16 children were assessed to have a parental score of four, (Figure 1). It is concluded that oral dexmedetomidine produced better parental

separation than oral midazolam. This result correlates with Pant et al.[23] study on sublingual midazolam and dexmedetomidine where the median of sedation score at parental separation was 6 in children administered midazolam and the median of sedation score at parental separation was 3.5 in children administered dexmedetomidine. *p* - value was < 0.001, they concluded that sublingual dexmedetomidine provided more effective preoperative sedation as compared to sublingual midazolam.

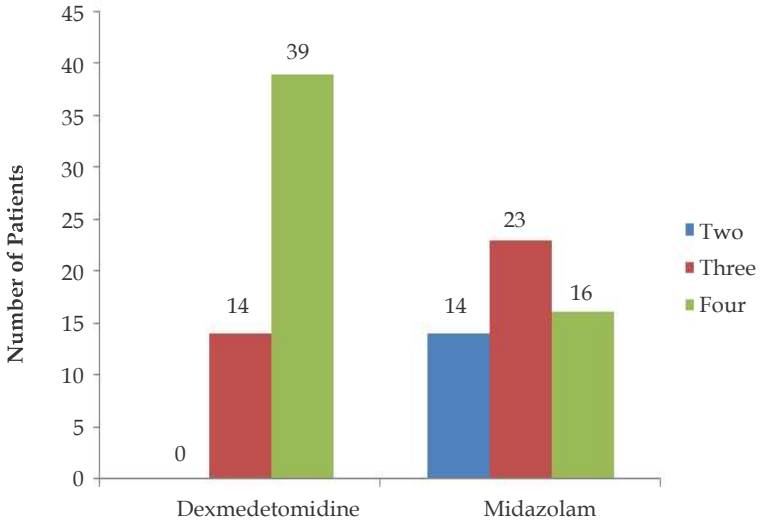

Fig. 1: Comparison of parental separation.

Mask acceptance was compared between two groups. In Group D, two children were assessed under Score 3 for mask acceptance, 30 children were assessed under Score 4 for mask acceptance and 21 children were assessed under Score 5 for mask acceptance. In Group M, 34 children were assessed under Score 3 for mask acceptance, 7 children were assessed under Score 4 for mask acceptance and 12 children were assessed under Score 5 for mask acceptance, (Figure 2). This led to the conclusion that dexmedetomidine is more effective in terms of mask acceptance similar to the results of Pant et al.[23] study on sublingual midazolam and dexmedetomidine. In that study, the median of mask acceptance score was 2 in children administered midazolam and the median of mask acceptance score was 1 in children administered dexmedetomidine. *p* - value was < 0.001, they concluded that sublingual dexmedetomidine provided more effective preoperative sedation for mask acceptance as compared to sublingual midazolam.

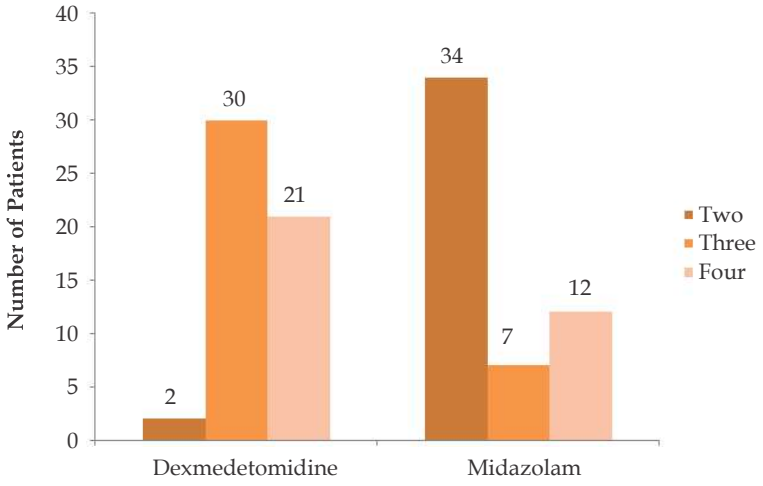

Fig. 2: Comparison of mask acceptance.

Recovery profile was compared between two groups and the *p* - value was found to be 0.0001 which is statistically highly significant. Group D has a better effect on recovery profile when compared with Group M, (Figure 3). Jannu et al.[20] compared oral dexmedetomidine and oral midazolam as pediatric premedication. In that study, they calculated the postoperative agitation score and concluded that children administered oral dexmedetomidine has a better recovery profile compared to oral midazolam. This result is similar to our study result.

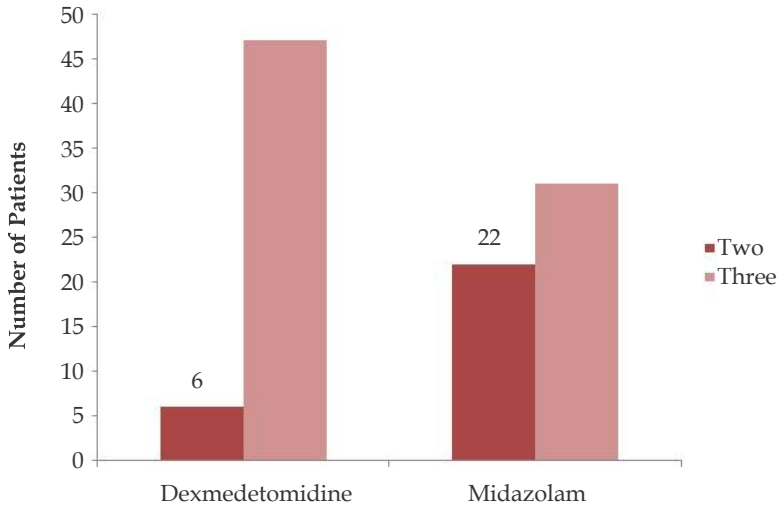

Fig. 3: Comparison of recovery profile.

Conclusion

In this study, we concluded that oral dexmedetomidine as a premedication in children is better than midazolam in achieving sedation, better mask acceptance and better recovery profile from anesthesia.

Support: Nil

Conflicts of interest: Nil

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