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ORAL DEXMEDETOMIDINE VERSUS ORAL MIDAZOLAM FOR PREMEDICATION IN PEDIATRIC PATIENTS.

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ABSTRACT

Background and Aims: Midazolam is frequently used a premedication in children. It is often given orally and gives a reliable sedation and helps in child-parent separation. Oral and parenteral dexmedetomidine have also been increasingly used in paediatric population in recent years. In this study we have compared the use of dexmedetomidine and midazolam and determined the efficacy and safety of dexmedetomidine in pediatric patients. **Methods:** A prospective, randomized double blind study in pediatric patients aged 6-12 years evaluated the preoperative sedative effects, anxiety level and the ease of child-parent separation, the recovery profile and postoperative analgesic properties of preoperative oral dexmedetomidine compared with those of oral midazolam. We also evaluated safety and efficacy of dexmedetomidine as oral premedication in children. The patients were randomly allocated into two groups: Group-1(GD) children received dexmedetomidine as premedication 3µg/kg diluted in 5ml dextrose 5% orally (n = 50), one hour prior to anesthesia induction and Group-2 (GM) children received midazolam premedication, 0.5 µg/kg diluted in 5ml dextrose 5% orally (n=50), one hour prior to induction of anesthesia. The data was collected for Heart rate (HR), Mean Arterial Pressure (MAP) pulse oximetry ($SPO_{2)}$ and respiratory rate (RR) in pre and post operative period, response to separation, post operative sedation and any adverse event. The data was collected up to 60 minutes postoperatively at various predetermined intervals for each patient. Data was analyzed statistically using the student t- test, chi square test and repeated measurement analysis to detect differences between two groups. P value of <0.05 was considered statistically significant. **Results:** Mean heart rate in midazolam group was

higher which was statistically significant with p value of <0.05. The MAP in intra operative and post operative period in midazolam group was higher than in dexmedetomidine group which was statistically significant (p< 0.001). The RR at 30 min, 45 min and 60 min was lower in midazolam group than dexmedetomidine group (p< 0.001). The Parent - Child Separation Scores at one hour after administering the study drugs was found to be significantly better in dexmedetomidine group. The Postoperative recovery score was lower in dexmedetomidine group (p <0.05). The recovery for patients who received dexmedetomidine was better and the difference was found statistically significant .The Postoperative Pain Scores were 2.844±.051 in midazolam group and 2.060±.051 in dexmedetomidine group and was statistically significant (p <0.05). **Conclusion:** Oral dexmedetomidine as a premedicant in pediatric patient is a safe alternative to oral midazolam and has lesser effect on respiratory rate than midazolam. Post operative analgesia was better with dexmedetomidine.

KEYWORDS: Dexmedetomidine, Midazolam, Premedication, Children.

INTRODUCTION

One of the challenges for anesthesiologist is to minimize distress for children in the operating room (OR) environment and to facilitate a smooth induction of anesthesia.[1] Preoperative anxiety increases distress, and produces difficulty in managing control of postoperative pain difficult. [2] Reducing perioperative distress and have a child arrive in operating room calm and quiet, is an important perioperative goal achieved through premedication.

Midazolam has become the most frequently used preanesthesia medication given to children scheduled for surgery and is used in greater than 90% of surgical cases involving premedication in the United States.[1] Midazolam has a number of beneficial effects of fast onset and limited duration of action.[3] but it is far from an ideal premedicant having untoward side effects such as restlessness, paradoxical reaction, cognitive impairment, amnesia and respiratory depression.[4,5] Dexmedetomidine, a highly selective α2-agonist with both sedative and analgesic properties and devoid of respiratory depressant effect has emerged as an alternative premedication in pediatric anesthesia. In this study we evaluated the preoperative sedative effects, anxiety level changes and the ease of child-parent separation (as a primary end-point) and the recovery profile and postoperative analgesic properties (as a secondary end-point) of preoperative oral dexmedetomidine sedation

compared with those of oral midazolam in children aged 6-12 years. We also evaluated safety and efficacy of dexmedetomidine as oral premedication in children.

METHODS

An informed consent was taken from parents of patients between age groups 6-12 years belonging to ASA grade1 undergoing elective surgical procedures. The study received a departmental and institutional ethical committee clearance before the patients could be enrolled for the study.

One hundred patients were recruited for the study and were randomly allocated into two groups: Group-1(GD) children received dexmedetomidine as premedication, 3µg/kg diluted in 5ml dextrose 5% orally (n = 50), one hour prior to induction of GA and Group-2 (GM) children received midazolam as premedication, 0.5 µg/kg diluted in 5ml dextrose 5% orally (n=50), one hour prior to induction of GA.

Heart rate (HR), pulse oximetry ($SPO_{2)}$ and respiratory rate (RR) and level of sedation were monitored before and after administration of drug. These parameters were recorded every 15 min. Level of sedation was assessed by using a 5-point sedation scale.

After one hour children were separated from parents and transferred to the operating room, response to separation was recorded using 4 point separation and induction scores.

The patients were induced with injection propofol 2mg/kg, oxygen and halothane as required. After induction injection atracurium 0.5mg/kg for tracheal intubation and injection fentanyl 2µg/kg for analgesia was given. Either ETT(Endotracheal tube) or LMA (Laryngeal mask airway) was placed according to age of child. Anesthesia was maintained with O_2 in N_2O in ratio 1:1 with halothane.

At the end of surgical procedure residual effect of relaxant was reversed by giving injection neostigmine 0.07mg/kg and injection atropine 0.02mg/kg body weight, thereafter patients were extubated, shifted to recovery room and assessed by post anesthesia recovery score. In the post operative period an assessment in the recovery room was for one hour after surgery. Pain was assessed every 15 mins in the recovery room using the Observer Pain Scale.

Vomiting episodes, including non-productive attempts to vomit, from the end of anesthesia for one hour postoperatively were recorded.

Blood Pressure, Heart Rate, Respiratory rate and Pulse oximetry were recorded every 15 min in the postoperative period. Any incident of hypotension and bradycardia was recorded. Data was analyzed statistically using the student t- test, chi square test and Repeated Measurement Analysis to detect differences between two groups. A P value of <0.05 was considered statistically significant.

Table 1: SCORING SYSTEMS

Sedation scoring		**Child Parent Separation Score**		**Post Anesthesia Recovery Score**		**Observer Pain Score**	
Criteria	Score	Criteria	Score	Criteria	Stage/ Score	Criteria	Score
Agitated, clinging to the parent.	1	Patient unafraid, cooperative, asleep	Excellent	Awake; does not feel sleepy and initiates conversation.	I	Laughing, euphoria	1
Awake but not clinging to parent.	2	Slight fear, crying, quiet on reassurance	Good	Awake; but feel sleepy.	II	Happy, contended	2
Calm, sitting or lying with eyes open, relaxed.	3	Moderate fear, crying, not quiet with reassurance	Fair	Asleep; responds to both verbal and painful stimuli.	III	Calm or asleep	3
Drowsy, eyes close but respond to minor stimulation.	4	Crying, need for restraint.	Poor	Asleep; responds to painful stimuli only.	IV	Crying, grimacing, restlessness	4
Asleep, does not respond to minor stimulation	5			Asleep; does not respond to painful stimuli.	V		

Table 2: Demographic Data

Variable	**Midazolam (N=50) Mean ± S.D**	**Dexmedetomidine (N=50) Mean ± S.D**	**p value**
Age (years)	8.42 ±1.727	8.96 ± 1.551	0.103
Weight (kgs)	23.73±4.721	24.24±3.724	0.550
Male (%)	31 (62.0)	27 (54.0)	0.418
Female (%)	19 (38.0)	23 (46.0)	

Table 3: Preoperative Data for first 60 Minutes: from premedication to separation

	Heart Rate beats / min Mean ±SE	**MAP mm Hg Mean ±SE**	**RR b/min Mean ±SE**	**SpO2 % Mean ±SE**	**Sedation Score Mean ±SE**	**Separation Score by frequency**	
Midazolam Group (N=50)	87.840 ± 0.298	86.70 ± .236	15.152 ±.097	97.844 ±.050	2.392 ±.046	Excellent	0
						Good	23
						Fair	14
						Poor	13
Dexmedetomidine	84.552	84.13	16.836	98.144	2.136	Excellent	17

Group (N=50)	± 0.298	± .236	±.097	±.050	±.046	Good	23
						Fair	41.6
						Poor	0
P value	0.001	0.001	0.001	0.171	0.001		
Remarks	Statistically significant	Statistically significant	Statistically significant	Not Significant	Statistically significant	Better separation score in dexmedetomidine group	

Table 4: Post Operative Data

	Post Op HR beats/min Mean ±SE	Post Op MAP mmHg Mean ±SE	Post Op RR B/min Mean ±SE	Post Op Sp02 % Mean ±SE	Post Op Recovery Score Mean ±SE	Post Op Pain Score Mean ±SE	PONV Frequency %
Midazolam Group (N=50)	82.948 ±0.143	84.764 ±.193	15.720 ±.090	98.316 ±.040	2.488 ±.036	2.844 ±.051	66.7%
Dexmedetomidine Group (N=50)	77.136 ±.143	74.168 ±.193	16.648 ±.090	98.372 ±.040	2.220 ±.036	2.060 ±.051	33.3%
P Value	0.001	0.001	0.001	0.320	0.001	0.001	
Remarks	Statistically significant	Statistically significant	Statistically significant	Statistically Insignificant	Statistically significant	Statistically significant	Lesser in Dexmedet-omidine group

RESULTS

Both the groups were homogenous in their demographic profile with respect to ASA class, age, weight and sex. Mean heart rate in midazolam group was higher which was found statistically significant with p value of <0.05. The postoperative mean heart rate was higher in midazolam group at all the time intervals as compared to dexmedetomidine group and the difference was statistically significant (p <0.001). Table 2.

The baseline Mean Arterial Pressure in the midazolam and dexmedetomidine groups was statistically insignificant. Overall the MAP in intra operative and post operative period in midazolam group was higher than in dexmedetomidine group which was statistically significant (p 0.001). Table 3.

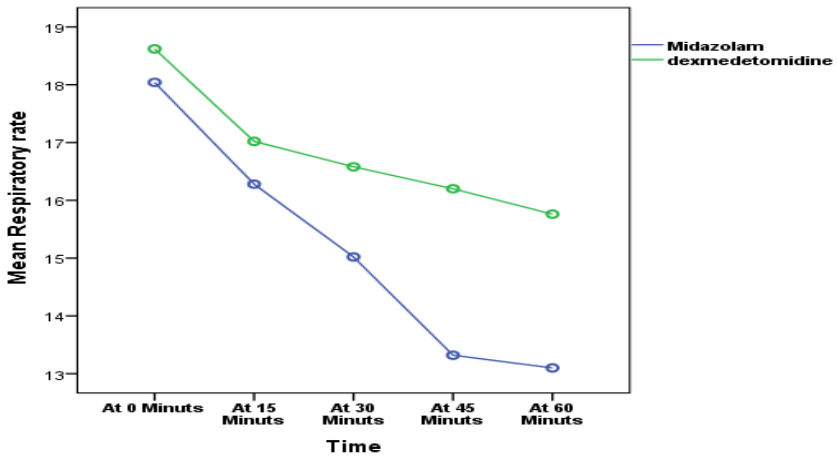
In midazolam group there was a reduction in respiratory rate that continued in the postoperative period for approximately 30 min and returned to the baseline values at 60 min. The baseline RR in midazolam and dexmedetomidine groups which was statistically insignificant (p 0.054). The RR at 30min, 45min and 60min was lower in midazolam group than dexmedetomidine group (p value 0.001). Comparison of post-operative RR at 0 min,15 min and 30 min between two groups was statistically significant (p value<0.05) but this became statistically insignificant (p value >0.05) at 45min and 60min. SPO2 in both groups was statistically insignificant at all intervals of time. Graph1-4.

Onset of sedation was faster in midazolam group. Overall sedation scores were higher in midazolam group compared to dexmedetomidine group and were statistically significant (p value 0.001).

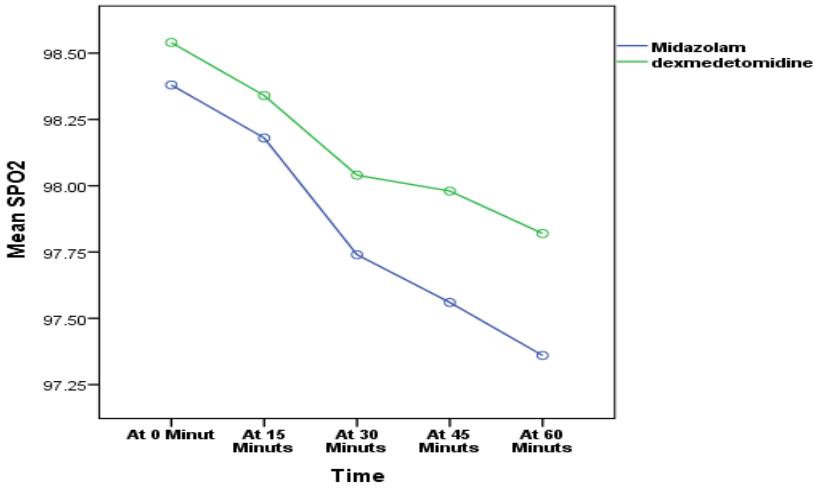
The Parent - Child Separation Scores at one hour after administering the study drugs was found to be significantly better in dexmedetomidine group compared to midazolam group (P value 0.001).

The Postoperative recovery score between midazolam group and dexmedetomidine group for first 60 minunites was found statistically significant with lower scoring in favour of dexmedetomidine group (p value of <0.05). Overall recovery profile was better in the patients who received dexmedetomidine and the difference was found statistically significant between two study groups with p value of <0.05. The Postoperative Pain Score were 2.844±.051 in midazolam group and 2.060±.051 in dexmedetomidine group and was statistically significant

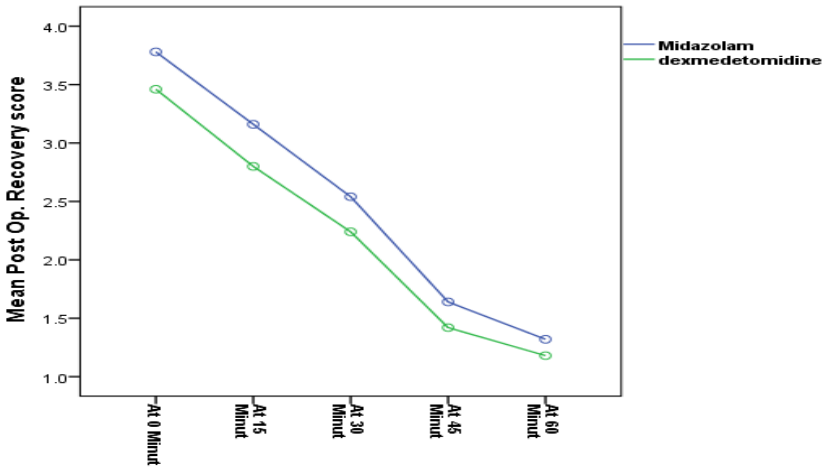
(p value <0.05). Post-operative nausea vomiting (PONV) between midazolam group and dexmedetomidine group was statistically insignificant (p value 0.061). Table 1.



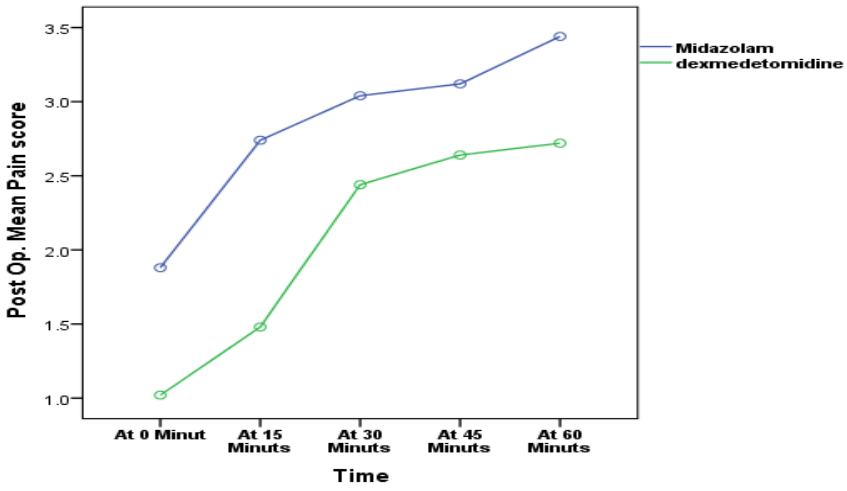
Graph 1: Post Operative Respiratory Rate



Graph 2: Post Operative Pulse Oximetry SPO2



Graph 3: Post Operative Recovery Scores



Graph 4: Post Operative Pain Scores

DISCUSSION

This study was undertaken to evaluate the sedative effects, anxiety level changes and the ease of child-parent separation and the recovery profile and postoperative analgesic properties of preoperative oral dexmedetomidine sedation compared with those of oral midazolam in children age group of 6-12 years.

The mean heart rate was higher in midazolam group at all the time intervals as compared to dexmedetomidine group and the difference was statistically significant (p 0.001). In concordance with our study, Karim Kamal et al[6] and the study of Kumar L et al[7] also found significantly lower levels of heart rate in dexmedetomidine group than in midazolam group during both intra-operative and post-operative periods.

The baseline MAP in the midazolam and dexmedetomidine groups was statistically insignificant. The MAP in intra operative and post operative period in midazolam group was higher than in dexmedetomidine group which was statistically significant (p 0.001).

This is in concordance with the study of Venn et al,[8] Talke et al[9] and Kumar L et al[7] who received dexmedetomidine experienced significant drop in blood pressures who also observed similar results.

In our study we observed a respiratory depression in the patients who received midazolam premedication, which was manifest in the form of reduction in their respiratory rate at 30 min, 45 min and 60 min that continued in the postoperative period for approximately 30 min,

and returned to the baseline values at 60 min. RR Fukuta O et al.[10] also noted minor respiratory depression with administration of midazolam.

Onset of sedation was faster in midazolam group. Sedation scores were higher in midazolam group (2.39±.046) compared to dexmedetomidine group (2.13±.046) and was statistically significant (p 0.001). Similar results were observed by Karim Kamal et al.[6]

The separation score between the parents and the child at 1 hour was significantly better in dexmedetomidine group compared to midazolam group (p 0.001). This is in concordance with the study of Shailesh Bhadla et al.[11] who found that the mean value of separation score in dexmedetomidine group was 1.60 ± 0.67 whereas in midazolam group it was 2.51 ± 0.89 (p value 0.001) which is statistically significant.

Postoperative recovery score comparison between midazolam group and dexmedetomidine was found statistically significant at 0 min,15 min,30 min,45 min with lower scoring in favour of dexmedetomidine group ($p < 0.05$). The recovery profile was better in the patients who received dexmedetomidine, $p < 0.05$. Similar results were observed by Karim Kamal[7] and Prabhu MK.[12]

The comparison of postoperative pain score between Midazolam and Dexmedetomidine was found statistically significant with lower pain scores in dexmedetomidine group. Our results are consistent with a study by Schmidt[13] who compared transmucosal dexmedetomidine to oral midazolam and oral clonidine as premedication in school children. Their results showed that α_2 agonists were related to lower pain scores than midazolam in both verbal and visual scales. Similar results were observed by Karim Kamal.[7]

One major drawback for the routine use of dexmedetomidine as a sedative premedicant is its slow onset of action. Our findings confirmed that the onset of sedation and peak sedative effect was slower after oral dexmedetomidine as compared to oral midazolam. Oral dexmedetomidine needs to be administered at least 45 min prior to induction to achieve optimum sedation whereas satisfactory sedation can be achieved 30 min after ingestion of oral midazolam. The meta-analysis conducted by Peng K, Wu SR[14] and by Yu Sun, Yi Lu, and Yan Huang[15] which also concluded that dexmedetomidine is superior to midazolam as it enhanced preoperative sedation and decreased postoperative pain.

In this study, the premedication period was 60 min and all children were transferred to the OR at one hour as per study protocol. If the duration of premedication period had been kept longer, possibly more subjects could have attained satisfactory sedation at separation. The patients who received dexmedetomidine are easily aroused and cooperative at the end of surgery.

CONCLUSION

Oral dexmedetomidine as a premedicant in pediatric patient is an alternative and a safe alternative to oral midazolam and in patients and has a lesser effect on respiratory rate than midazolam. Post operative analgesia scores were better with dexmedetomidine. One major drawback of dexmedetomidine as a sedative premedicant is its slow onset of action. Our data confirm that onset of sedation and peak sedative effect was significantly slower after oral dexmedetomidine compared with oral midazolam.

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