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A COMPARATIVE STUDY BETWEEN ORAL MIDAZOLAM AND INTRANASAL DEXMEDETOMIDINE FOR PREMEDICATION IN PAEDIATRIC ANAESTHESIA –A RANDOMIZED CONTROLLED TRIAL

Anesthesiology

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KEYWORDS

Introduction- One of the challenges for paediatric anaesthesiologists is to minimise distress in children in the operating room environment and to facilitate a smooth induction of anesthesia. This is often accomplished by prior administration of a sedative drug before transfer to the operating room.

Midazolam is the most commonly used drug for this purpose.[1,2,3] Premedication with midazolam has shown to be more effective than parental presence or placebo in reducing anxiety and improving compliance at induction of anesthesia.[4,5] The beneficial effects of midazolam include sedation, anxiolysis and reduction of postoperative vomiting.[5-10] A recent evidence-based clinical update has shown that oral midazolam 0.5 mg/kg is effective in reducing both separation and induction anxiety in children, with minimal effect on recovery time.[11] However, the acceptability of oral midazolam by pediatric patients is only 70%.[12] Other undesirable effects including restlessness, paradoxical reaction, and negative postoperative behavioral changes have made it a less than ideal premedication.[13-16]

Clonidine, an α_2 agonist, has been suggested as an alternative [17] and previous studies have shown it to be equally as effective as midazolam.[18-20] Oral clonidine premedication has also been shown to reduce the incidence of sevoflurane induced emergence agitation.[21]

Dexmedetomidine is a newer, more selective α2-agonist with a shorter half-life. Its bioavailability is 81.8% (72.6–92.1%) when administered via the buccal mucosa. [22] Yuen et al., demonstrated that intransal 1 and 1.5 µg/kg dexmedetomidine produces sedation in 45–60 min and peaks in 90–105 min. In addition, they observed only a modest reduction of heart rate (HR) and arterial blood pressure (BP). [23]

In this study, 80 children, between 2-12 yrs of age, of either sex, of ASA physical status I or II scheduled for elective minor surgery under General anaesthesia were randomly selected into one of the two groups. Group M received oral midazolam 0.5mg/kg & intranasal placebo. Group D received intranasal dexmedetomidine 1 µg/kg & oral placebo. Patients' sedation status, behaviour score, BP, HR, SpO_2 were recorded by an observer, not part of the study, until induction of General anaesthesia. Recovery characteristics were also recorded.

The purpose of the study was to compare the effects of oral midazolam and intranasal dexmedetomidine for premedication in paediatric anaesthesia.

Primary objective: To find out any difference between two groups regarding Sedation status.

Secondary objectives: To find out any difference between two groups regarding – Parental separation acceptance,behaviour score at induction,wake-up behaviour score,hemodynamic changes. respiratory changes,any adverse reaction.

1. STUDY AREA: Paediatric Surgery OT, I.P.G.M.E.R Hospital, Kolkata.
2. TIME LINES: one and half years.
3. STUDY POPULATION: Children of age group 2-12 yrs, of either sex of ASA physical status I or II undergoing elective minor surgeries under General anaesthesia.
4. INCLUSION & EXCLUSION CRITERIA: Age group 2 - 12 yrs, of either sex, ASA physical status I or II, patients put for elective minor surgeries under General anaesthesia.

Parental refusal for inclusion in the study,ASA physical status III or IV,known allergy or hypersensitivity to the study drugs,Cardiac arrhythmia or congenital heart diseases,Significant respiratory, hepatic or renal diseases,Mental retardation,If the child vomits out the study drug or sneezes after intranasal drug administration.

5. STUDY DESIGN/ SAMPLE DESIGN: Prospective randomized double blind comparative study.

6. PARAMETERS TO BE STUDIED: Comparison between the two groups was done in the following manner –

i. Sedation status (6-point sedation scale)
ii. Parental separation acceptance.
iii. Behaviour score at induction (4-point behaviour score)
iv. Hemodyanamic changes (HR, BP)
v. Respiratory changes (respiratory rate, depth, SpO2)
vi. Wake-up behaviour score.
vii. Any adverse reactions.

7. STUDY TOOLS: Pulse oxymeter, NIBP monitor.
8. STUDY TECHNIQUE:

Methodology: The study was carried out in the department of Anaesthesiology Paediatric surgery OT at main OT complex of the institute IPGMER, after approval of the institutional ethics committee. The patients were randomly allocated in two groups using a computer generated randomised sheet. Written informed consent was taken from the parents of all patients. Complete pre-anaesthetic check-up was performed in each patient.

Children were randomly allocated to one of the two groups, namely Group M & Group D. All children received intranasal medication or placebo at approximately 60 min before induction of anaesthesia. Oral

medication or placebo was given at 30 min before induction of anaesthesia. Group M received 0.5 mg/kg oral midazolam, up to a maximum 15 mg (5 mg/ml parenteral preparation) and 0.4 ml intranasal placebo (Normal saline). Group D received intranasal dexmedetomidine at 1µg/kg and oral placebo. All study drugs were prepared by an independent investigator not involved in the observation or administration of anesthesia for the children. Observers and attending anaesthesiologists were blinded to the study drug.

Intranasal drug was dripped into both nostrils using a 1-mL syringe with the child in the recumbent position. HR, SpO2, Respiratory rate and BP were measured as baseline, before and every 15 min after intranasal drug administration until transfer to the OR. Sedation status was assessed by a blinded observer every 5 min with a 6-point sedation scale (modified from the Observer Assessment of Alertness and Sedation Scale). Behaviour was evaluated every 5 min with a 4-point behaviour score. The duration of premedication is approximately 60 min. Sedation status and behaviour were evaluated at induction by the attending anesthesiologist using the same scale. Intraoperative vitals (HR, SpO2, and BP) were monitored. When surgery finished the children were placed in the recovery position and allowed to wake up naturally in the postanaesthesia care unit (PACU). Behavior at awakening was evaluated with a four-point wake up score in PACU. Time taken for readiness to be discharged from PACU was recorded.

Evaluation Scales –
6- point Sedation scores:

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

4-point Behavior scores:	Wake-up behavior scores:
1 - Calm and cooperative.	1 - Calm and cooperative.
2 - Anxious but reassurable.	2 - Not calm but could be easily calmed.
3 - Anxious and not reassurable.	3 - Not easily calmed, moderately agitated or restless.
4 - Crying, or resisting.	4 - Combative, excited, disoriented.

STATISTICAL ANALYSIS: Numerical variables compared between groups by students independent sample t test, if normally distributed or by Mann-Whitney U test, if otherwise. The Chi-square test or Fischer's exact test were used for intergroup comparison of categorical variables. All analysis was two-tailed and p<0.05 were considered statistically significant.Statistical Analysis was done with standard statistical software: Statistica version 6, SPSS Statistics version 17, Graph Prism version 4 [San Diego, California: GraphPad Software Inc., 2005].

Results-This prospective randomized double blind comparative study was conducted under the Department of Anaesthesiology, IPGMER, Kolkata in the period between 2011-2013. Eighty children aged between 2-12 years, of either sex, ASA grade I and II were randomly divided into two groups. Group D (n=40) received intranasal dexmedetomidine 1 µg/kg & oral placebo. Group M (n=40) received oral midazolam 0.5mg/kg & intranasal placebo.

DEMOGRAPHIC CHARACTERISTICS OF THE PATIENTS:
Table 4.1: **Demographic distribution of patients between two groups:**

	Mean	Standard deviation		p value
Group D	5.46	1.838		p<0.731
Group M	5.60	1.861		
	Mean body weight	Standard deviation		p-value
Group D	17.175	4.355		<0.889
Group M	17.325	5.249		
	Mean BMI (kg/m2)	Standard deviation		p- value
Group D	14.11	1.499		<0.498
Group M	13.87	1.70		
	Male	Female	Total	p value
Group D	23 (57%)	17 (53%)	40	0.502
Group M	19 (43%)	21 (47%)	40	

Table 4.1 shows that there is no statistically significant difference in age distribution between the groups (p>0.05) [Student's unpaired t-test].

Table shows the sex distribution in between the two groups. Both the groups are comparable in terms of sex distribution.(p>0.05) [Fisher's exact probability test].There is no statistically significant difference in body weight distribution between the groups (p>0.05) [Student's unpaired t-test].Table shows the BMI distribution between two groups. The groups are comparable in terms of BMI and the difference between them is statistically insignificant (p>0.05) [Student's unpaired t-test].

Figure 4.2 **HEART RATE (beats per minute) during the study period:**

Fig 4.2 summarizes the descriptive statistics for the heart rate per minute of patients in Group D and Group M at various points of time-- at 0 min, after 15min, after 30min, intra-operative after 30min, intra-operative after 60min, PACU-in (admission in PACU) and PACU-out (discharge from PACU). On statistical analysis using unpaired Student t-test, the statistical differences are found to be significant at 30 min and 60 min intra-operatively and at PACU-in.(p<0.05){ Student's unpaired t test}.

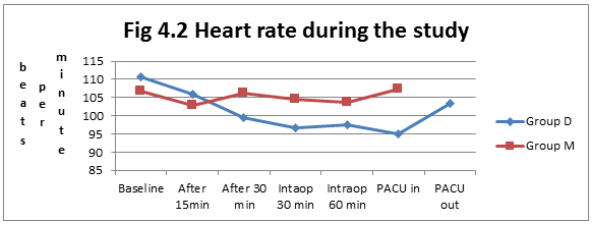


Fig 4.3: Comparison of SEDATION LEVEL (6-point sedation scale) between groups at various time points:

Fig 4.3 summarizes the descriptive statistics for the sedation level of patients in Group D and Group M at various points of time-- after 5min, after 10min, after 15 min, after 20min, after 25min, after 30min, at parental separation and at induction. The median sedation level scores are statistically significant after 15 min, after 20min, after 25min, after 30min, at parental separation and at induction. (p<0.05){Mann-Whitney U test}

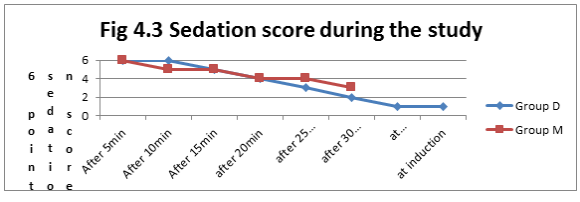


Table 4.4: Comparison of **BEHAVIOUR** SCORE (4- point)

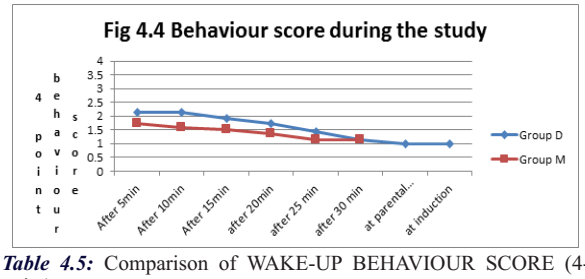


Table 4.5: Comparison of WAKE-UP BEHAVIOUR SCORE (4-point)

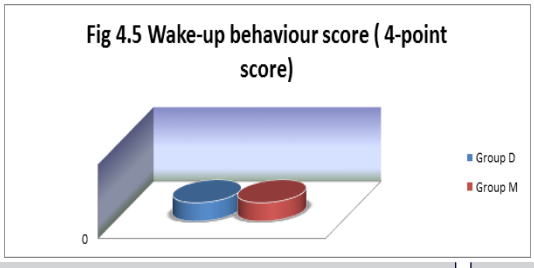
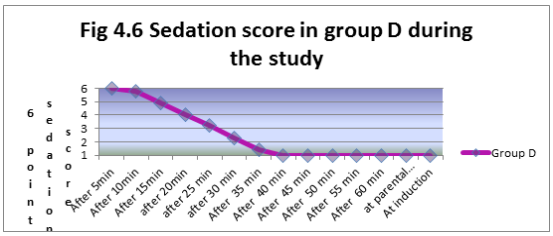


Table 4.6: SEDATION LEVEL (6-point)



Discussion-

One of the challenges for paediatric anaesthesiologists is to minimise distress in children in the operating room (OR) environment and to facilitate a smooth induction of anesthesia. This is often accomplished by prior administration of a sedative drug before transfer to the operating room. Sedation before surgery is an effective method that is widely used for young children for decreasing anxiety.[2] The primary goals of premedication in children are to facilitate a smooth and anxiety-free separation from the parents and induction of anesthesia.

The present study was designed to compare the effects of oral midazolam and intranasal dexmedetomidine for premedication in paediatric anaesthesia. The dose of midazolam (0.5 mg/kg) and dexmedetomidine (1 µg/kg) .

Demographic characteristics are comparable and statistically not significant.

Table 4.2, Figure-4.2 shows the distribution of heart rates during the study period and their comparison between the two study groups at various points of time. Statistical differences are found to be significant only at 30 min and 60 min intra-operatively and at PACU-in. ($p<0.05$)

α_2 -agonists produce a modest reduction in BP and HR. When dexmedetomidine is infused as an IV bolus at doses ranging from 0.25 to 2 µg/kg over 2 min in healthy volunteers,[25] it causes a dose-dependent decrease in BP ranging from 14% to 27%. 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 surgery.[18] Munro et al.[26] reported that the reduction of blood pressure and HR were < 20% of baseline in children who were sedated with an initial dose of 1 µg/kg IV dexmedetomidine, followed by a maintenance infusion during cardiac catheterization.

In this study, it is apparent that preoperative 1 µg/kg intranasal dexmedetomidine reduces HR (17.55%), but minimal change in blood pressure (0.01%) in healthy children during the first hour after drug administration. HR is decreased in both the groups but more in group D, and difference in decrease is statistically significant only at 30 min and 60 min intra-operatively and at PACU-in.

Figure- 4.3 the median sedation level scores are statistically significant after 15 min, after 20min, after 25min, after 30min, at parental separation and at induction. ($p<0.05$) .Sedation scores were categorized as being satisfactory when rated between 1 and 4 and unsatisfactory when rated 5 or 6. Behavior scores and wake-up scores were categorized as satisfactory when they were 1 or 2, and unsatisfactory when they were 3 or 4.

Group-D attained more significant and satisfactory sedation at parental separation and at induction of anesthesia than those patients who received oral midazolam. A recent study has demonstrated that 75% and 92% of adult healthy volunteers attained significant sedation after 1 and 1.5 µg/kg intranasal dexmedetomidine, respectively.[23] In this investigation, it was found that the average time to attain a satisfactory level of sedation after 1 µg/kg intranasal dexmedetomidine was 20 min whereas in case of oral midazolam it was 25 min. The reported sedative effects of midazolam are quite variable. Effective sedation has been reported to range from 39% to 75% [27] when a parenteral preparation was used for oral administration. In two different studies, commercially prepared oral midazolam has been shown to produce satisfactory sedation in 97%and 81% of children[6,10] .This study showed that from 20 min onwards sedation level was more in dexmedetomidine group in comparison to midazolam group.

Figure 4.6 show the trend of sedation level after giving dexmedetomidine in Group D over time. It was evident that lowest median sedation score was achieved after 30 min of the drug administration and satisfactory level of sedation after 20 mins.

Figure-4.5 summarize the descriptive statistics for the behaviour score of patients between the two groups. The median behaviour score are statistically significant after 10 min and after 15min of giving study drug. ($p<0.05$) . The median wake-up behavior scores were not statistically significant. ($p>0.05$)

Although previous studies have documented the effectiveness of oral midazolam as a preoperative anxiolytic,[4, 5, 11, 27,28] behavior scoring system did not allow evaluation of the anxiety level of children. The present study revealed that the behaviour of children at separation from parents and at induction of anesthesia were similar irrespective of administration of either oral midazolam or intranasal dexmedetomidine, based on behavior scale and in both groups it was satisfactory. Although oral midazolam produced satisfactory sedation in the subjects, it could have produced significant anxiolytic and/or amnesic effects.

None of the patients in either group suffered from respiratory depression, apnoea, bradycardia, hypotension, hypoxia or any hypersensitivity to the study drugs.

Thus, it may be concluded that, Group-D produces significant sedation and also modest reduction of heart rate. Behavior of the children at parental separation and at induction of anesthesia was comparable to children who received oral midazolam.

SUMMARY: One of the challenges for paediatric anaesthesiologists is to minimise distress in children in the operating room environment and to facilitate a smooth induction of anesthesia.

This double-blind, prospective, randomized controlled study was carried out in the department of Anaesthesiology, Institute of Post Graduate Medical Education and Research, Kolkata after taking institutional ethicS committee clearance .

The study was conducted in 80 children aged 2-12 years after taking informed parental consent. Group M received oral midazolam 0.5mg/kg & intranasal placebo. Group D received intranasal dexmedetomidine 1 µg/kg & oral placebo. Sedation status was assessed by a blinded observer every 5 min with a 6-point sedation scale. Behaviour was evaluated every 5 min with a 4-point behaviour score. Sedation status and behaviour were evaluated at parental separation and at induction using the same scale. When surgery was finished, the child was placed in the recovery position and allowed to wake up naturally in the postanaesthesia care unit (PACU). Behaviour at awakening was evaluated with a four-point wake-up score in PACU. Time taken for readiness to be discharged from the PACU was recorded. Any adverse effect to the study drugs was also noted.

CONCLUSION: Intranasal dexmedetomidine premedication produced significant sedation in children between 2 and 12-yr-of-age. Behavior of the children at parental separation and at induction of anesthesia was comparable between two groups. The dexmedetomidine showed modest reduction of heart rate in comparison to midazolam.

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