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COMPARISON OF EFFECTIVENESS OF ORAL MIDAZOLAM WITH INTRANASAL DEXMEDETOMIDINE AS PREMEDICATION IN CHILDREN UNDERGOING AN ELECTIVE SURGERY

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ABSTRACT Background: Inadequate handling of an uncooperative child preoperatively and children who are extremely anxious during induction of anesthesia are extremely at risk of developing post-operative behaviour problems compared to children who appear calm during induction. To eliminate anxiety induced post-operative behaviour problems in children we compared the effectiveness of oral midazolam 0.5 mg/kg with intranasal dexmedetomidine 1µg/kg as premedication in children undergoing elective surgery. Material and methods: A randomized double blind study was conducted in 60 children of either gender divided in two groups (Group M n=30 and Group D n=30). Group M received 0.5 mg/kg oral midazolam. Group D received 1µg/kg intranasal dexmedetomidine in 0.4ml normal saline. Hemodynamic variables were monitored at every 10 mins interval after administration of drug. These groups were compared using one-way analysis of variance (ONE –WAY ANOVA) and difference between the groups compared using unpaired T-Test. **Results:** The intranasal dexmedetomidine produced superior sedation scores at separation and induction. **Conclusion:** We concluded that intranasal dexmedetomidine provided better relief in anxiety.

KEYWORDS :

Introduction

One of the challenges for pediatric anesthesiologists is to minimize distress for children in the operating room (OR) environment and to facilitate a smooth induction of anesthesia [1].The emotional and psychological trauma in children due to unfamiliar hospital environment, fear of operation, injections and separation from parents prior to anesthesia is well known[2]. Inadequate handling of an uncooperative child preoperatively and children who are extremely anxious during induction of anesthesia are extremely at risk of developing post-operative behaviour problems compared to children who appear calm during induction. Various methods available to decrease anxiety are: sedative premedication, parental presence during induction and pre-operative preparation programs [3] .

Premedicating the pediatric patients has always been a challenge to the anesthesiologist because of their lack of co-operation, preferred nontraumatic route of administration and susceptibility to respiratory depression[4]. The ideal premedication for children should have anxiolytic, sedative, analgesic and anti-sialagogue action when administered non parentrally, with rapid onset, short duration of action and devoid of adverse hemodynamics and respiratory effects[5].

Benzodiazepines are routinely used in children and adults for their anxiolytic and hypnotic properties. Midazolam has the advantage of a rapid onset and relatively short duration of action. Though the oral preparation of midazolam is commercially available now, the parenteral preparation is still being used by the oral route after mixing it in a vehicle to make it more palatable[6,7].

Alpha -2-Adrenergic receptor (AR) agonists have been the focus of interest for their sedative, analgesic, perioperative sympatholytic, anestheticsparing, and hemodynamic-stabilizing properties[8]. Dexmedetomidine, a highly selective Alpha -2 receptor agonist with a relatively high ratio of Alpha -2/Alpha 1-activity (1620:1 as compared to 220:1 for clonidine), possesses all these properties and lacks respiratory depression[9,10], making it a useful and safe adjunct in diverse clinical applications[11]. The intranasal method of administration is easy to administer apart from being painless, odourless and tasteless[1]. The onset of action of intranasal drug is within 20 minutes of its administration , as it bypasses the first pass metabolism[12].

The purpose of the present study was to compare the effectiveness of oral midazolam 0.5 mg/kg with intranasal dexmedetomidine 1µg/kg as premedication in children.

Material and method

After obtaining approval from the Institutional Ethics Committee a written and informed consent was obtained from the parents of all children after explaining the nature of the study. In this prospective, randomized and comparative study, sixty children of either gender participated. Each group had thirty children each. All of them belong to American Society of Anaesthesiologists physical status I or II of the age group 1–12 years.

Pre-operative assessment was performed and nil per oral orders was as per the standard ASA protocol. The premedication was administered 30 min before induction of anesthesia in preoperative area in the presence of one of the parents after applying standard monitoring BP, heart rate and SPO2. The BP, heart rate and SPO2 were monitored at every 10 mins interval after the drug administration. Group M received 0.5 mg/kg oral midazolam. Group D received 1µg/kg intranasal dexmedetomidine in 0.4ml normal saline.

Owing to the non-availability of oral midazolam at the time of this study, injectable midazolam was used for this study. Oral premedication was made by the mixing the specific drug to a fixed volume 5 ml of fruit juice without pulp (orange juice) to mask the bitter taste. Oral midazolam was used for this study in dose of 0.5 mg/kg. Group D received intranasal dexmedetomidine which was prepared from 100 µg/ml of parenteral preparation of the drug. Normal saline added to the calculated dose to make a final volume of 0.4 ml. Intranasal drug was dipped into both the nostrils at 0.2 ml per nostril using 1 ml insulin syringe with children in recumbent position. After administration of premedication, the children were made to relax along with their parents in preoperative area where there were some colourful toys. There systolic BP, heart rate and oxygen saturation were monitored and recorded at every 10 mins interval after administration of drug. The parameters assessed were level of sedation post premedication, ease of separation from parents and the behaviour during intravenous cannulation and face mask acceptance. The assessment was made and the level of sedation was graded by 5 point sedation score[23] (1 = asleep not readily arousable, 2 = asleep responds slowly to gentle stimulation, 3 = drowsy readily responds, 4 = awake calm and quiet, 5 = awake active). The behaviour at the time of separation from parents was assessed when the child was separated from parents to shift to operating room using 4 point separation score (1=excellent happily separated, 2 good separated without crying, 3 = fair separated with crying, 4 = poor need for restraint). Score of ≤2 was considered successful while score >2 will be considered unsuccessful. Ketamine 3 mg/kg IM with glycopyrrolate (10 µg/kg) was given if the separation was difficult. In the operation theatre, sedation score, systolic BP, oxygen saturation and heart rate were noted before induction of anaesthesia. Once the child was asleep, an intravenous

line was set up. Behaviour during face mask placement was assessed by 3 point cooperation score (1 = cooperative, 2 = mildly resistant,3 = resists placement of mask). Systolic BP, heart rate and SPO2 were monitored. Then surgery started under general anaesthesia. After surgery patient reversed from general anaesthesia and transferred to postoperative recovery room and monitoring was done. Side effects of oral premedicants such as nausea, vomiting, hiccups, airway obstruction, restlessness, or slurring of speech hypotension, bradycardia were noted for both group in the recovery period.

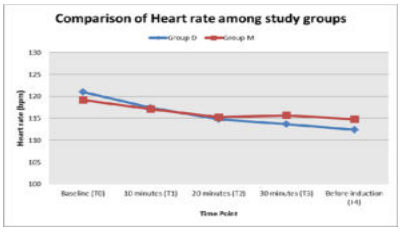
Results

The demographic data of the three studied groups are summarized in Table 1, statistical analysis revealed nonsignificant differences between the three groups as regards age, height and weight. No patients were excluded after inclusion to the study.

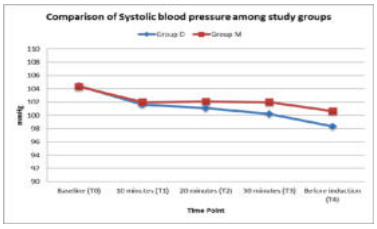
Table 1: Demographic Data

	Group D	Group M	P value
Age (Years)	5.70±2.79	4.93±4.38	0.257
Weight (Kg)	20.2±8.45	16.4±6.62	0.057
ASA I/II	26/4	26/4	1.0
Data are presented as mean±SD or ratio of patients. P>0.05 is considered statistically nonsignificant. SD=Standard deviation			

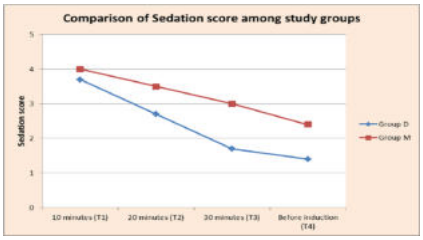
There was gradual decrease in mean heart rate after study drug administration in both groups, but the difference in heart rate among the two groups was not statistically significant at any time. Before induction, the mean heart rate in group M was slightly more (114.8 bpm) as compared to Group D, but this difference was not statistically significant (P=0.407).



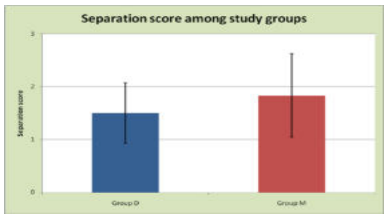
The baseline Systolic blood pressure was comparable between the two groups (P=0.970). There was slight decrease in Systolic blood pressure after study drug administration in both groups (T1), but the difference between the two groups was not statistically significant. No significant difference was seen in Systolic blood pressure between the two study groups at any time till before induction (p>0.05).



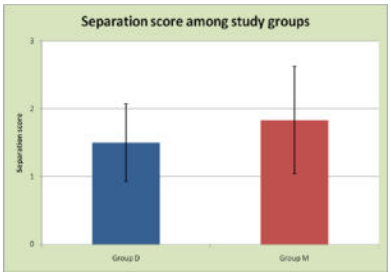
The sedation score at 10 minutes was 4 in all Group M subjects, while mean sedation score in Group D was 3.6. This difference was statistically significant (p=0.001). The sedation score decreased gradually in both groups, but it was significantly more in group M at all times as compared to Group D. Before induction the mean sedation score in Group D (1.4 ± 0.6) was lower as compared to Group M (2.4 ± 0.5) and this difference was found to be statistically significant (p<0.001).



The mean Separation score in Group D was 1.5 ±0.57 ranging from 1 – 3, while in Group M the mean separation score was 1.83± 0.79 ranging from 1 – 4. This difference in separation score between the study groups was however not found to be statistically significant (p>0.05) i.e. separation score was higher in Group M but not statistically significant.



The mean Cooperation score in Group D was 1.43 ± 0.5 ranging from 1-2, while in Group M the mean Cooperation score was 1.6 ± 0.56 ranging from 1-3. This difference in Cooperation score between the study groups was however not found to be statistically significant (P=0.328) i.e. Cooperation score was higher in Group M but not statistically significant.



Discussion

In our study, the groups were comparable with respect to HR at baseline and at the any point of time, there was decreasing trend in both group at 30 mins and before of induction decrease in Heart Rate was significantly more in Group D as compared to Group M. **Kumar et al**[13] performed a prospective randomized double blinded trial comparing the effects of premedication with 0.5 mg/kg oral midazolam versus 1µ/kg intranasal dexmedetomidine in children between 2 and 12 years undergoing abdominal surgery. Sedation scores at separation and induction were the primary outcome measures. Comparison of baseline mean arterial blood pressure (MAP), HR and oxygen saturation in Groups A and B showed no difference between groups. However, intraoperatively, significantly higher values of HR were seen in midazolam group at 30, 45 and 60 min. **Rajalakshmi**[14] **et al** conducted a prospective randomized doubleblinded trial to evaluate the effects of intranasal dexmedetomidine over placebo (0.9% saline) as a premedicant in paediatric cardiac surgeries. A total of 60 children of ASA physical status I and II, between the ages of 2 and 8 years undergoing various cardiac surgeries were assigned randomly into two groups. In group D, patients received intranasal dexmedetomidine (2 µg/kg), and in group P, patients received intranasal saline. At intervals of 10, 20, 30 and 45 min after intranasal administration of the study drug, parameters such as heart rate, blood pressure, respiratory rate and SpO2 (oxygen saturation) were monitored. At 45 min, sedation, the ease of separation and intravenous cannula acceptance were evaluated. They found statistically significant reductions in heart rate and blood pressure from 30 min onwards in group D ($P < 0.05$) when compared with the placebo group.

We did not found a statistically significant reduction in SBP, but we noted a higher decreasing trend in SBP in group D as compared to group M. **Kumar et al**[13] also not found any significant change in MAP in both groups However intraoperatively significantly higher values of MAP were seen in midazolam Group at 30, 45 and 60 min. But **Yuen et al**[1] noted that SBP decreased significantly in group D1 when compared with group M. Moreover SBP decreased with time and it was significantly different from baseline at 30 min (P 0.003), 45 min (P 0.001), and 60 min (P 0.001) after drug administration in group D1. In our study we found that the mean Separation score in Group D was 1.5 ± 0.57 ranging from 1-3, while in Group M the mean separation score was 1.83± 0.79 ranging from 1-4. This difference in separation score between the study groups was however not found to be statistically significant (p>0.05) but higher in group M. In our study all patients except two children in group M were satisfactorily separated from parents, in our study the behaviour at the time of separation from parents was assessed using the separation score. Rajalakshmi **et al**[14] observed in their study that the median behaviour score in Group A was higher than Group B at separation (2 vs. 1). They

were both in the range considered satisfactory (≤2) and were not significantly different between the groups at separation and induction. Yuen et al[1] observed that there was no evidence found for a difference in behaviour scores at separation from parents among the three groups, Rani J et al[15] also noted that there was no evidence found for a difference in behavior scores at separation from parents among the two groups. All children except one in group B had satisfactory behaviour at separation from parents. Rajlakshmi et al[14] also noted a significantly lower separation score in dexmedetomidine group compared to placebo group, Jambure et al[16] also noted a significantly lower separation score in group D. Like our study Kumar et al[13], Yuen et al[1] and Rani J et al[15] did not found any significant difference in separation scores. Rajlakshmi et al[14] and Jambure et al[16] found a significantly lower separation score in group D which may be due to use of higher dose of dexmedetomidine in their study.

The mean Cooperation score in Group D was 1.43 ± 0.5 ranging from 1–2, while in Group M the mean Cooperation score was 1.6 ± 0.56 ranging from 1–3. This difference in Cooperation score between the study groups was however not found to be statistically significant (P=0.328) i.e. Cooperation score was higher in Group M but not statistically significant. In our study behaviour during face mask placement or induction was assessed by cooperation score. Kumar et al[13] and Yuen et al[1] in their studies also did not found any significant difference in behaviour score at the time of induction.

Conclusion:

This study concluded that the intranasal dexmedetomidine at a dose of 1µg/kg produced superior sedation scores at separation and induction but normal behaviour scores in comparison to oral midazolam at a dose of 0.5 mg/kg in pediatric patients without any adverse effects which required pharmacological intervention for correction. The main advantage of dexmedetomidine lies in the fact that the patients were sedated but easily arousable, which resembles natural sleep. They were quite easily shifted to OR and there were no incidences of bradycardia, hypotension, respiratory depression or any untoward incident.

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