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Comparison of Oral Dexmedetomidine Vs Oral Midazolam as Pre-Medication for Children Undergoing Elective Surgical Procedures

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Abstract

Pre-medications are frequently administered in children to alleviate the stress and fear of treatment as well as to ease child-parent separation and promote a smooth induction of anesthesia. Various drugs have been tried ranging from midazolam, ketamine, fentanyl, promethazine, and triclorfos. Of late alpha-2 agonists like Dexmedetomidine are being used, it has both sedative and analgesic properties and is devoid of respiratory depressant effect. These properties render it potentially useful for anesthesia pre-medication. Aim is to compare the effects of midazolam and dexmedetomidine when administered orally as pre-anesthetic medication for children. *Materials and Methods:* Children are randomised into Group M receiving midazolam 0.5 *mg/kg* and Group D receiving dexmedetomidine 2 *mcg/kg* orally. *Results:* Demographic and hemodynamic parameters are comparable between two drugs. Child separation Score 1 in Group D is 29 out of 35 (83%) and in Group M is 16 out of 35 (45.7%) with *p* value of < 0.05. Mask acceptance Score 1 and 2 in Group D is 34 out of 35 (97.2%) where as in Group M is 22 out of 35 (62.8%) with *p*-value of < 0.05. Sedation score of 2 and 3 in Group D is 29 out of 35 (82.9%) and Group M is 32 out of 35 (91%) with *p* value of > 0.05. Dexmedetomidine is a better drug in terms of child parent separation and mask acceptance score than midazolam. However, sedation scores were comparable. To conclude Dexmedetomidine is a superior pre-medication compared to Midazolam when given by oral route. Dexmedetomidine may find a regular place for pre-medication in children pre-operatively.

Keywords: Dexmedetomidine; Midazolam; Oral pre-medication.

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Introduction

Anesthesia practice is a major contributor to the outcomes of surgical operation. Distress and the psychological trauma from maternal separation are major challenges in the practice of paediatric anesthesia.[1] Pre-medications are frequently administered in children to alleviate the stress and fear of treatment as well as to ease child-parent separation and promote a smooth induction of anesthesia.[2] Oral midazolam, the most common anesthetic pre-medication in children, is being widely used to ease the children's separation anxiety during maternal deprivation on transfer into the operation room. Despite several advantages of midazolam for anesthetic pre-medication in children, some of its side effects such as paradoxical reaction, restlessness, and other unfavorable behavioral changes (post-surgery) have limited it's application as an ideal option.[3]

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New drugs such as the α_2-agonists have emerged as alternatives for pre-medication in pediatric anesthesia.[4] Dexmedetomidine is a highly selective α_2-agonist with both sedative and analgesic properties and is devoid of respiratory depressant effect. These properties render it potentially useful for anesthesia pre-medication.[5] Hence, this study intended to compare oral midazolam and oral dexmedetomidine as a pre-anesthetic medication for children.

Aim and Objectives

Primary: To compare the effects of midazolam and dexmedetomidine when administered orally as pre-anesthetic medication for children;

Secondary: To compare hemodynamic parameters and side effects of study drugs;

Expected outcome: To know the better premedication drug among children, between midazolam and dexmedetomidine.

Materials and Methods

Source of data: MS Ramaiah teaching hospital;

Sample size: 60 patients with 30 in each group.

Rationale for sample size calculation: A study carried out by Sayedeh *et al.*[5] revealed that the mean sedation scores to be 1.93 (0.6) and 2.0 (0.63) with midazolam and dexmedetomidine respectively. Based on the above findings, with power of 90% and error of 1% it has been estimated that 24 subjects need to be included in each group. However, allowing for drop outs we proposed to include 30 children in each group. The above sample size would be sufficient to evaluate the mask acceptance and child parent separation score too.

Inclusion criteria

1. Age *1–6 yrs;*
2. ASA 1 and 2;
3. Children posted for elective surgical procedures.

Exclusion criteria

1. Anticipated difficult airway cases;
2. Syndromic children;
3. Child with recent respiratory tract infections.

Methods

After institutional ethical committee clearance and informed written consent from the parents, 60 children satisfying the inclusion criteria were enrolled into the study. They were randomised using computer generated random numbers into two groups, Group M receiving midazolam *0.5 mg/kg* and Group D receiving dexmedetomidine *2 mcg/kg* orally. After confirming fasting status, child was shifted to pre-operative room, monitors connected and baseline parameters noted. *45 minutes* prior to the surgery, patient received the study drug diluted to *5 ml* by reconstituting with 5% dextrose solution and given orally by dropper. The child's parent and the observing anesthetist were blinded to the study. Child was observed for child-parent separation score, mask acceptance behavior and sedation during anesthesia, hemodynamic parameters like heart rate, blood pressure, saturation and adverse effects if any.

Statistics

Data was analysed using Statistical Package for Social Science SPSS V18 software. p - value < 0.05 was considered for statistical significance. Descriptive statistics like blood pressure, saturation, respiratory rate and heart rate were analysed and presented with mean and standard deviation. Child-parent separation score, mask acceptance behavior, sedation and any adverse events during anesthesia, was summarised in terms of percentage.

Independent *t*-test was used to compare the blood pressure, saturation, respiratory rate and heart rate between the groups at different time. Chi-square test was used to compare child-parent separation score, mask acceptance behavior, sedation and any adverse events during anesthesia between two groups. Continuous covariates were compared using analysis of variance (ANOVA).

Results

The demographic parameters of the patients like age, weight, height, type of surgery and gender in the study were comparable with a p - value of > 0.05. The mean age in Group D was *4.33 ± 1.5 years* and Group M was *3.53 ± 1.4 years*. The mean weight was *15.1 ± 4.9 kgs* and *17 ± 5.5 kgs* in Group D and M respectively. The mean height was *65.1 ± 7.23 cms* and *56 ± 11.1 cms* in Group D and M respectively. All these were statistically not significant.

Out of 70 patients, 39 were males and 31 were females. In Group D 18 were males and 17 were females. In Group M 21 were males and 14 were females. The results were statistically not significant.

Heart rate changes from baseline upto *15 minutes* in both the groups are not statistically significant. From *15 minutes* to the end of the surgery (mean *120 minutes*) there is decrease in heart rate in Group D with a *p* - value of > 0.05 which is statistically not significant. In Group M the decrease in heart rate is not statistically significant.

Mean arterial blood pressure changes in Group D and M from baseline till end of the surgery with a mean duration of *120 min*. The decrease in mean arterial blood pressure in both the groups is not statistically significant with a *p* - value of > 0.05. Demographic and hemodynamic parameters are comparable between two drugs.

Child-Parent separation score: in group D, Score 1 in 29 out of 35 (83%), Score 2 in 6 out of 35 (17%) and Score 3 in none of the patients. In Group M, Score 1 in 16 out of 35 (45.7%), Score 2 in 17 out of 35 (48.6%) and Score 3 in 23 out of 35 (32.9%). Child-Parent separation Score is clinically better in Group D when compared to Group M with *p* - value of < 0.05, which is statistically significant, (Graph 1).

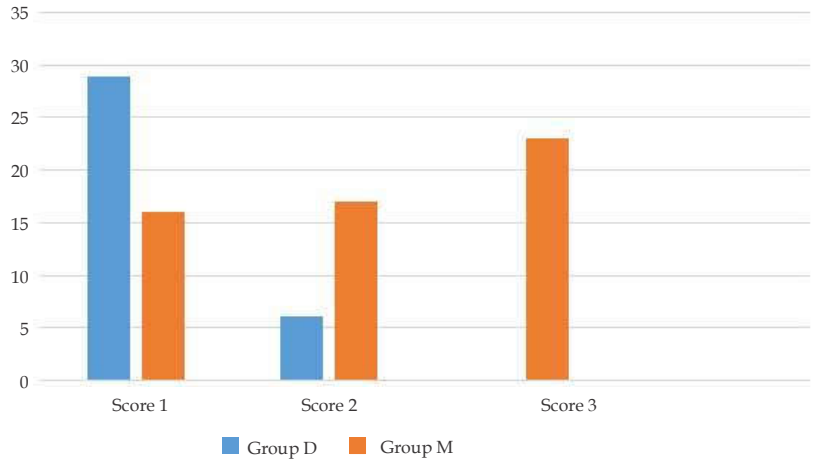
Child-parent Separation Score[3]

Patient unafraid, co-operative, or asleep 1

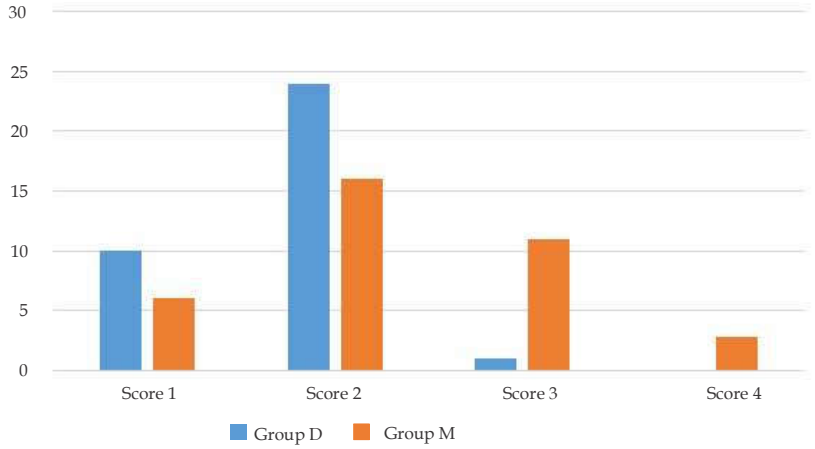
Patient slightly fearful and/or crying; quieted with reassurance 2

Patient fearful and crying; not quietened with reassurance 3

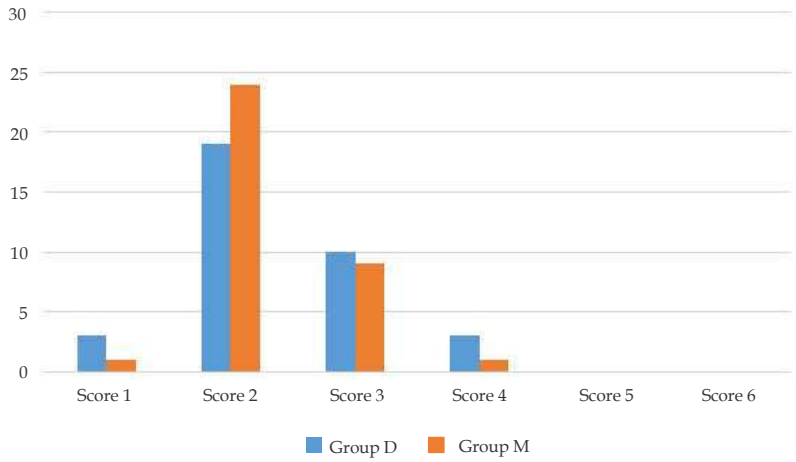
In Group D Mask acceptance Score 1 is 10 out of 35 (28.6%) patients, Score 2 is 24 out of 35 (68.6%) patients, Score 3 is 1 out of 35 (2.9%) patient and Score 4 is 0 patient. In Group M Mask acceptance Score 1 is 6 out of 35 (17.1%) patients, Score 2 is 16 out of 35 patient (45.7%), Score 3 is 11 out of 35 patient (31.4%) and Score 4 is 2 out of 35 (5.7%) patients.



Graph 1: Shows Child-Parent separation Score between Group D and Group M



Graph 2: Showing Mask Acceptance Score between the Groups D and M



Graph 3: Showing sedation score between the groups D and M

Mask acceptance Score 1 and 2 in Group D is 34 out of 35 (97.2%) where as in Group M is 22 out of 35 (62.8%) indicating Mask acceptance score is better in Group D when compared to Group M with *p* - value of < 0.05, which is statistically significant, (Graph 2).

***Mask Acceptance Score*[5]**

Score	Description
1	Calm and co-operating
2	Anxious but without resistance
3	Anxious with slight resistance
4	Crying and/or struggling against mask

In Group D sedation Score of 1 is 3 out of 35 (8.6%) patients, Score 2 is 19 out of 35 (54.3%) patients, Score 3 is 10 out of 35 (28.6%) patients, Score 4 is 3 out of 35 (8.6%) patients and no patients in Score of 5 and 6.

In Group M sedation Score is 1 is 1 out of 35 (2.9%) patient, Score 2 is 24 out of 35 (68.6%) patient, Score 3 is 9 out of 35 (25.7%) patient, Score 4 is 1 out of 35 (2.9%) and no patients in Score of 5 and 6.

Sedation Score of 2 and 3 in Group D is 29 out of 35 (82.9%) and Group M is 32 out of 35 (91%) which is statistically comparable with *p* - value of > 0.05 between the Groups, (Graph 3).

***Ramsay Sedation Score*[2]**

Score	Description
1	Anxious and agitated or restless, or both
2	Co-operative, oriented, and calm
3	Responsive to commands only
4	Exhibiting brisk response to light glabellar tap or loud auditory stimulus
5	Exhibiting a sluggish response to light glabellar tap or loud auditory stimulus
6	Unresponsive

No complications were observed in terms of nausea, vomiting, bradycardia, hypotension, desaturation, and pruritis in both the Groups.

Discussion

Midazolam is the most commonly used anxiolytic pre-medication in young children. It facilitates Gamma Amino Butyric Acid (GABA) receptor-mediated chloride conductance, which has an inhibitory effect on neurons in the cerebral cortex. It has been successfully used through various routes, *e.g.* intravenous, intramuscular, oral and intranasal route.[6] 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.[7]

Dexmedetomidine possesses many properties that are advantageous for a sedative and anesthetic drug. It has been reported to provide sedation that parallels natural sleep, anxiolysis, analgesia, sympatholysis, and an anesthetic-sparing effect with minimal respiratory depression. These favorable physiological effects combined with a limited adverse effect profile make dexmedetomidine an attractive adjunct to anesthesia.[8]

Demographic and hemodynamic parameters are comparable between two drugs. Even though there was marginally decrease of heart rate in dexmedetomidine Group when compared to midazolam Group, this was not statistically significant.

This infers both dexmedetomidine and midazolam have safe hemodynamic margin. Child separation Score 1 means child unafraid, co-operative, or asleep. Score 1 in Group D is 29 out of 35 (83%) and in Group M is 16 out of 35 (45.7%).

Child-Parent separation score is clinically better in Group D when compared to Group M with *p* - value of < 0.05, which is statistically significant. This indicates dexmedetomidine provides adequate conscious sedation which is helpful to separate children from parents while taking inside the operating theatre. Similar to Shailesh *et al*.[7] study where both drugs were give intranasal. However, Jannu *et al*.[9] found no difference in both the Groups probably due to different doses used by them.

Mask acceptance Score 1 is child being Calm and co-operating and Score 2 is child is anxious but without resistance. 1 and 2 score is taken as an acceptable score for mask ventilation. Mask acceptance Score 1 and 2 in Group D is 34 out of 35 (97.2%) where as in Group M is 22 out of 35 (62.8%) indicating Mask acceptance is better in Group D when compared to Group M with *p* - value of < 05, which is statistically significant. This is in accordance with syeedah *et al*.[5] and Deepak *et al*.[6] This indicates dexmedetomidine will provide better mask acceptance for children during pre-oxygenation in general anesthesia without any struggle during mask holding.

Ramsay sedation Score of 2 was child being Co-operative, oriented, and calm, where as Score of 3 is responsive to commands only. Score of 2 and 3 is taken as adequate sedation required for pre-medication. Sedation Score of 2 and 3 in Group D is 29 out of 35 (82.9%) and Group M is 32 out of 35 (91%). The sedation appears clinically better in Group M but it's not statistically significant with *p* value of > 0.05. This implies dexmedetomidine provides equal and effective sedation comparable to midazolam. This is in accordance with studies of Lakshmi *et al*.,[10] Sukanya *et al*.[1]

The sedation produced by dexmedetomidine differs from other sedatives as patients may be easily aroused and co-operative. It affords sedative, anxiolytic, and analgesic effects without causing excessive drowsiness.[3]

In our study, we used the oral administration route as the children are less likely to resist receiving the pre-medication itself. This is in contrast to what is seen in other routes like intranasal which required a separate drug delivery system and resistance offered by the children to this route. In our study, we diluted the drug in a *5 ml* syringe to maximum of *0.4 ml/kg* with 5% dextrose solution and was given orally by the parents. This technique was acceptable by the child and was comfortable to the parents also. The only limitation being the bio availability of the drug and the cost of dexmedetomidine.

Conclusion

Dexmedetomidine is superior than Midazolam as pre-medication in pediatric patients with excellent child-parent separation, favorable mask acceptance score. It also provides equally effective sedation with comparable hemodynamic parameters and no adverse effects as of midazolam.

To conclude Dexmedetomidine is a superior pre-medication compared to Midazolam when given by oral route. Dexmedetomidine may find a regular place for pre-medication in children pre-operatively.

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