VOLUME-7, ISSUE-12, DECEMBER-2018 • PRINT ISSN No 2277 - 8160

Original Research Paper

Anaesthesiology

A COMPARATIVE STUDY OF INTRANASAL DEXMEDETOMIDINE AND INTRANASAL MIDAZOLAM AS PREMEDICATION IN CHILDREN UNDERGOING SHORT SURGICAL PROCEDURES

Dr. Rahul Fernandez	Senior Resident, Dept. of Anesthesiology & Critical care, St. John's Medical College Hospital, Bangalore , Karnataka, India
Dr. Moses Charles Dsouza*	Professor, Dept. of Anesthesiology & Critical care, St. John's Medical College Hospital, Bangalore, Karnataka, India *Corresponding Author
Dr. Surbhi Gupta	Associate Professor, Department of Anesthesiology and critical care, St John's Medical College Hospital, Bangalore, Karnataka, India
Dr. Sumithra Selvam	Senior Resident, Division of Biostatistics , St. John's Research Institute, Bangalore Karnataka, India

ABSTRACT

INTRODUCTION : Anaesthetizing children for surgery can be challenging due to parental separation anxiety and an unfamiliar OT environment. Various drugs have been tried for pre- medication to alleviate this anxiety and facilitate induction of anesthesia. We compared Intranasal Dexmedetomidine and Intranasal midazolam for premedication in children undergoing short surgical procedures.

MATERIALS AND METHODS: 104, ASA grade I and II children between 2-10 years, scheduled for elective short surgical procedures were randomly allocated to receive intranasal Dexmedetomidine (1µg/kg) (Group D) or intranasal Midazolam (0.2mg/kg) (Group M) . The Parental Separation Anxiety Score, MOAA/S scores ,Mask Acceptance Score and 24 hr vitals were assessed

RESULTS: The parental separation and MOAA/S scores attained with intranasal Dexmedetomidine premedication were found to be superior to intranasal Midazolam ($p<0.0001$). The mask acceptance was better among children premedicated with intranasal Dexmedetomidine than with Midazolam . There was a statistically significant decline in the heart rate in the group D compared to group M after premedication

CONCLUSION: Children premedicated with intranasal Dexmedetomidine separated much more easily from parents with a better degree of sedation and better mask acceptance compared to those premedicated with intranasal Midazolam.

KEYWORDS : Intranasal; premedication; Dexmedetomidine; Midazolam; pediatrics;

INTRODUCTION

Pediatric patients have varying degrees of anxiety[1] during the preoperative period, which may be due to separation from parents, fear of injections or unfamiliar operating theatre environment. This leads to ,agitation and excessive crying, tachycardia, nausea, , more painful postoperative recovery[2] and a higher incidence of sleep disturbances with emergence delirium[3].Children of 1-5 years of age are at the highest risk for developing extreme anxiety[4] Alleviation of this anxiety and psychological stress are major challenges in pediatric anesthesia.

Pharmacological intervention before surgery was found to be more effective than either parental presence or music therapy[5] Adequate premedication can achieve better control over anxiety and fear, and provide amnesia, analgesia, smoother emergence and relaxation Preanesthetic medication also facilitates the induction of anesthesia without prolonging the recovery[2]. Several drugs like Midazolam, Ketamine, Clonidine and Dexmedetomidine have been tried, in order to find the best sedative agent and the best route of administration of these drugs in children. Nasal administration allows easy access to the vascular bed and avoids first pass metabolism allowing more drug bioavailability. We compared the efficacy of intranasal dexmedetomidine and intranasal midazolam as preanesthetic medication in children undergoing short surgical procedures.

MATERIALS AND METHODS:

This prospective, double blind study was undertaken in a tertiary care teaching hospital after obtaining Institutional Ethics Committee approval. The sample size was calculated based on a previous study by Mostafa G et al[6], which compared the efficacy of intranasal premedication with Midazolam and Dexmedetomidine in children undergoing bone marrow biopsy. Considering the proportion with respect to Mask acceptance in Dexmedetomidine group as 0.9 and Midazolam group as 0.67, with an estimated risk difference of 0.23, the required sample size for each arm was 52, with power of 80% and Alpha error of 5%.One hundred and four pediatric patients of ASA grade I and II in the age group 2-10 years who were scheduled for minor elective surgical procedures, requiring general anesthesia for duration of 60 minutes were included in the study. .Exclusion from the study were patients with known allergy to the study drugs ,Cardiac dysrhythmias and/or congenital heart disease, psychotropic medication use, mental retardation, nasal disorders interfering with administration of medication as recurrent nasal bleeding or nasal masses and children who spat or refused intranasal administration of medication. The pre-anesthetic check up of each child was done and a detailed medical and surgical history was obtained from the parents. Weight of the child was recorded. Thorough general and systemic examination was done. The procedure adopted for administering the premedication was explained to the parents in a language best understood by them. Written and informed consent regarding the voluntary participation of their child in the study was obtained from the parents. Baseline heart rate, blood pressure, oxygen saturation and respiratory rate were measured. Intravenous cannula was inserted before premedication in all children. All children were required to have 6 hours of fasting prior to the surgical procedure .Availability of adequate monitoring equipment was ensured in the patient receiving preop room. 104 patients were randomly allocated into two groups by computer generated table method with 52 patients in each group. Group D patients received intranasal Dexmedetomidine 1µg/kg and group M patients received intranasal Midazolam 0.2mg/kg .

The study drugs were reconstituted into a syringe according to the child's weight and the mucosal atomization device was attached to it using a luer lock. After positioning the child in the parents lap with a head tilt of 15°-30°, the plunger was pressed briskly to administer about half dose of the drug (1 ml) in each nostril. The children who sniffed or snorted the drug administered were excluded from the study. The pulse rate, blood pressure, respiratory rate and oxygen saturation were measured ,at the time of premedication (0 minutes)

and every 10 minutes thereafter for 30 minutes. After 30 minutes of administration of the intranasal medication, Modified Observer's Alertness Assessment/Sedation Scale was used to assess the alertness of the child (Table 1)

Table 1 : Modified observer's Assessment of Alertness/Sedation scale (MOAA/S) -Cohen LB et al[7]

Appears alert and awake, responds readily to name spoken in normal tone	6
Appears asleep but responds readily to name spoken in normal tone	5
Lethargic response to name spoken in normal tone	4
Responds only after name is called loudly or repeatedly	3
Responds only after mild prodding or shaking	2
Does not respond to mild prodding or shaking	1
Does not respond to noxious stimulus	0

Then the child was transferred to the operating room and the ease of separation from the parent was assessed using a four point Parental Separation Anxiety Scale (PSAS)

Table 2 : Parental Separation Anxiety scale (PSAS)- McMillan C.O. et al[8]

Crying and clinging to parents	4
Crying and cannot or is difficult to be assured (not clinging to parents)	3
Child whimpers, but is easily assured (not clinging to parents)	2
Child separates easily	1

In the operating room standard monitors were attached to the child before induction of anesthesia. The child was pre-oxygenated. The mask acceptance score was assessed using a five point likert scale.

Table 3: Mask Acceptance Score - Shukry[9] and Weldon et al[10]

Asleep, easy induction	5
Calm, cooperative	4
Cooperative with reassurance	3
Moderate fear of mask, not easily calmed	2
Combative and crying	1

Child was induced with injection Fentanyl (2µg/kg) and injection Propofol(2-3mg/kg) . Injection Atracurium (0.5mg/kg) was used as muscle relaxant and patient was intubated using appropriate size endotracheal tube. Anesthesia was maintained with isoflurane and 60% nitrous oxide in oxygen. At the end of the surgical procedure reversal of neuromuscular blockade was done using injection Glycopyrrolate 10 µg/kg intravenous and Neostigmine 50 µg/kg intravenously. The child was extubated when he was awake and breathing efforts were adequate. The children were observed postoperatively in the pediatric post-operative care room for 2 hours after surgery. Vital signs of pulse rate, BP, respiratory rate and oxygen saturation were recorded at every 10 minute interval for 30 minutes from the time of extubation. Children were followed up for 24 hours thereafter to observe for nausea, vomiting and nasal mucosal irritation.

STATISTICAL METHODS:

The collected data was compiled in Microsoft Excel™ and statistical analysis of the data was done using the Statistical Package for the Social Sciences for Windows (SPSS Inc., Chicago) software version 21.0. Data was presented as number and percentages for categorical variables, mean and standard deviation for the continuous variables. Qualitative data was analyzed using chi-square test. For quantitative data, unpaired t-test was used. Probability value less than 0.05 was considered as statistically significant.

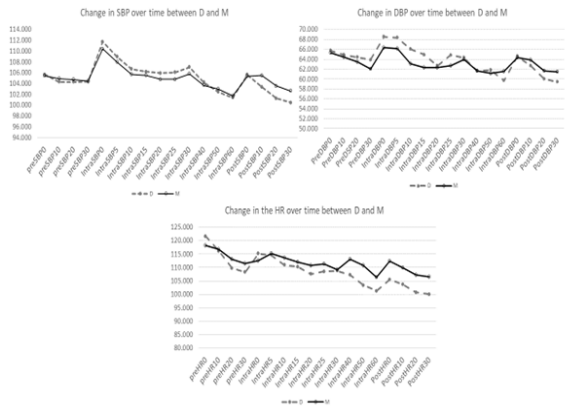
RESULTS:

Among 104 patients studied, the mean age of the patients was comparable between the two groups (Age: D- 4.9 ± 2.9 and M- 4.6 ± 2.6). Similarly, the mean weight of the patients was comparable between the study groups. Comparison of outcome parameters is given in Table 4. The parental separation scores attained was lower with intranasal Dexmedetomidine premedication was found to be superior to intranasal Midazolam (p<0.0001). The MOAA/S scores attained with intranasal Dexmedetomidine premedication was better compared to Midazolam (p<0.0001) with the child being more calm prior to induction of anesthesia. The mask acceptance was better among children premedicated with intranasal Dexmedetomidine than with Midazolam (p=0.001). There was no statistically significant difference between the study groups in any of the vital parameters except HR (Figure 1). There was a statistically significant decline in the heart rate in the group D (p<0.014) compared to group M after premedication.

Table 4: Comparison of outcome parameters between Dexmedetomidine and Midazolam:

	Dexmedetomidine n=52	Midazolam n=52	P value
Parental separation anxiety score	2.18 + 0.94	2.90 + 0.87	<0.0001
Mask Acceptance scores	3.37 + 0.92	2.84 + 0.70	0.0001
Modified Observer Assessment of Anxiety/Sedation scores	4.92 + 1.25	5.37 + 0.89	0.039

Figure 1: Line diagram showing mean SBP, DBP and heart rate over time between study groups



DISCUSSION: One of the major challenges in Paediatric Anaesthesia is anesthetizing an anxious child prior to surgery. Preschool children are least likely to cooperate for any type of procedure. Most of them are at risk of experiencing a negative psychological impact irrespective of the technique used. Hence all paediatric patients must be premedicated to avoid undue stress. Premedication aims at not only relieving the psychological stress caused due to parental separation but also facilitates easy induction of anaesthesia. In order to find the ideal sedative agent and the best route of administration, several drugs like Midazolam, Ketamine, Clonidine and Dexmedetomidine have been used as premedicants in children.Due to the relatively better safety profile Dexmedetomidine and Midazolam have emerged as agents frequently used in pediatric populations. Hence they have been used in this study. Intranasal route was used in this study, as it is a relatively easy, non-invasive route with high bioavailability and fast onset of action because of the rich blood supply of the airway mucosa and bypassing the first pass hepatic metabolism. In this study, 104 ASA grade I and II children between 2-10 years, who were scheduled for elective surgical procedures were randomly assigned to either group D who received intranasal Dexmedetomidine 1 µg/kg or group M who received 0.2 mg/kg dose of intranasal Midazolam.After premedication the parental separation was found to be better with Dexmedetomidine (p-value <0.0001) with median scores of 2 on the Parental Separation Anxiety Scale. In similar studies by Prabhavati K et al[11] and Sheta SA etAl[12], it was found that children premedicated with intranasal Dexmedetomidine achieved

faster and better sedation than intranasal Midazolam. A randomized controlled trial by Mostafa G et al[6] for intranasal premedication of Dexmedetomidine vs. intranasal Midazolam for children undergoing bone marrow aspiration, concluded that the average time to achieve adequate parental separation was faster in the children premedicated with intranasal Dexmedetomidine (p<0.01).The PSAS score was higher in group D, similar to the findings in our study, indicating that Dexmedetomidine premedication achieved better parental separation than Midazolam. There was a significant ease of mask acceptance among the children premedicated with intranasal Dexmedetomidine (group D) compared to intranasal Midazolam (group M), (p-value 0.001). This was similar to other studies done by Yuen VM et al[13],Mountain B et al[14], Prabhavati K et al[11]and Soamavamshi M et al[15] it was found that children premedicated with intranasal Dexmedetomidine accepted mask induction better than Midazolam**.** A similar study conducted by Akin et al[16] comparing intranasal Dexmedetomidine and Midazolam on children undergoing elective tonsillectomy, the findings concluded that 82.2% of children achieved better mask acceptance score with Midazolam compared to Dexmedetomidine (60%), without statistical differences between the sedation scores or the parental separation. However, contradictory to the above study, in our study it was found that better mask acceptance scores were obtained in the intranasal Dexmedetomidine than Midazolam(p=0.001). This is probably because the study by Akin et al[16] had a shorter preinduction period (20 minutes) and hence the peak action of Dexmedetomidine might have not been achieved. In a study by Darshana D. Patel[17] to evaluate pre-operative sedation scores and post-operative recovery scores on children undergoing elective surgeries, found that intranasal Dexmedetomidine had better sedation scores (p<0.0001) than intranasal Midazolam. The Modified Observer's Assessment of Alertness/Sedation Score in our study, was found to be better with group D than group M (p-value 0.039). It was observed that the children premedicated with intranasal Dexmedetomidine were calm and cooperative during their transit to the operating room. Studies done by Mountain B et al[14], Peng K et al[18], Cimzen Z et al [19]and Sheta SA et al[12] concluded that sedation was much faster and better in the group that received intranasal Dexmedetomidine than Midazolam.

The baseline vitals (Heart rate, BP, respiratory rate and oxygen saturation) of the two groups were comparable. In studies done by Faritus S et al[20], Mahmoud GM et al[21],Dabiss MA et al[22] and Peng K et al[18]it was found that there was a significant drop in heart rate in children premedicated with Dexmedetomidine (p<0.05).In our study, after administering the intranasal premedication the heart rate declined over time in both groups and was found to be statistically significant (p<0.001). In the intranasal Dexmedetomidine group, there was a greater decline in heart rates compared to intranasal Midazolam which was statistically significant(p=0.014).There was no significant differences with respect to the blood pressure (p=0.84) and respiratory rate (p=0.58). A randomized controlled trial by Mostafa G et al[6] for intranasal premedication of Dexmedetomidine vs. intranasal Midazolam for children undergoing bone marrow aspiration, concluded that there was a significant drop in heart rates and systolic BP (p<0.05) in the groups compared. In a similar study done by Rajalaxmi J et al[23] comparing intranasal Dexmedetomidine and placebo on 60 children undergoing various cardiac surgeries concluded that 30 minutes onwards, intranasal Dexmedetomidine administration there was a significant drop in heart rate (p<0.05). Similarly a study by Darshana D. Patel[17] found that in intranasal Dexmedetomidine there was a significant drop in pulse rate after 30 minutes of administration (p<0.0001) and respiratory rate declined (p<0.05) without a drop in oxygen saturation as compared to the Midazolam group. In our study the patients were intubated and were on controlled ventilation.

Post operatively, in our study there was no statistically significant variation in the heart rate (p=0.942), SBP (p=0.057) and respiratory rate (p=0.269). In a similar study by Akin et al[16] NIBP, heart rate, oxygen saturation were found to have no significant difference between the intranasal Dexmedetomidine and Midazolam groups. .Post operatively no adverse reactions like nasal irritation, excessive drowsiness, nausea and vomiting were seen.

CONCLUSION

Children premedicated with intranasal Dexmedetomidine had better MOAA/S scores. The children premedicated with intranasal Dexmedetomidine separated easily from their parents and had better mask acceptance than those premedicated with intranasal Midazolam.

It is concluded that intranasal Dexmedetomidine in the dose of 1 µg/kg is more efficacious than intranasal Midazolam in the dose 0.2 mg/kg as premedication in children undergoing short elective surgical procedures.

REFERENCES:

1. Kain ZN, Linda MC, Theresa OZ, Cicchetti DV. Preoperative anxiety in children: predictors and outcomes. Archives of Pediatric Adolescent Medicine 1996; 150(12): 1238-1245.
2. Singla D, Chudary G, Dureja J, Mangla M. Comparison of Dexmedetomidine versus Midazolam for intranasal premedication in children posted for elective surgery: a double-blind randomized study. South African Journal of Anesthesia and Analgesia2015; 1(1):1-4.
3. Kain ZN, Linda MC, Theresa OZ, Cicchetti DV. Preoperative anxiety in children: predictors and outcomes. Archives of Pediatric Adolescent Medicine 1996; 150(12): 1238-1245.
4. McClain ME, Kain ZN. The management of preoperative anxiety in children: an update. Anesthesia Analgesia 2001; 93: 98-105.
5. Kain ZN, Caldwell AA, Krivutza DM, Weinberg ME, Gaal D, Wang SM, Linda MC. Interacive music therapy as a treatment for preoperative anxiety in children: a randomized controlled trial. Anesthesia Analgesia 2004; 98: 1260-1266.
6. Mostafa GM, Morsey KM. Premedication with intranasal Dexmedetomidine, Midazolam and Ketamine for children undergoing bone marrow biopsy aspirate. Egyptian Journal of Anesthesia2013 April; 29(2): 131-135
7. Cohen LB , Hille B, Keynes RD. Infant cognition perception and language. Handbook of Child Physiology. 2007 June: 205.
8. McMillan CO, Schopfer SIA, Sikich N, Hartley E, Lerman J. Premedication of children with oral Midazolam. Canadian Journal of Anesthesia 1992; 39(6)545-550.
9. Shukry M, Miller JA. Update on Dexmedetomidine: Use in non-intubated patients requiring sedation for surgical procedures. Therapeutic Clinical Risk Management. 2010; 6: 111-121.
10. Weldon BC, Watcha MF, White PF. Oral midazolam in children: effect of time and adjunctive therapy. Anesthesia Analgesia. 1992; 75(5):51-55.
11. Prabhavati R, Kumar GC, Reddy PN, Prasad GV, Sujit TR. Evaluation of intranasal Midazolam as preanesthetic medication for pediatric surgical procedures. International Journal of Scientific Study 2014 November; 2(8): 87-92.
12. Sheta SA, Al Sarheed MA, Abdelhalim AA. Intrnasal Dexmedetomidine vs Midazolam for premedication in children undergoing complete dental rehabilitation: a double blinded randomized control trial. Pediatric Anesthesia. 2014 February; 24(2): 181-189.
13. Yuen VM, Hui TW, Irwin MG, Yuen MK. A comparison of intranasal Dexmedetomidine and oral Midazolam premedication in pediatric anesthesia: a double blind randomized controlled trial. International Anesthesia research society 2008 June; 106(6) 1715-1721.
14. Mountain BW, Smithson L, Cramolini M, Wyatt TH, Newman M. Dexmedetomidine as a pediatric anesthetic premedication to reduce anxiety and to deter emergence delirium. American Journal of Nurse Anesthetists 2011 June; 79(3):219-224.
15. Somavanshi M, Tripathi A, Rajoriya A. Preanesthetic sedation with different dose of Midazolam: a randomized clinical study in children. Indian Journal of Clinical Anesthesia. 2015 March; 2(1): 1-5.
16. Akin A, Bayram A, Esmaoglu A, Tosun Z, Aksu R. Comaprison between intranasal Midazolam and intranasal Dexmedetomidine. Pediatric Anesthesia 2012 September; 22(9): 871-876.
17. Patel DD, Lisha, Upadhyay MR. Preanesthetic medication in children : a comparison of intranasal Dexmedetomidine versus intranasal Midazolam. Journal Medical Research 2015 April;1(2):59-63.
18. Peng K, Wu S, Ji F, Li j. Premedication with Dexmedetomidine in pediatric patients: a systematic review and meta-analysis. Sao Paulo Clinics 2014 November; 69(11):777-786.
19. Cimen ZS, Hanci A, Sivrikaya GU, Kilinc LT, Erol MK. Comparison of buccal and nasal Dexmedetomidine premedication for pediatric patient. Pediatric Anesthesia. 2013 February; 23(2): 134-138.
20. Faritus SZ, Khoohpar KM, Ziyaeifard M, Mehrabanian MJ. Oral Dexmedetomidine versus Midazolam as anesthetic premedication in children undergoing congenital heart surgeries. Anesthesia and Pain Medicine. 2015 June; 5(3): 250.
21. Mohmoud GM, Haggag IAEF. Comparison of Dexmedetomidine and Midazolam for conscious sedation in pediatric dental patients: a clinical randomized trial. Journal of American Science. 2014; 10(10): 300-308.
22. Daabiss MA, Hasish M. Dexmedetomidine versus Ketamine combined with Midazolam: a comparison of anxiolytic and sedative premedication in children. British Journal of Medical Practitioners. 2011; 4(4): 441.
23. Rajalakshmi J, Kumar KS. A study to evaluate effects of intranasal Dexmedetomidine as a premedicants in pediatric patients undergoing cardiac surgeries. Egyptian Journal of Cardiothoracic Anesthesia. 2015 November; 9(2): 17-22.