The Journal of Medical Research

Research Article

JMR 2015; 1(2): 59-63
March- April
ISSN: 2395-7565

www.medicinearticle.com

Pre anaesthetic medication in children: A comparison of intranasal dexmedetomidine versus intranasal midazolam

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ABSTRACT

Background & objectives: Children are more anxious and fearful due to their limited cognitive capabilities, lack of understanding of health care system and lack of self control. It becomes an important concern for an anaesthesiologist to relieve their pre-operative anxiety. Midazolam is frequently used as premedication agent in children. New drugs such as the alpha-2 agonists have also been introduced as alternatives for premedication in pediatric patients. The present study was planned to compare intranasal Dexmedetomidine with intranasal Midazolam as a preanaesthetic medication in children with the primary objectives of assessing preoperative sedation & ease of child parent separation and secondary objectives of assessing analgesia in the postoperative period. **Materials and methods:** Seventy children, aged between 2-6 years of either sex,belonging to ASA Grade I & II and weighing between 10-16kg were enrolled in this prospective,single blinded, randomized and comparative clinical study. The children were divided into two groups of 35 each. Forty five minutes before induction, Group-D(n=35)-received intranasal Dexmedetomidine 1mcg/kg and Group M(n=35) –received intranasal midazolam 0.3mg/kg. **Results:** Children who were premedicated with intranasal dexmedetomidine had lower sedation (MOAA/S Scale) scores (P<0.0001), and easier child-parent separation than children who received intranasal midazolam. Postoperatively, less number of patients required rescue analgesia in the dexmedetomidine group. **Conclusion:** Intranasal Dexmedetomidine can be used effectively and safely as a preanaesthetic medication in children undergoing minor surgical procedures under General anaesthesia.

Keywords: Dexmedetomidine, Midazolam, Pediatric patients, Intranasal premedication.

INTRODUCTION

Children are most susceptible to fear and stress of surgery due to their limited cognitive capabilities, limited self experience of life, poor understanding of health care system, lack of self control and dependency. In children, pharmacologic agents are frequently used as pre-anaesthetic medication to relieve the fear of surgery, to make child-parental separation easy and to carry out a smooth induction of anaesthesia [1].

Premedication with midazolam has shown to be more effective in reducing anxiety and improving compliance on induction of anaesthesia as compared to presence of parents inside the operation theatre during induction of anaesthesia[2,3]. The favourable effects of midazolam as preanaesthetic medication include sedation, anxiolysis, amnesia and reduction of post operative vomitting[3-8]. Dexmedetomidine is the latest addition to the Group of α2-adrenergic receptor agonist approved by the FDA in 1999 for use in humans for analgesia and sedation. It is a highly selective α2 adrenergic receptor agonist, sympatholytic, sedative, analgesic and is devoid of respiratory depressant effect. Both these drugs can be given through various routes for preoperative sedation. The intramuscular, intravenous, subcutaneous and intraosseous routes provide optimal drug delivery,but they are painful and children dislike the needle prick. Administration by rectal route is associated with unpredictable absorption and sensation of discomfort. Oral route has got poor palatibility and low bioavailability. Intranasal route of administration offers certain advantages.This route is a quick, painless, non-invasive way to give medications, with the onset of action generally comparable to that of intravenous administration[9].

So considering all these aspects, the present study was planned to evaluate sedation level and ease of child parent separation(primary end points) while transferring the child to operation theatre and post operative analgesia(secondary end point) by comparing Intranasal Dexmedetomidine(1microg/kg) with Intranasal Midazolam (0.3mg/kg) as premedication in paediatric patients posted for general surgical procedures under general anaesthesia.

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MATERIALS AND METHODS

After obtaining approval from the institutional ethics committee, seventy paediatric patients scheduled for minor general surgical procedures under general anaesthesia, meeting the following selection criteria were included in the study.

Inclusion Criteria: 1) Children of ASA I/II 2) Age range between 2-6 years of either sex with weight 10-16 kg. 3) Elective minor surgical procedure under general anaesthesia

Exclusion Criteria: 1) Known allergy or hypersensitivity reaction to Dexmedetomidine or Midazolam. 2) Patients taking any other sedatives. 3) Patients with nasal infection & nasal pathology for intranasal route. 4) Patients with any cardiac or respiratory disease. 5) Patients with mental Retardation.

Thorough preoperative assessment was done. Haemogram, Random blood sugar and Urine albumin and Sugar were noted. Weight of the child was noted. All the selected patient's parents were explained in detail regarding the purpose, procedure of the study and possible side effects. A written informed consent was obtained.

All the patients were kept nil by mouth: three hours for clear fluids and six hours for solids and milk. Patients were randomly divided into two groups of thirty five in each. Forty five minutes before induction, Group-D(n=35)-received intranasal Dexmedetomidine 1mc/kg and Group M(n=35) –received intranasal midazplam 0.3mg/kg. With the help of EPIINFO software,35 random numbers were generated and they were assigned to Dexmedetomidine group.

The baseline parameters i.e. Pulse, SpO2 and Respiratory rate were noted. Dexmedetomidine (group-D) 1 mcg/kg or Midazolam(groupe-M) 0.3mg/kg was given intranasally with the child in a recumbent position,45 minutes before induction. The Drug was taken undiluted in a one ml tuberculin syringe. Dexmedetomidine in 100mcg/ml and Midazolam in 5 mg/ml strength used. Equal volume of drug is to be instilled into each nostril. Pulse, Respiratory rate and spo2 were monitored every 5 minutes for 45 minutes. We did not observe the acceptance score by the child for intranasal route. The Sedation score was assessed at 45 minutes with the help of modified observer assessment of alertness/sedation scale MOAA/S Scale)[10].

Modified Observer's Assessment Of Alertness/Sedation Scale

- 6-Agitated
- 5-Responds readily to name spoken in normal tone.
- 4-Lethargic response to name spoken in normal tone.
- 3-Responds only after name is called loudly and/or repeatedly
- 2-Responds only after mild prodding or shaking.
- 1-Does not respond to mild prodding or shaking.
- 0-Does not respond to deep stimulus.

Child Parent Separation score[11] was observed at the time of transferring the patient to operation theatre using Child Parent Separation Score.

Child- Parent Separation Score

- 3-Patient fearful and crying; not quieted with reassurance
- 2-Patient slightly fearful and/or crying; quieted with reassurance
- 1-Patient unafraid, cooperative or asleep

After Pre-oxygenation for 3 minutes with 100% oxygen, 8% inhaled concentration of Sevoflurane were administered with Jackson Rees Circuit till the loss of eyelash reflex. It took 45-60 seconds for induction. After induction, intravenous line with proper size IV cannula was established and Inj. Glycopyrrolate 5mcg/kg i.v, Inj Paracetamol 5 mg/kg i.v and Inj. Suxamethonium 1.5mg/kg i.v were given and the patient was intubated with appropriate size of an endotracheal tube. Maintenance of anaesthesia was done with (50 : 50) O_2 : N_2O with Sevoflurane 1-2% and intermittent dose of Inj. Vecuronium bromide i.v. Patient was reversed with Inj. Neostigmine 50 mcg/kg i.v and Inj. Glycopyrrolate 10 mcg/kg.i.v and was extubated after all criteria for extubation were fulfilled. In the Post-operative Period, the following parameters were observed every 30 minutes for three hours: 1)Analgesia using Modified Objective Pain Score(MOPS)[12]. 2) Pulse rate 3) Arterial O2 saturation i.e.SpO2 4) Rescue Analgesia. When MOPS 5, Rescue analgesia was given with Inj. Paracetamol 5 mg/kg iv.

Perioperative Complications like nasal irritation, bradycardia and respiratory depression; if occurred, were treated as shown in Table-3.

Sample Size estimation: With reference to the study done by Ashraf M. Ghali *et al*[13], the mean values of sedation score in the Dexmedetomidine group and Midazolam group were 2.94 and 3.99 respectively. Their standard deviations were 1.37 and 1.58 respectively. With the help of Medcal-c software, considering type -1(alpha) error as 0.05 and type-2 (beta) error as 0.2, sample size came to be 32 in each group. To further authenticate the study and minimize any error, we chose to select a sample size of 35 per group.

STATISTICAL ANALYSIS

All the data obtained were presented in mean ± SD form and percentage form. Analysis or their significance was done by using the p values obtained through student t test. The Mann- Whitney test was used for comparing the sedation score between two groups and chi-square test for discrete variables. The test for significance was done using Medcal-c statistical software.

RESULTS

As shown in Table-1, the two groups were comparable in terms of age, weight, ASA physical status and duration of surgery. Figure 1 shows that on intra-group comparison, in group D at 30 minutes onwards highly significant decrease in mean pulse rate was observed. Mean pulse rate at 30 min was 113.4±6.25 minutes($p<0.0001$) and at 45 min was 107.86±9.39 minutes($p<0.0001$). On intra-group comparison, In group M there was no significant decrease in pulse rate during the preoperative observation period. On inter-group comparison, there was a highly significant decrease in pulse rate at 30minutes onwards in group D($p<0.0001$) as compared to group M, which had never decreased <25% from the baseline & did not require treatment. There was no statistically significant difference in oxygen saturation(SpO2) while comparing intra group as well as inter group comparison. As shown in Figure 2, On intergroup comparison, there was a significant decrease in mean respiratory rate from 15 minutes onwards in group M as compared to group D($p<0.05$). But there was no significant reduction in oxygen saturation in any of these groups. 100% O2 was supplemented with face mask when SpO2 reduced to <95%.As shown in Table-2, the mean sedation score in group D at 45 minutes was 2.52±0.74 and in group M, it was 3.69±0.87($p<0.0001$). Figure 3 & Figure 4 shows that 54% of children in Group D achieved Child Separation Score of 1 as compared to 40% of children in Group M at the time of transferring the patients to operation theatre. Thirty seven (37%) percent of children achieved child parent separation score of 2 in group D as compared to 43% of children in group M. Only 9% of children achieved score of 3 in group D as compared to 17% of children in group M. There was no statistically significant difference between both groups.(P= 0.3867) In the post operative period, from 30 minutes onwards, Modified objective pain score was significantly increased in group M as compared to group D and as shown in Graph-V, 37% of

children required rescue analgesia in group-M as compared to only 11% of children who required rescue analgesia in group-D.

Nasal irritation was observed in ten children in group M. No other complications were observed in any of the two groups(Table-3).

Table 1: Demographic Data

	Group- D	Group- M	P value
Age (years) (Mean ± SD)	4.3±1.2	3.9±1.5	p>0.05
Weight (Kg) (Mean± SD)	13.29±1.69	13.14±1.87	p>0.05
ASA Grade (I/II)	30/5	27/8	p>0.05
Duration of surgery(minutes)	25.42±2.81	25.43±2.81	p>0.05

Table 2: Sedation score at 45 minutes

	Group D	Group M	P value
Sedation score at 45 minutes	2.52±0.74	3.69±0.87	P<0.0001

Table 3: Perioperative complications

	Group D	Group M	Treatment
Nasal irritation (At the time of intranasal administration)	nil	10(28%)	Parents were reassured
Bradycardia(Heart rate<25% of base line)	nil	nil	Inj.Atropine 0.01mg/kg i.v.
Respiratory Depression(Spo2 <95% or RR<16 breaths/minutes)	nil	nil	100% O2 through face mask

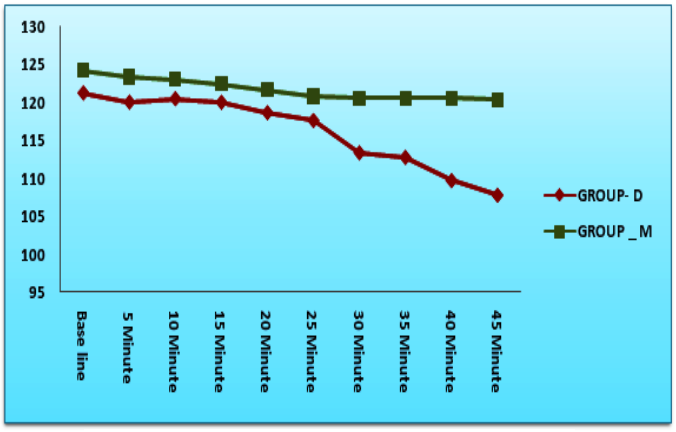

Figure 1: Changes in mean pulse rate

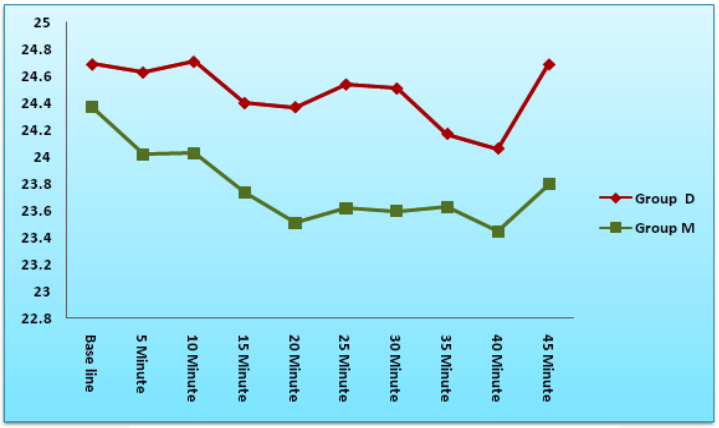

Figure 2: Changes in mean respiratory rate

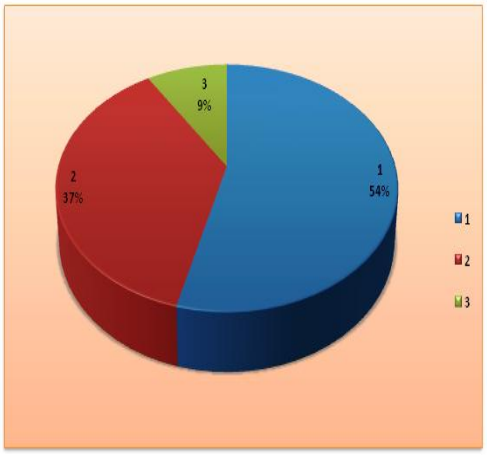

Figure 3: Child parent separation Score (Group D)

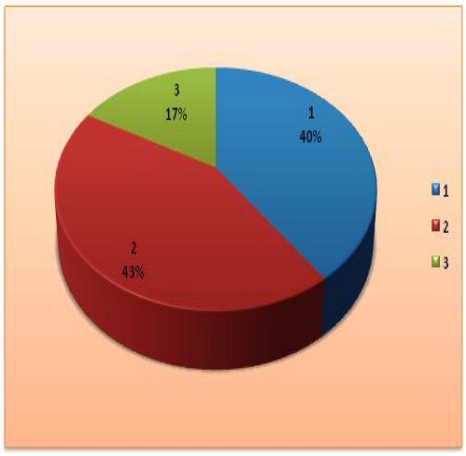

Figure 4: Child parent separation Score (Group M)

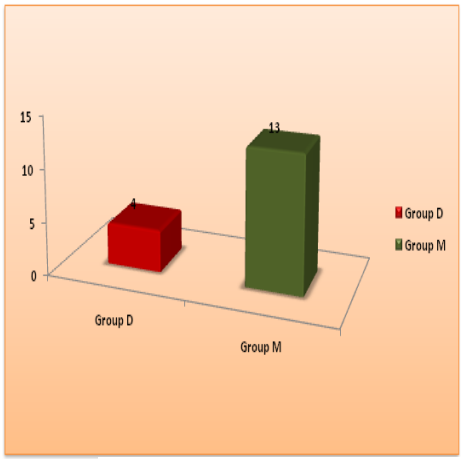

Figure 5: Rescue Analgesia

DISCUSSION

Midazolam is the most widely used agent as a preanaesthetic medication. The major problem in everyday practice when using intranasal midazolam is associated with an unpleasant burning sensation in the nasal cavity. Therefore, the nasal administration of midazolam is not favoured in practice. However, there are also studies that report that the intranasal administration

of midazolam is better tolerated by infants than its oral administration [14]. Moreover, the

plasma concentration of midazolam is higher after nasal administration than after the oral route. Two recent studies have reported clinically significant sedative effects when dexmedetomidine was administered intranasally to healthy adult volunteers and to children undergoing minor surgery[15,16]. For that reason, we aimed to compare the intranasal application of both agents. Intranasal application is a preferred route of preanaesthetic drug administration. Advantages of it are; it is non- invasive and it does not require cooperation. On the other hand, child should be co-operative for swallowing the medication in case of oral route. Intranasal route is well tolerated and child would not be having an unpleasant taste or pungency. Wolfe *et al*[17] suggested that intranasal drug administration offers a quick, painless, non-invasive way to give medications, with the onset of action generally comparable to that of intravenous administration where the central nervous system is the site of action. The intranasal route for Midazolam has been used since 1988 and has the advantage of rapid absorption directly into the systemic circulation with no first- pass effect and a bio-availability of 55-83% (Wilton NC *et al*[18], Walberg EJ *et al*[19], Rey *et al*[20] and Bjorkman G *et al*[21]). Antilla *et al*[22] documented the high bioavailablity (73%-92%) when dexmedetomidine was given via the buccal route. The children in group D achieved lower MOAA/S score(more sedated) than group M($p<0.0001$). Dexmedetomidine produces sedation by stimulating alpha2-adrenergic receptors in the locus coeruleus, a part of the brain stem involved in the sleep- awake cycle. Stimulation of alpha2-adrenergic receptors at this site reduce central sympathetic output, resulting in increased firing of inhibitory neurons[23]. Dexmedetomidine does not act on the gamma-amino butyric acid (GABA) receptors[24,25]. Therefore, it causes sedation and analgesia without causing respiratory depression. It produces "cooperative sedation", which means that though the patient is sedative,he/she can still interact with healthcare professionals[26,27]. Midazolam produces sedation by stimulating gamma amino butyric acid (GABA)–receptors in the cerebral cortex. This will increase the conductance of chloride ions. This leads to hyperpolarization that inhibits normal neuronal function. Our results are in consensus with Ashraf M Ghali *et al*[13], Yuen M *et al* [16] and Sankar roy *et al*[28]. On the other hand, Schmidt *et al*[29]. did not find any difference in sedation between intranasal dexmedetomidine and oral midazolam. This could have resulted from the different scale used for assessment of sedation. They used a 4-point sedation scale which was less sensitive than the scale used in our study.

With regard to child parent separation score, children in group D were satisfactorily separated from parents than in group M. Our results are in consensus with Ashraf M Ghali *et al*[13] and Akin *et al*[30]. However, this might be because of timing of intranasal application i.e.45 minutes. By the time of transferring the child to operation theatre, the peak sedative effect of midazolam might be wearing off in some children and therefore not satisfactorily separated.

Dexmedetomidine decreases sympathetic outflow and circulating catecholamine levels and increases cardiac vagal activity and therefore it would be expected to cause a decrease in heart rate in patients receiving Dexmedetomidine. Midazolam acts on GABA-mimetic system and therefore it is known to decrease the respiratory drive in a dose dependent manner (Miller's anaesthesia 7 th edition)[31]. Though we found a statistically significant decrease in mean respiratory rate in group-M , the arterial oxygen saturation was well maintained throughout the perioperative observation period.We did not observe respiratory depression in any of the children. The number of children who required rescue analgesia were higher in the group M as compared to group D. Mechanism of action of Dexmedetomidine for providing analgesia is that the activation of α2 receptors in the dorsal horn of spinal cord suppresses the activity in the descending medullospinal noradrenergic pathway, which modulates nociceptive neurotransmission. Thus it terminates the propogation of pain signals leading to analgesia. In our study 28% of children in group M suffered nasal irritation at the time of intranasal administration. Griffith *et al*[32] suggested that nasal irritation may be caused by the acidity of midazolam (pH 3.5), sensitizing pain receptors in the distribution of trigeminal nerve in the nasal mucosa. Ashu Mathai *et al*[33] observed that the intranasal route of midazolam administration was not comfortable to most children as it produced a stinging sensation when administered. The major limitation of this study is the timing of the drug administration, as dexmedetomidine was not allowed to reach its peak effect before mask induction. For midazolam, 45–60 min is too long, and for some children, the effect will be wearing off. For dexmedetomidine, this length of time may be too short, and for some children, the drug may be yet to have an effect. It is possible that we may have noted greater sedative effects in the intranasal dexmedetomidine group if we had waited longer. But if we would have waited longer, than the effect of midazolam would have disappeared.

CONCLUSION

Intranasal Dexmedetomidine as compared to intranasa Midazolam was associated with lower sedation score, easier child-parent separation & better analgesia in the post operative period without any adverse side effects. Thus, it can be concluded that intranasal Dexmedetomidine can be used effectively and safely as a preanaesthetic medication in children undergoing minor surgical procedures under General anaesthesia.

ACKNOWLEDGEMENT

The authors would like to acknowledge the faculty and residents of the department of Anaesthesiology, Medical college, Vadodara for valuable suggestions and cooperation.

Source of support-Nil

Conflicts of interest-Non declared

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