A Comparative Evaluation of Intranasal Dexmedetomidine & Intranasal Midazolam for Pre-Operative Sedation in Children

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ABSTRACT

BACKGROUND
Prior to any operative procedure, children are often susceptible to fear & anxiety of being separated from parents & entering the operating room (OR) environment. One of the ways a paediatric anaesthesiologist can deal with this challenge is to sedate the child beforehand. We wanted to compare the efficacy of intranasal dexmedetomidine & intranasal midazolam for preoperative sedation.

METHODS
Study subjects comprised of children aged 2-8 years posted for elective surgery under general anaesthesia. It was a double-blind randomized control trial comprising of 90 subjects divided into 2 groups. Group A (n=42) received 0.2 µg/Kg dexmedetomidine & Group B (n=48) 0.5 mg/Kg midazolam by intranasal route 45 minutes prior to induction. Sedation & analgesia scores were assessed by Ramsay Sedation Scale & Observer Pain Scale respectively. Heart rate & systolic blood pressures were recorded every 15 minutes pre-operatively after administration of drugs. Sedation & analgesia scores were recorded at induction, recovery, after 3 hours & 6 hours post operatively.

RESULTS
93% subjects in group A & 60% in group B achieved satisfactory sedation at the time of induction. Sedation status & analgesia obtained at the time of induction, recovery, 3 hours & 6 hours post operatively were significantly better in group A. Pre-operative changes in HR & SBP in both groups were comparable.

CONCLUSIONS
Intranasal dexmedetomidine is safe & more effective than intranasal midazolam for pre-operative sedation in children. Also, intranasal dexmedetomidine is a superior agent than intranasal midazolam for post-operative analgesia in paediatric population.

KEY WORDS
Dexmedetomidine, Midazolam, Sedation

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BACKGROUND

Prior to any operative procedure, children are often susceptible to fear & anxiety of being separated from parents & entering the operating room (OR) environment. One of the ways a paediatric anaesthesiologist can deal with this challenge is to sedate the child beforehand.[1,2] Children tolerate oral and nasal route better than intravenous route for needle fear. Intranasal midazolam, fentanyl, ketamine have been tried out for this purpose with reasonable success. Among these, intranasal midazolam has been found to be the most suitable. The beneficial effect of midazolam includes rapid sedation, anxiolysis and reduction of post-operative nausea and vomiting.[3,4] Premedication with 0.5 mg/Kg midazolam has shown better results than parental presence or placebo in terms of reducing separation & induction anxiety.[5] A recent evidence based clinical update has shown that nasal midazolam 0.5 mg/Kg is effective in reducing both separation and induction anxiety in children with minimal effect on recovery time.[6] Intranasal route is a non-invasive route well tolerated by the paediatric patients. Bioavailability is high primarily due to the rich vasculature in the nasal mucosa.[7] Onset of action is quicker than other systemic routes.[7,8]

As midazolam has high hepatic clearance, avoidance of hepatic first pass metabolism offers greater systemic bioavailability.[9] However, the major drawback of intranasal midazolam is that at least 50% children cry on administration because it transiently irritates nasal passages.[10] Other undesirable effects including restlessness, paradoxical reaction, and negative postoperative behavioural changes have made it a less than ideal premedication.[11,12] Although amnesia is considered an advantage by some authorities, it has also been regarded as a possible disadvantage by others.[4] Dexmedetomidine is a newer alpha 2 agonist with more selective alpha 2: alpha 1 (1600:1) adrenoceptor activity with a short half life.[13,14] At doses of 1-1.5 µg/Kg, it produced sedation in 45-60 minutes with peak effect at 90-105 minutes.[15] Antilla et al documented the high bioavailability of 81.8% (73%-92%) when dexmedetomidine was given via the nasal route.[16] Onset occurred in 45-60 minutes with a peak effect at 90 minutes. It has a pKa of 7.1. Since this drug has a neutral pH, it is virtually painless when given intranasally and it is also tasteless and odourless.[16] Recently, it has been recommended for procedural sedation in children.[17] But, in doses of 1-1.5µg/Kg it produced sedation in only about 50% of children at the time of induction.[15] So in this study we used 2µg/Kg intranasal dexmedetomidine as a premedication 45 minutes before surgery.

Thus, the study aimed at comparing the efficacy of intranasal dexmedetomidine & intranasal midazolam for preoperative sedation. The primary end point was sedation achieved at the time of induction. The secondary end- points were preoperative heart rate & systolic blood pressure changes after administration of either drugs. We also looked at sedation & analgesia status at the time of induction, recovery as well as 3 hours & 6 hours post operatively.

METHODS

This is a double-blind randomized control study carried out in the paediatric OR & post anaesthesia care unit in association with Department of Anaesthesiology, R G Kar Medical College, Kolkata for a period of one year. Data organization & analysis of the results was done in the Department of Pharmacology, RG Kar Medical College, Kolkata.

Ethical Consideration

Necessary clearance from institutional ethics committee was obtained prior to start of the study. (CTRI/2018/04/013123) Parental or care provider informed consent was taken for each study subject after explanation of the study & the risk/s entailed.

Sample Size

We considered a difference of 30% as acceptable. Considering alfa error to be 5% & beta error 20%, power of study 80%, the sample size was 78, each group having 39 subjects. We recruited 90 children in the given time period.

Study Population

The study population consisted of children aged 2-8 yrs. of both sexes who came to the paediatric or for elective surgery. Cases with expected operating time of more than 30 minutes were included. Sampling was purposive.

Inclusion Criteria

Children aged 2-8 yrs. belonging to ASA physical status I or II scheduled for elective surgery

Exclusion Criteria

Children with known allergy or hypersensitive reaction to dexmedetomidine or midazolam, organ dysfunction, cardiac arrhythmia or congenital heart disease, and mental retardation were excluded.

Procedure

Study subjects were randomly divided into two groups. The randomization was done by computer generated random numbers. Group A received intranasal dexmedetomidine 2 µg/Kg & group B intranasal midazolam 0.5 mg/Kg. Observers and attending anaesthesiologists were blinded to the study drug given. Children got premedication in the preoperative holding area in presence of parent. In each study subject intranasal drug was dripped into both nostrils using a 2-ml syringe with the child in the recumbent position. Baseline heart rate (HR), oxygen saturation (SpO_2), and blood pressure (BP) were to be measured before and every 15 min after intranasal drug administration until transfer to the operating room (OR). Sedation level was evaluated by Ramsay sedation scale preoperatively 45 minutes after administration of both the study drugs. General anaesthesia was administered according to a standard protocol. Induction was done with halothane 2-3% in oxygen. Intravenous line was secured, glycopyrrolate 0.004 mg/Kg and fentanyl 2 mcg/Kg administered intravenously. Other analgesic used was diclofenac suppository 2 mg/Kg. The children were then intubated using atracurium 0.5 mg/Kg. Anaesthesia was maintained with 0.5% Halothane in 33% Nitrous Oxide &

33% Oxygen. After surgery, residual neuromuscular block was reversed with injection neostigmine and injection glycopyrrolate. Patients were extubated when they achieved satisfactory recovery of motor power and were fully awake. Sedation & analgesia scores were recorded at recovery, 3 hours & 6 hours post operatively in PACU.

Patient Status	Score
Patient anxious, agitated & impatient	1
Patient cooperative, oriented & calm	2
Patient only responds to verbal commands	3
Patient demonstrates a brisk response to glabellar tap test or auditory stimulus	4
Patient demonstrates a sluggish response to glabellar tap test or auditory stimulus	5
Patient does not respond to glabellar tap test or auditory stimulus	6

Table 1. Ramsay Sedation Score of 3 or More was Considered Satisfactory

Item	Score
Laughing, euphoric	1
Happy, contended	2
Calm or asleep	3
Mild to moderate pain: crying, grimacing, restlessness; can distract with toy, food, parental presence	4
Crying, screaming, inconsolable	5

Table 2. Subjects with OPS Score of 3 or Less were Assumed to Have Adequate Analgesia

Materials & Equipment

For measurement of SBP, mercury sphygmomanometer was used. HR & SpO_2 were recorded by a pulse oximeter. Drugs & syringes were purchased by the investigators. For dexmedetomidine we used Dexem™ injection manufactured by Themis Medicare Limited, Haridwar, Uttarakhand. It contained dexmedetomidine hydrochloride 100 µg/ml. For midazolam, Mezolam™ injection manufactured by Neon Laboratories Limited Mumbai, was used.

Statistical Analysis

Student - t – test was used to compare age groups & subgroups. Fisher's exact - t – test was used to compare sedation status & pain scores. It was used to compare the acceptance of medication between two groups. Paired t- test was done to assess change in HR & SBP before & 45 minutes after drug instillation. Test was done within groups. Results were calculated on www.vassarstats.net. p Value <0.05 was considered significant. 2-tailed P value was considered.

RESULTS

90 subjects were recruited in the study in a period of 1 year. The children were randomly divided into 2 groups, group A (n=42) & group B (n=48). 5 children in group B cried on medication & spat out the drug after intranasal administration. All subjects in group A accepted the intranasal drug well (p=0.05). Those 5 children were included in the study. Fall in mean HR from the initially observed value was 9.97% in group A (p<0.0001) & 9.19% in group B (p<0.0001). Fall in mean HR from the initially observed value was 6.11% in group A (p<0.0001) & 6.35% in group B (p<0.0001).

	Group A (n=42)	Group B (n=48)	p value
Age	5.73±1.78	5.5±1.72	0.52
Male	34(81%)	36(75%)	
female	8(19%)	12(25%)	0.6135
Age 2-4 yrs.	24%	27%	0.92
Age 5-6 yrs.	45%	42%	0.25
Age 7-8 yrs.	31%	31%	0.10

Table 3. Demographic Characteristics

	Group A		Group B		
	Yes	No	Yes	No	P Value
At induction	39(93%)	3(7%)	29(60%)	19(40%)	0.0002
At recovery	25(60%)	17(40%)	14(29%)	34(71%)	0.0054
After 3 hours	18(43%)	24(57%)	10(21%)	38(79%)	0.03
After 6 hours	8(19%)	34(81%)	3(6%)	45(94%)	0.1

Table 4. Sedation Status at Induction, Recovery, after 3 Hours & 6 Hours in the Post-Operative Period

	Group A		Group B		
	Yes	No	Yes	No	p value
At induction	39(93%)	3(7%)	29(60%)	19(40%)	0.0002
At recovery	26(62%)	16(38%)	14(29%)	34(71%)	0.0054
After 3 hours	19(45%)	23(55%)	4(8%)	44(92%)	0.00007*
After 6 hours	9(19%)	33(81%)	3(6%)	45(94%)	0.05

Table 5. Analgesia Achieved at Induction, Recovery, after 3 Hours & 6 Hours in the Post-Operative Period

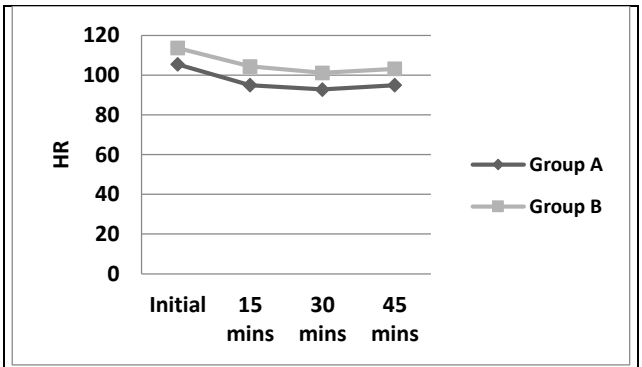

Figure 1. Variations in Mean HR in Both Groups During the Premedication Period

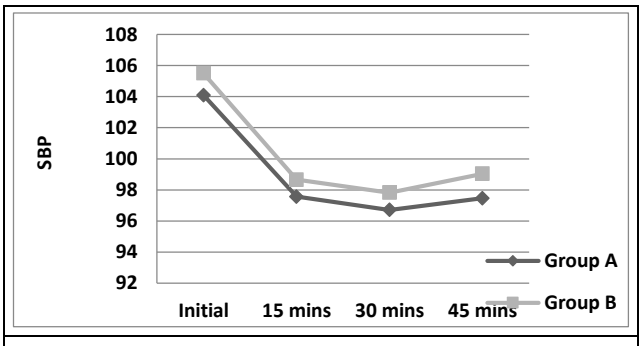

Figure 2. Variations in Mean SBP in Both Groups During the Premedication Period

DISCUSSION

Our study was a prospective double-blind randomized trial with children of 2-8 years of age. In our study, children tolerated intranasal medication well. Previous studies have shown that intranasal drug delivery system is effective & well accepted in paediatric age group.[18,19] Dexmedetomidine, an α_2- adrenoreceptor agonist belongs to imidazole subclass of drugs.[20] It produces sedation by decreasing the central sympathetic outflow from locus ceruleus in the brainstem. This causes firing of inhibitory neurons including GABAergic

neurons. Thus, it induces electroencephalogram activity similar to natural sleep. Primary analgesic effects and potentiation of opioid induced analgesia results from activation of α_2 adrenergic receptors in the dorsal horn of spinal cord and inhibition of substance P release.[21,22]

In our study, 93% of the subjects receiving intranasal dexmedetomidine achieved satisfactory sedation at the time of induction, in contrast to 60% of subjects receiving intranasal midazolam. This was the first study which compared efficacies of intranasal dexmedetomidine at a dose of 2 µg/Kg & intranasal midazolam at a dose of 0.5 mg/Kg. In a study which compared sedation with 1 µg/Kg & 2 µg/Kg doses of dexmedetomidine revealed 66% cases achieving satisfactory sedation with dexmedetomidine used in 2 µg/Kg dose.[23] A more recent study has revealed 80% of children being sedated with 2 µg/Kg intranasal dexmedetomidine.[24]

Post-operative analgesia was also assessed in our study. Studies on healthy volunteers have suggested that dexmedetomidine produces significant analgesic effects, which has rendered it useful in perioperative period. Mild to moderate analgesia was observed in some experimental pain models.[25] However other models like heat pain stimulation & heat and electrical pain threshold and tolerance have shown that dexmedetomidine lacks broad analgesic activity.[26,27] Thus, although our study has shown promising results with respect to subjects acquiring satisfactory analgesia at recovery, 3 hours & 6 hours post-operative respectively, more studies are required to demonstrate the analgesic activity of dexmedetomidine in children.

Centrally acting α_2-adrenergic agonists cause modest reduction in HR & BP.[28] In a pharmacokinetic study of IV dexmedetomidine in children, it has been shown that 1 mcg/Kg IV dexmedetomidine given over 10 min produce a significant reduction of heart rate (15% compared with baseline) and blood pressure (25% compared with baseline).[29] Munro et al. reported that the reduction of blood pressure and HR were <20% of baseline in children who were sedated with an initial dose of 1 mcg/Kg IV dexmedetomidine, followed by a maintenance infusion during cardiac catheterization. In this study, change in HR & SBP after 45 minutes was about 10% & 6% respectively. Although both changes are statistically highly significant, they are clinically acceptable. Despite our sincere efforts, the study had a few limitations. The sample size was small. The study was unicentric, thus the study subjects might not represent the true population. As dexmedetomidine is not yet approved by FDA for intranasal use, syringes were used for drug delivery. A suitable device would have been more acceptable for the study subjects.

CONCLUSIONS

Intranasal dexmedetomidine is safe & more effective than intranasal midazolam for pre-operative sedation in children. Also, intranasal dexmedetomidine is a superior agent than intranasal midazolam for post-operative analgesia in paediatric population.

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