A Comparative Evaluation of Intranasal Dexmedetomidine and Intranasal Midazolam for Premedication in Children : A Double Blind Randomised Controlled Trial

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Abstract

Premedications frequently are 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. Midazolam is the most commonly used drug for this purpose till now. Midazolam may not be the most suitable preoperative sedative and anxiolytic in all children and in all circumstances. Clonidine, an α_2 agonist, has been suggested as an alternative. Dexmedetomidine is a more α_2 selective drug with favorable pharmacokinetic properties than clonidine. Intranasal administration is relatively easy and with high bioavailability than oral route. This study is conducted to evaluate whether intranasal dexmedetomidine is as effective as intranasal midazolam for premedication in children. Children premedicated with 1 µg/kg of intranasal dexmedetomidine attained more significant and satisfactory sedation at parental separation and at induction of anesthesia than those patients who received 0.2mg/kg of intranasal midazolam. The sedation produced by dexmedetomidine differs from other sedatives as patients may be easily aroused and cooperative.

Key Words : Premedication in children, Intranasal, Dexmedetomidine, Midazolam, Bioavailability.

Introduction

Premedications help to alleviate the stress and fear of treatment as well as to ease child-parent separation and promote a smooth induction of anesthesia.[1-4,6-8] Most commonly used midazolam has shown to be more effective than parental presence or placebo in reducing anxiety and improving compliance at induction of anesthesia.[9,10,11] The beneficial effects of midazolam include sedation, anxiolysis and reduction of postoperative vomiting.[13] A recent evidence-based clinical update has shown that intranasal midazolam 0.2 mg/kg is effective in reducing both separation and induction anxiety in children, with minimal effect on recovery time.[5,12] However, the acceptability of intranasal midazolam by pediatric patients may vary.[12] Other undesirable effects including restlessness, paradoxical reaction, and negative postoperative behavioral changes have made it a less than ideal premedication.[14,15] Although amnesia is considered an advantage by some authorities, it has also been regarded as a possible disadvantage by others.[16]

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Clonidine, an alpha 2-agonist, has been suggested as another option for premedication in children and previous studies have shown it to be equally as effective as midazolam.[17,21] Dexmedetomidine is a newer alpha 2-agonist with a more selective action on the alpha 2-adrenoceptor and a shorter half-life.[18,20,22,24] Its bioavailability is 81.8% (72.6–92.1%) when administered via the nasal mucosa. In a randomized, crossover evaluation of healthy adult volunteers, demonstrated that intranasal dexmedetomidine produces sedation in 45–60 min. In addition, they observed only a modest reduction of heart rate and arterial blood pressures were observed.[19] Although many studies proved that intranasal dexmedetomidine can be used as a premedication in children, studies to compare the sedative effects of midazolam and dexmedetomidine administered intranasaly as preanaesthetic medication have been scarcely done.

Material And Methods

This study was carried out in the Department of Pedodontics and Preventive Dentistry in association with the Department of Anesthesiology, Rajah Muthiah Dental College & Hospital, after obtaining the parent consent. Prior to the study we obtained official approval of the ethical committee

90 children aged 2-9 years were selected for this randomized double blind controlled clinical trial in

accordance with American Society of Anesthesiologists (ASA) physical status 1 scheduled for elective full mouth rehabilitation. 90 ASA 1patients aged between 2 & 9 yrs (wt 16 ± 6.2), 45 males and 45 females, posted for elective dental treatment are divided into two groups: M group-intranasal midazolam (0.2 mg/kg and D group-intranasal dexmedetomidine (1/kg). Exclusion criteria included known allergy or hypersensitive reaction to dexmedetomidine or midazolam, organ dysfunction, cardiac arrhythmia or congenital heart disease, and mental retardation. Standard protocol was followed.

Dose too low

Children were randomly divided into two groups. Group M received 0.2 mg/kg intranasal midazolam; up to a maximum 5 mg. Group D received intranasal dexmedetomidine 1 µg /kg. To avoid bias, drugs were prepared by an unknown investigator. Observers and attending anesthesiologists were blinded to the study drug given. Children had premedication in the preoperative holding area in the presence of parent. Intranasal drug was dripped into both nostrils using a 1-ml syringe with the child in the recumbent position. Baseline heart rate (HR), oxygen saturation (SpO2), and blood pressure (BP) were measured before and every 15 min after intranasal drug administration until transfer to the operating room (OR) Sedation status was assessed by a blinded observer every 5 min with a 6-point sedation scale. Behavior was valuated every 5 min with a 4-point behavior score. The duration of premedication was approximately 60min; however, it could be longer or shorter depending on treatment procedure. Sedation status and behavior were evaluated by the attending anesthesiologist at induction using the same scale. Mode of induction (IV versus inhalation) was decided by the attending anesthesiologist. The airway was maintained with a facemask or laryngeal mask airway throughout the operation. Anesthesia was maintained with sevoflurane and 60% nitrous oxide in oxygen. Regional anesthesia was administered whenever it was appropriate. When surgery was finished, the child was placed in the recovery position and allowed to wake up naturally in the post anesthesia care unit (PACU). Behavior at awakening was evaluated with a four-point wake-up score. Time taken for readiness to be discharged from the PACU was recorded.

The primary end-points were behavior and sedation status at separation from the parent and at induction of anesthesia. Secondary end-points included systolic BP (SBP) and HR changes, wake-up behavior, and time until ready for discharge from the PACU. Standard discharge criteria were used in the PACU. Patients were discharged from the PACU to the ward when they were awake, with reasonable control of pain and with vital signs within 20% of baseline values. Observations of sedation status and vital signs, including HR and SpO2, were made at 5min and BP at 15 min intervals until the patient was ready to be discharged.

Evaluation Scale

A. Sedation scores

1 - Does not respond to mild prodding or shaking

2 - Responds only mild prodding or shaking

3 - Responds only after name is called loudly or repeatedly

4 - Lethargic response to name spoken in normal tone

5 - Appear asleep but respond readily to name spoken in normal tone

6 - Appear alert and awake, response readily to name

B. Behavior scores

1 - Calm and cooperative

2 - Anxious but reassurable

3 - Anxious and not reassurable

4 - Crying, or resisting

C. Wake-up behavior scores

1 - Calm and cooperative

2 - Not calm but could be easily calmed

3 - Not easily calmed, moderately agitated or restless

4 - Combative, excited, disoriented

Statistical Analysis

Comparisons between the study groups were conducted using ANOVA by using multivariate ANOVA test, one-way ANOVA test, repeated measures ANOVA and Kruskal–Wallis ANOVA test as well as comparing mean and standard deviation. The Tukey test was applied for post hoc pairwise comparisons. The changes of BP and HR from baseline among the groups were tested by Kruskal–Wallis t-test. P-value below 0.05 was considered significant. The statistical software used was NCSS - PASS. For statistical analysis, sedation scores were categorized as being satisfactory when rated between 1 and 4 and unsatisfactory when rated 5 or 6. Behavior scores and wake-up scores were categorized as satisfactory when they were 1 or 2, and unsatisfactory when they were 3 or 4.

Results

Two groups were comparable with respect to age, weight, gender, duration of surgery, and type of induction (Table 1). Six of 90 (6.5%) children resisted intranasal drug administration. No child complained of pain or discomfort with intranasal drug administration. The children who resisted the medication were also included in the analysis.

The median sedation scores at separation from the parent were 6 and 1.5 for groups M and D respectively. 28.3% and 83% of the children from groups M and D achieved satisfactory sedation at separation from parents (Table 2). The median sedation scores at induction were 6and 4 for groups M and D respectively. At induction of

Table 1 : Patients' demographic data

	Group M (n _ 32)	Group D1 (n _ 32) P	p
Age (yr)	5.8 2.7 (4-14)	5.6 2.9 (3-11)	0.745
Body weight (kg)	16.1 ± 6.8	17.3 ± 7.4	0.215
Sex, M:F	20:20	20:20	0.757
Type of induction, gas: IV	8:32	14:26	0.452
Duration of surgery (min)	34.5 ± 9.1 (12-45)	43.6 ± 16.3 (17-68)	0.136
Time from premedication to induction (min)	30.5 ± 14.9 45-90)	57.0 ± 14.3 (50-100)	0.174

Values in mean ± SD (range) or no. (%).

EUA- examination under anesthesia.

anesthesia, 24.7.8% and 67.4% of the children from groups M and D respectively were satisfactorily sedated. Significantly more children from group D achieved satisfactory sedation when compared with group M (P - 0.004) (Table 2). Most children had satisfactory behavior at induction of anesthesia with no evidence of a difference among groups (P - 0.137) (Table 2).

The proportions of children who had satisfactory behavior at separation from parents, but became distressed at induction of anesthesia, were 0% and 10.0% from groups M and D respectively. Although there was a tendency for more children who had received dexmedetomidine to develop unsatisfactory behavior at induction of anesthesia, and the P value from test was 0.014, post-hoc pair-wise comparisons did not reveal any significant difference among the groups. Of the children from groups M and D respectively, 16.7% and 31.5% were awoken by the transfer from the preoperative holding area to the operation theatre. There was a tendency for more children who had received dexmedetomidine to awaken during this transfer, although these differences were not statistically significant (P - 0.734) (Table 2).

The median behavior score and sedation score were further analyzed with the children divided into different age groups age 2–5 and age 7–9 yr. The median behavior scores at baseline, at separation from parent, and at induction were not different among the children from groups M and D in all age groups. The median sedation scores of group D were significantly different from group M at separation from parent and at induction in children of age 2–5 yr. In age Group 2–5 yr, the median sedation scores at separation from parent were 6 and 2 from group M and D respectively (P - 0.001). For the same age group, the median sedation scores at induction of anesthesia were 6 and 2 for group M and D, respectively (P - 0.001). These differences were not observed in older children. Seven children receiving midazolam were noted to become euphoric or restless after premedication, but none after dexmedetomidine. As this paradoxical behavior was not prospectively sought in our observations, it was

Table 2 : Distribution of behavior and sedation status at parental separation and at induction

	Group M	Group D	p
Successful parental separation			
Yes	38 (95.0%)	40 (100%)	0.681
No	2 (5.0%)	0 (0%)	
Sedation at separation from parent			
Satisfactory	11 (27.5%)	34 (85%)	<.001*+
Unsatisfactory	29 (72.5%)	6 (12.5%)	
Behavior at induction			
Satisfactory	38 (95.0%)	36 (90.0%)	0.137
Unsatisfactory	2 (5.0%)	4(10.0%)	
Sedation at induction			
Satisfactory	26 (62.5%)	27 (65%)	0.018*
Unsatisfactory	14 (37.5%)	13 (35.%)	
Change of behavior at induction from satisfactory to unsatisfactory= *n*/total (%)	0/40 (0)	4/40 (10.0%)	0.014
Change of sedation at induction from Satisfactory to unsatisfactory *n*/total (%)	1/9 (14.3)	8/32 (27.3)	0.734

Values in number (%) or mean ± SD.

* Significantly different between Group M and Group D1 at 0.05 level.

† Significantly different between Group M and Group D0.5 at 0.05 level.

not statistically tested. Respiratory and Hemodynamic Effects Overall, we did not observe any clinically significant effects of the study drugs on SpO2 and no child had a reduction of SpO2 to below 95% during the observation period after premedication. The mean systolic blood pressure (SBP) and HR during the premedication period are shown in Figs. 1 and 2. Only children who stayed for more than 60 min after premedication were included in the analysis of SBP and HR during the premedication period by repeated measures of ANOVA. Consequently 20 and 13 children from groups M and D, respectively, were included in this analysis.

There were significant group and time effects on SBP (P - 0.025 and - 0.001, respectively). There was no significant group - time interaction (P _0.085). Post hoc analysis showed that SBP decreased significantly in group D when compared with group M (P - 0.004). 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 D (Chart 1). The SBP was reduced by 12.3% at 60 min in group D. There was also a significant time effect on HR (P - 0.001) and group - time interaction (P - 0.001). The group effect on HR was not significant (P - 0.102). Post hoc analysis showed that HR decreased significantly with time in group D (P - 0.001). The HR became significantly reduced from baseline at 45 and 60 min after drug administration in

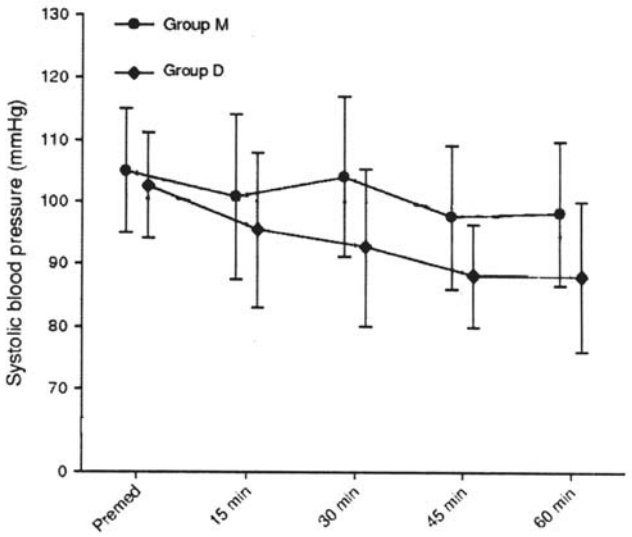

Chart 1 : Mean systolic blood pressure ± sd during the premedication period.

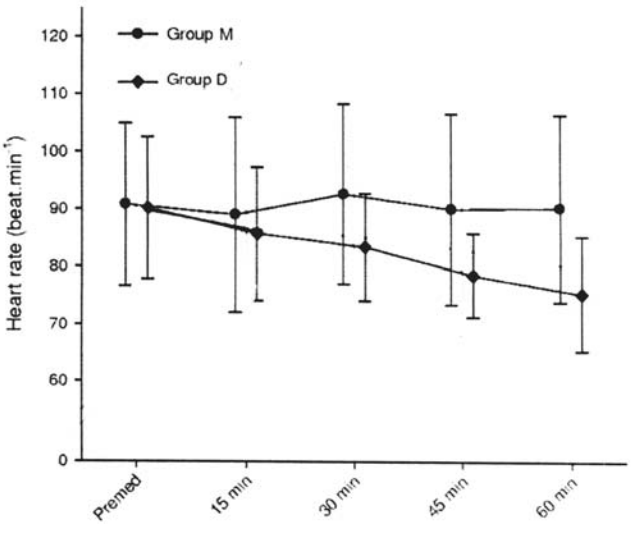

Chart 2 : Mean heat rate ± sd during the premedication period.

group D (P - 0.001) (Chart 2). It was decreased by 14.7% from baseline in group D at 60 min, after drug administration.

Discussion

This prospective, double-blind, randomized, controlled trial compared intranasal dexmedetomidine and midazolam as premedication in healthy children between 2 and 9yrs of age. Children premedicated with intranasal dexmedetomidine attained more significant and satisfactory sedation at parental separation and at induction of anesthesia than those patients who received midazolam. Most children tolerated the intranasal administration of drugs. Previous studies have shown that intranasal administration is an effective way to administer premedication and sedation to children.[5,12] It is a relatively easy and non-invasive route with a high bioavailability. However, cooperation is still required and it may be more difficult in younger children.

only due to using a dropper

Dexmedetomidine's site of action in the central nervous system is primarily in the locus coeruleus where it induces electroencephalogram activity similar to natural sleep.[20,22] Patients are also less likely to become disorientated and uncooperative. In this investigation, we have shown that 85% of the children attained a satisfactory level of sedation after 1 mcg/kg intranasal dexmedetomidine. Moreover, 70.8% of these sedated patients allowed IV or inhaled induction without showing signs of distress or awakening. Subgroup analysis revealed that children from age group 2–5 yr seemed to be more sedated with intranasal dexmedetomidine. However, the lack of a significant sedative effect of intranasal dexmedetomidine in age groups 6–9 could be real or due to an inadequate sample size. Since this study was not designed to investigate the sedative effect of intranasal dexmedetomidine in different age groups, we cannot draw a conclusion on this.

The reported sedative effects of midazolam are quite variable.[17] Our study has shown that only 27.5% of children receiving 0.2mg/kg of intranasal midazolam were sedated. The variability may be due to a difference in study design, and different bioavailabities of the midazolam preparation. Although previous studies have documented the effectiveness of intranasal midazolam as a preoperative anxiolytic, our behavior scoring system did not allow us to evaluate the anxiety level of children. We have shown in this investigation that the behavior of children at separation from parents and at induction of anesthesia were similar in children who received intranasal midazolam and intranasal dexmedetomidine based on our behavior scale. Although intranasal midazolam did not produce significant sedation in our subjects, it could have produced significant anxiolytic and/or amnesic effects. It is also uncertain if the sedative effect of intranasal dexmedetomidine is associated with any anxiolytic effect.

Alpha 2-Agonists produce a modest reduction in BP and HR. In a recent study comparing midazolam, clonidine, and dexmedetomidine for premedication in children, both clonidine and dexmedetomidine were shown to reduce mean BP and HR before and during surgery.[24] In a pharmacokinetic study of IV dexmedetomidine in children, it was shown that 0.66 and 1mcg/kg IV dexmedetomidine given over 10 min produced a significant reduction of HR (_15% compared with baseline) and SBP (_25% compared with baseline).[25] 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, we have shown that preoperative 1 mcg/kg intranasal dexmedetomidine reduces HR and blood pressure in

healthy children during the first hour after drug administration.

In this study, the onset time and peak effect of the intranasal dexmedetomidine or the blood concentrations was not evaluated. The onset time of 1 mcg/kg intranasal dexmedetomidine was about 45 min with a peak effect at 60–105 min after intranasal dexmedetomidine in healthy adults.[20] In this study, the premedication period was 60 min for intranasal dexmedetomidine; however, some children were transferred to the OR slightly earlier in order not to interfere with the normal OR schedule. If a longer premedication period had been allowed, possibly more subjects could have attained satisfactory sedation at separation from parents and at induction of anesthesia.

Conclusion

Intranasal drug administration is relatively quick, simple, and may have benefits over transmucosal routes or rectal administration, which requires more patient cooperation. We have established that this route is feasible for dexmedetomidine administration and future studies could now be directed to further evaluate dexmedotomidine administration.

In summary, 1 mcg/kg intranasal dexmedetomidine produces significant sedation in children between 2 and 9 yr-of-age. Behavior of the children at parental separation and at induction of anesthesia was comparable to children who received oral midazolam. The hemodynamic effects of intranasal dexmedetomidine were modest.

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