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Research Article

Intranasal Dexmedetomidine Versus Midazolam Premedication in Paediatric Patients: A Prospective Study

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Abstract

Background: The preoperative period is a stressing occurrence for most people undergoing surgery, in particular children. Effective premedication minimizes emotional trauma in children undergoing surgery, reduces preoperative anxiety, facilitates separation from parents, decreases the incidence of emergence agitation (EA).

This study was designed to evaluate the effects of midazolam and dexmedetomidine premedication on sedation and emergence agitation when used intranasally in preschool children.

Methods: Seventy patients, aged 2–6 years, undergoing minor elective surgery were randomly allocated into two groups to receive dexmedetomidine or midazolam intranasally for premedication 45 min before induction of anaesthesia. Levels of sedation was assessed every 10 min until transport to the operating room. Drug acceptance, parental separation, anxiety and face mask acceptance scores were recorded. Haemodynamic parameters were measured before and every 10 min after administration of the drugs in all children.

Results: Median sedation score in group D was significantly lower than in group M at 45 min after premedication. Seven (20%) children from Group D and 5 (14,3%) children from group M resisted intranasal medication ($p > 0,05$). Parental separation score was significantly higher in group D than group M. The percentage of children who had satisfactory parental separation was 91,4% and 71,5% in group D and group M, respectively ($p < 0,05$). Anxiety score and mask acceptance score were comparable between the groups. Haemodynamic parameters were comparable between the groups before and at 45 min after premedication. Peroperative HR values were significantly lower in group D than group M ($p < 0,05$). Incidences of EA were significantly lower in group M in comparison with group D, up to the first 15 min; although, after then, the difference was both statistically and clinically comparable.

Conclusion: This study demonstrates comparable results between intranasal dexmedetomidine and midazolam in the peroperative period as a preanesthetic medication in preschool children according to their sedative effects and their effects on preventing emergency agitation.

Keywords: *Premedication; Intranasally; Paediatric; Midazolam; Dexmedetomidine*

Introduction

The preoperative period is a stressing occurrence for most people undergoing surgery, in particular children. Approximately 50-75% of children undergoing surgery develop anxiety which is associated with distress during preoperative period and after emergence from anaesthesia and with later postoperative behavioral problems. Effective premedication may facilitate a smoother induction of general anaesthesia with minimal haemodynamic alterations and minimize emotional trauma in children undergoing surgery [1,2]. It also reduces preoperative anxiety, facilitates separation from parents, and promotes acceptance of mask induction [3].

A noninvasive approach is preferred for anaesthetic premedication because children often exhibit an exaggerated psychological response to the needle [4]. Oral and rectal routes are not reasonable methods for titrating drugs and have considerable delays in onset. The advantages of intranasal route are lack of pain and ease of use, avoidance of injection and rapid absorption of the drug directly into the systemic circulation from an area rich in blood supply without the disadvantage of passing through portal circulation [5].

Midazolam is one of the drugs most used for premedication in children. Intranasal midazolam for premedication in preschool children was first described by Wilton., *et al*. and later studied by García-Velasco., *et al*. [6,7]. The different routes of administration of midazolam as a sedative premedication have been investigated. Its use intranasally has been compared with the oral, sublingual, and rectal routes [8,9].

Alpha-2 adrenergic agonists produce sedation, facilitate parental separation and improve conditions for induction of general anaesthesia while preserving airway reflexes. Dexmedetomidine (DEX) is a newer, highly selective and specific α2-adrenergic agonist with sedative, analgesic, and anxiolytic effects. It is also tasteless, odorless and painless [10]. Intranasal use of DEX offers effective premedication before general and regional anaesthesia [2,11,12].

Emergence agitation (EA) is one of the most common postoperative complications in children. It occurs typically in preschool children, with a high intensity of anxiety, after sevoflurane or desflurane anaesthesia. Prevention of this complication relies on some different approaches. Effective premedication is one them [13].

This study was designed to evaluate the effects of midazolam and dexmedetomidine premedication on sedation and emergence agitation when used intranasally in preschool children.

Methods

This prospective, randomized, double-blind, controlled study was performed after the approval of Ethical Committee of Sisli Etfal Training and Research Hospital, Istanbul, Turkey. All proposed procedures were explained and written informed consent was obtained from the person legally responsible for each child before inclusion of participants in the study. Seventy, American Society of Anesthesiologists' classification I (ASA I) paediatric patients between the ages of 2 and 7 years, scheduled for elective surgery participated in the study. Minor elective surgical procedures were circumcision, inguinal hernia repair and tonsillectomy/adenoidectomy. Exclusion criteria included lack of consent, known adverse reactions to the study drugs, mental retardation, autism, using analgesics and anticonvulsants during the perioperative period, and cerebral palsy.

Children were randomly allocated to one of two groups by a computer-generated table of random numbers: Group D (n = 35) received 2 μg/kg dexmedetomidine and group M (n = 35) received 0.2 mg/kg midazolam by intranasal route (dripped into both nostrils with the child in the recumbent position). Half an hour before sedation, the children were transported to the premedication room near the operating room; parental presence was allowed throughout the sedation period. Prior to arrival of the child, a resident doctor in anaesthesiology who did not participate in clinical assessment, drew up the study drug (either dexmedetomidine or midazolam) into a tuberculin syringe that was labeled study drug. Neither the researcher who made the clinical observations and records nor the parents were informed as to which drug was administered to which child. The response of the child to drug administration was recorded on a two-point scale (1: poor, crying; 2: good, not crying). Before (basal) and after premedication, routine monitoring was performed, including heart rate (HR), respiratory rate (RR), and peripheral oxygen saturation (SpO_2) and recorded at 10-min intervals. Level of sedation

was assessed by using Observer Assessment of Alertness and Sedation Scale (OAA/S) [14] (Table 1). Observations of sedation status were made at 10 min intervals until induction of anaesthesia. Sedation score of 4 or less was considered satisfactory. A 4-point scale was applied for preoperative anxiety (1 = Crying, very anxious, 2 = Anxious, not crying, 3 =Calm, but not cooperative, 4 = Calm, cooperative or sleep). Parental separation scores was assessed using three point scale (1 = Poor, anxious and combative, 2 = Good, anxious but easly reassured, 3 = Excellent, sleepy and calm). The parent was not allowed to accompany the child at induction of anaesthesia. Mask acceptance was evaluated by a 4-point scale: 1 = Poor (combative, crying), 2 = Fear (moderate fear of the mask, 3 = Good (cooperative with reassurance), 4 = Excellent (calm, cooperative, or sleeping). Satisfactory parental separation and mask acceptance scores were determined 3 or 4.

Observation	Score level
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 and/or repeatedly	3
Responds only after mild prodding or shaking	2
Does not respond to mild prodding or shaking	1

Table 1: *Observer's assessment of alertness/sedation (OAA/S) scale.*

About 45 min after premedication, children were brought to the operating room where anaesthesia was induced with sevoflurane in 100% oxygen (6 L/min) through a face mask. All patients had the same standardized anaesthesia induction and maintenance with sevoflurane in oxygen. After establishing a venous access, rocuronium 0.6 mg/kg was given. Orotracheal intubation was performed and anaesthesia was maintained with 60% nitrous oxide in oxygen, supplemented by of 2-3% sevoflurane with controlled ventilation, to maintain an end-tidal CO_2 of 35 ± 4 mmHg. At the conclusion of the procedure, following the discontinuation of sevoflurane and nitrous oxide, residual muscle relaxation was reversed with neostigmine 0.05 mg/kg and atropine 0.02 mg/kg i.v and patients received with O_2 100% (6 L/min) for at least 3 minutes. Upon arrival to the PACU, all children were received by one of their parents, who stayed with them until discharge. In the PACU, the incidence of EA was assessed with Aono's four-point scale [15] (1 = calm; 2 = not calm but could be easily consoled; 3 = moderately agitated or restless and not easily calmed; 4 = combative, excited, or disoriented, thrashing around) upon admission and 5,15 and 25 min, respectively. In PACU, the agitated children were planned to manage by giving intravenous increments of fentanyl 1 μg/kg with at least a 10 min time interval between each dose, during which time the children were monitored for any signs of respiratory depression. A resident in anaesthesiology who was blinded to study groups recorded all the scores and observations at PACU. Adverse effects, including respiratory depression (RR < 12/min), desaturation (SpO_2 < 90% for 15s) and bradycardia (< 60 beats/min) were noted. If the SpO_2, RR or HR fell below expected levels, oxygen via facemask or intravenous atropine would be administered.

The data are presented as mean values with standard deviations (SDs), medians with ranges, or as proportions with a 95% confidence interval (CI). Student's t-test was used to compare normally distributed continuous variables between the two groups, and the nonparametric Mann-Whitney U-test was used for the sedation scores, anxiety scores, parental separation and mask acceptance scores. Categorical data were analyzed by the chi-square test or Fisher's exact test. A P-value of < 0.05 was considered to be statistically significant. A power analysis indicated that a simple size of 29 was sufficient to detect a significant statistical difference with $\alpha = 0.05$ and power of 80% in satisfactory sedation scores at parental separation between the two groups. We decided to study 70 patients to account for possible dropouts.

Results

A total of 70 children were included in the study, with 35 children in each group. All patients received premedication according to their group allocation. No patients were excluded from the study because of incomplete data. Patients were comparable in both groups

with respect to age, weight and gender (Table 2). Also, the durations of sevoflurane administration among two groups were similarly comparable (Table 2).

	Group D	Group M
Age (years)	4,42 ± 1,12	3,97 ± 1,44
Weight (kg)	22,05 ± 6,30	22,81 ± 6,23
Gender (F/M) (n)	21/14	16/19
Duration of sevoflurane administration (min)	38,88 ± 5,30	41,65 ± 5,63

Data are expressed as mean ± standard deviation (SD), numbers.

Table 2: *Demographic data and duration of sevoflurane administration.*

Median sedation score in group D was significantly lower than in group M at 45 min after premedication. At different times after premedication, level of sedation in group D was lower than those of group M (Table 3). But the difference was not significant. Satisfactory sedation score at 45 min after medication was achieved by 91,4% of group D and by 82,8% of group M (P = 0,069). 22 patients in group D (62,8%) and 19 patients (54,3%) in group M had satisfactory sedation score at 30 min after study drug delivery.

	Sedation scores		
	Group D	Group M	p
Baseline	5 (5)	5 (5)	
10 min	5 (4-5)	5 (4-5)	0,53
20 min	4 (4-5)[a]	5 (4-5)	0,093
30 min	4 (3-5)[a]	4 (4-5)	0,064
40 min	4 (3-5)[a]	4 (4-5)[a]	0,058
45 min	4 (3-4)[a]	4 (3-5)[a]	0,043*

Data are expressed as median (interquartile range).

For intergroup comparisons (with Mann-Whitney U-test).

**p < 0,05, for intragroup comparisons (with Kruskal Wallis) baseline-at different times, [a]p < 0,01.*

Table 3: *Sedation scores at different times.*

Response to the drug administration, parental separation score, anxiety score and mask acceptance score values are summarized at (Table 4). Seven (20%) children from Group D and 5 (14,3%) children from group M resisted intranasal medication. No child complained of any odor, pain, irritation or bad taste with either drug administration. Parental separation score was significantly higher in group D than group M. The percentage of children who had satisfactory parental separation was 91,4% and 71,5% in group D and group M, respectively (p < 0,05). Anxiety score and mask acceptance score were comparable between the groups (Table 4). Satisfactory mask acceptance score percentage was 88,6% in group D and 82,9% in group M (p > 0,05). In group D there was excellent favorable response to mask placement in 21 children (60%) and in group M 18 children (51,4%) (p > 0,05).

Haemodynamic parameters were comparable between the groups before and at 45 min after premedication (Table 5). Peroperative HR values were significantly lower in group D than group M (p < 0,05). Peroperative RR values had a tendency to be lower in group D than group M but the difference was not significant. Oxygen saturation in the two groups was the same throughout the study period. No patient had respiratory depression or bradycardia (Table 5).

		Group D	Group M	p
Response to the drug administration ≠	Poor, crying	11 (31,4%)	10 (28,6%)	0,256
	Good, not crying	24 (68,6)	25 (71,4)	0,245
Parental separation score		3 (2-3)*	3(1-3)	0,043
Anxiety score		2 (1-3)	2 (1-3)	0,183
Mask acceptance score		4 (2-4)	3 (2-4)	0,241

Data are expressed as median (interquartile range) and ≠ n (percentage).

**p<0,05 compared to group M.*

Table 4: *Response to the drug administration, parental separation score and mask acceptance score of the groups.*

		Group D	Group M	p
HR (beat/min)	*Before*	114,28 ± 13,24	117,46 ± 17,32	0,436
	After	92,74 ± 11,03 *	98,75 ± 10,43 *	0,216
RR (beat/min)	*Before*	24,67 ± 5,68	23,13 ± 4,26	0,652
	After	18, 54 ± 3,18 *	19,74 ± 5,17 *	0,742
SpO_2 (%)	*Before*	99,16 ± 1,53	99,46 ± 1,89	0,093
	After	98,11 ± 1.06	98,53 ± 2,04	0,145

Data are expressed as mean ± standard deviation (SD).

**p<0,05 compared before premedication.*

Table 5: *Heart rate (HR), respiratory rate (RR) and peripheral oxygen saturation (SpO_2) before and 45 min after premedication of the groups.*

Incidences of EA were significantly lower in group M in comparison with group D, up to the first 15 min; although, after then, the difference was both statistically and clinically comparable. Total number of patients suffering from ED after sevoflurane-based general anaesthesia was higher in group D (5 children) than group M (3 children). But the difference was not significant (p > 0,05).

Discussion

We designed this study to compare the perioperative sedative effects and emergency agitation of intranasal dexmedetomidine and midazolam for premedication in preschool children. The primary end points were the sedation score after premedication and postoperative emergence agitation. Secondary end points included preoperative anxiety status, parental separation score, mask acceptance at induction, haemodynamic changes during sedation. We found that intranasal 2 μg/kg dexmedetomidine and 0,2 mg/kg midazolam had almost comparable perioperative effects.

Preoperative sedation essentially reduces separation anxiety and improves mask acceptance in the paediatric population. Noninvasive approaches for sedating children are preferred because of psychological response to the needle [4]. The advantages of intranasal delivery of sedative medications are that they are painless, easy to use and they avoid first-pass metabolism, thus improving bioavailability over oral and rectal doses.

Midazolam has been used as a preoperative sedative agent via different routes [17-19]. Intranasal midazolam has been used in early studies and the absence of changes in respiratory rate, clinical respiratory depression and apnea during induction suggested that this medication is safe [18,19]. Midazolam when used intranasally dose was mostly preferred as 0,2 mg/kg in recent studies [19,20]. DEX is a newer α-2 agonist with a more selective action and a shorter half-life [21]. It has been shown that intranasally administered DEX is efficacious, and the onset of sedation has been reported to occur at 45 min in healthy volunteers [22] and at 25 min in children [23]. In

the literature DEX was used in different doses intranasally [19,24,25]. In our study based on the aboved reference studies we decided to use DEX as a dose of μg/kg and midazolam as a dose of 0,2 mg/kg, 45 min before transferring children to operation room.

Kamal., *et al*. studied the effect of oral dexmedetomidine vs. oral midazolam as premedication in 60 paediatric patients assigned to receive either oral midazolam 0.5 mg/kg or oral dexmedetomidine 3 g/kg prior to a standardized sevoflurane anaesthetia [26]. There was no significant difference in the pre- and postoperative levels of sedation between the two groups. Some other studies also revealed that dexmedetomidine premedication has similar effects with midazolam on preoperative anxiety [27,28]. Our findings were very similar to the findings of these studies and showed that dexmedetomidine induces good sedation, is safe and without remarkable adverse effects. It successfully eases the anxiety on separation from parents. These effects are comparable with midazolam.

In our study 7 children in group D and 5 children in group M resisted intranasal administration of the drugs. Since, intranasal midazolam might be irritant in a few patients, administration of 10 mg per puff of lidocaine spray, one minute before prescription of intranasal midazolam can reduce nasal mucosal irritation [29]. The same administration can be used during intranasal midazolam and DEX application.

We found that 91,4% of the children in group D had satisfactory parental separation scores compared with 82,8% of children in group M at 45 min after premedication. We evaluated these percentages as acceptable values for our study. Yuen., *et al*. showed that approximately 75% and 92% of subjects attained a sedation level of modified OAA/S of 3 or below after intranasal 1.0 and 1.5 μg kg^{-1} DEX, respectively, producing sedation in 45 to 60 min (peak, 90–105 min) with comparable results with us [22]. In another study similar to ours, intranasal dexmedetomidine vs. midazolam for premedication of paediatric patients undergoing anaesthesia separation from parents resulted with similar scores both groups [2].

Oral dexmedetomidine and midazolam as anaesthetic premedication in children undergoing congenital heart surgery equally relieved the children's anxiety in both groups [30]. Akin., *et al*. studied intranasal dexmedetomidine vs. midazolam for premedication of paediatric patients undergoing anaesthesia [2]. There was no evidence of a difference between the groups in anxiety score upon separation from parents. In our study anxiety score did not differ between our groups in accordance with these studies.

Intranasal 1 microg/kg dexmedetomidine vs. 0.2 mg/kg midazolam for premedication of paediatric patients undergoing anaesthesia resulted satisfactory mask induction 82.2% of the patients in group-M and 60% of those in group-D [2]. In a study by Faritus et al analysis of the mask acceptance behaviour at anaesthesia induction time revealed that more children receiving dexmedetomidine are calm and cooperate well in terms of mask acceptance than children receiving midazolam [30]. We had satisfactory mask acceptance scores with both midazolam and DEX in percentage 82,9% and 88,6% respectively comparable with these studies.

EA was first described in the 1960s and it is a dissociated state of consciousness in which the child is inconsolable, irritable, uncompromising, or uncooperative, typically thrashing, crying, moaning, or incoherent [31]. Sevoflurane is a widely used inhalational anaesthetic for paediatric anaesthesia because of its low pungency, low blood–gas partition coefficient, rapid onset, fast recovery properties, minimal cardiac depressive effect, and low toxicity [32]. The reported incidence of EA following sevoflurane anaesthesia varies from 10%–80% [15,33]. The aetiology of EA in children is not fully understood. Possible risk factors are rapid emergence from anaesthesia, preoperative anxiety, preschool age, otolaryngologic surgical procedures, pain, personality, surgery type, and anaesthetic [5,34,35].

Dexmedetomidine, has significantly reduced EA frequency after sevoflurane anaesthesia in paediatric surgery [26,36-38]. Our findings support these clinical trials. In a study Bhadla., *et al*. comparing dexmedetomidine to midazolam premedication in paediatric patients, postoperative agitation caused by sevoflurane is reduced significantly with dexmedetomidine compared to midazolam [39]. Nonetheless in Ni., *et al*. meta analyses study dexmedetomidine and midazolam were similarly efficacious in regard to preventing EA [3]. In our study, EA incidence was significantly lower in group midazolam than group DEX for the first 15 minutes postoperatively. But the difference between our study groups were comparable later. Our study allowed children to stay with one of parents in the PACU and this seemed to help them to acclimate themselves to a strange and naive environment.

The most important disadvantage of DEX is adverse haemodynamic effects. Hypotension and bradycardia have been reported, particularly with high bolus dosing regimens [40,41]. α-2 Agonists produced lower scores of peroperative mean arterial pressure and heart rate than did midazolam [41,42]. A pharmacokinetic study of I.V. dexmedetomidine in children done by Petroz., *et al*. showed that 0.66 and 1 μg/kg I.V. dexmedetomidine given over 10 min produced a significant reduction of heart rate (< 15% compared with baseline) and systolic BP (< 25% compared with baseline) [44]. In group DEX we had lower haemodynamic parameters than group M in accordance with these studies. No significant changes were achieved with either DEX or midazolam according to oxygen saturation in our study in accordance with some other studies [43].

We accept the fact that there are some limitations in our study, the first being the use of unvalidated sedation scales for children. When using these scales, we encountered some difficulties in evaluating children because of inadequate definitions. Another limitation is that intranasal route was not an acceptable way for children. Administration of lidocaine spray, before prescription of intranasal drugs can reduce nasal mucosal irritation.

Conclusion

This study demonstrates comparable results between intranasal dexmedetomidine and midazolam in the peroperative period as a preanesthetic medication in preschool children according to their sedative effects and their effects on preventing emergency agitation.

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