Original Article

Efficacy of intranasal dexmedetomidine versus oral midazolam for paediatric premedication

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ABSTRACT

Background and Aims: Premedication is an integral component of paediatric anaesthesia which, when optimal, allows comfortable separation of the child from the parent for induction and conduct of anaesthesia. Midazolam has been accepted as a safe and effective oral premedicant. Dexmedetomidine is a selective alpha-2 agonist with sedative and analgesic effects, which is effective through the transmucosal route. We compared the efficacy and safety of standard premedication with oral midazolam versus intranasal dexmedetomidine as premedication in children undergoing elective lower abdominal surgery. **Methods:** This was a prospective randomised double-blinded trial comparing the effects of premedication with 0.5 mg/kg oral midazolam versus 1 μg/kg intranasal dexmedetomidine in children between 2 and 12 years undergoing abdominal surgery. Sedation scores at separation and induction were the primary outcome measures. Behaviour scores and haemodynamic changes were secondary outcomes. Student's *t*-test and Chi-square were used for analysis of the variables. **Results:** Sedation scores were superior in Group B (dexmedetomidine) than Group A (midazolam) at separation and induction ($P < 0.001$).The behaviour scores at separation, induction and wake up scores at extubation were similar between the two groups. The heart rate and blood pressure showed significant differences at 15, 30 and 45 min in Group B but did not require pharmacological intervention for correction. **Conclusion:** Intranasal dexmedetomidine at a dose of 1 μg/kg produced superior sedation scores at separation and induction but normal behavioural scores in comparison to oral midazolam in paediatric patients.

Key words: Intranasal dexmedetomidine, oral midazolam, paediatric premedication

INTRODUCTION

Premedication plays an important role in allowing a smooth separation of the child from the parent. Inadequate premedication can result in the child experiencing turbulent anaesthetic induction and adverse behavioural sequelae. Midazolam is the most common oral premedication in children and is reportedly safe and effective both at separation and induction of anaesthesia.[1-3] Nasal premedication with midazolam and dexmedetomidine has been studied as alternatives to oral premedication with comparable results.[4] Dexmedetomidine is a selective alpha-2 adrenoceptor agonist with sedative and analgesic effects. However, it has poor oral bioavailability and absorption is better through the mucosal routes. The primary objective of our study was the comparison of sedation scores at separation and induction between orally administered midazolam and intranasal dexmedetomidine. The secondary outcomes were behavioural scores and haemodynamic changes after administration of the premedication.

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METHODS

This was a prospective randomised, double-blinded, comparative study conducted in sixty children of the American Society of Anesthesiologist (ASA) Physical Status 1 and 2, aged 2–12 years undergoing elective surgical procedures, during February 2012–April 2014. In a previous study by Yuen *et al*., 21.9% patients in midazolam group and 75% in dexmedetomidine group had satisfactory sedation scores at separation.[5] Targeting the same difference, with 95% confidence level and 80% power, minimum sample size was calculated as 17 in each group. We included thirty patients in each group during the period of our study.

After approval from the Institutional Ethics Committee, sixty children presenting for surgery were randomised to receive either dexmedetomidine or midazolam. Parental refusal for consent, children with a significant history of allergic disorders, ASA III or higher, those on long-term therapy with theophylline or hepatic enzyme inducing drugs were excluded.

The premedication was administered 60 min before induction of anaesthesia, in the holding area in the presence of one of the parents; after a random allocation to one of the two groups using a computer-generated sequence of random numbers in blocks of five.

Group A received midazolam 0.5 mg/kg (in 15 mg/kg acetaminophen syrup) and intranasal placebo (0.4 ml normal saline).

Group B received intranasal dexmedetomidine 1 μg/kg 0.4 ml normal saline and 15 mg/kg oral acetaminophen syrup.

Owing to the non-availability of oral midazolam at the time of this study, injectable midazolam was used for this study. Paracetamol syrup (250 mg/5ml) was used to mask the bitterness of the study medication and was used at a dose of 15 mg/kg. Group B received paracetamol syrup at 15 mg/kg with distilled water to a volume of 5 ml (1 tsp). Intranasal dexmedetomidine was prepared from the 100 μg/ml of parenteral preparation of the drug. Normal saline was added to the calculated dose to make a final volume of 0.4 ml. Intranasal drug was dripped into both nostrils at 0.2 ml per nostril using 1ml syringe with child in recumbent position.

Individuals who were not involved in observation or administration of anaesthesia for children prepared the study drugs. Heart rate (HR), oxygen saturation and blood pressure were measured before and every 15 min after intranasal drug administration until transfer to the operation room. The sedation status and behaviour scores were assessed every 15 min by a blinded observer using a 6-point sedation scale and a 4-point behaviour score [Table 1]. At the time of induction of anaesthesia, sedation and behaviour scores were evaluated by the anaesthesiologist using the same scoring system. Behaviour score at the time of awakening was evaluated using a 4-point wake up score [Table 1]. For statistical analysis, sedation scores were categorised satisfactory (≤4) and unsatisfactory (≥5). Behaviour scores were considered satisfactory (≤2) and unsatisfactory (≥3).[5]

Data analysis was performed using Statistical Package for the Social Sciences SPSS Statistics for Windows, Version 20.0 software (IBM, Bengaluru, India). Student's *t*-test was applied to compare age and weight, and the Chi-square test was applied to compare sex distribution.

RESULTS

Both groups were comparable with respect to age, sex, weight, duration and type of surgical procedures [Table 2]. The average time to induction from premedication was also comparable in Groups A and B (55.8 ± 6.2 min vs. 56.3 ± 5.7 min). Comparison of baseline mean arterial blood pressure (MAP), HR and oxygen saturation in Groups A and B showed no

Table 1: Sedation, behaviour and wake up behaviour scores

Scoring parameter	Scores
Sedation score	
Does not respond to mild prodding or shaking	1
Responds only to mild prodding or shaking	2
Responds after name is called loudly or repeatedly	3
Lethargic response to name spoken in normal tone	4
Appear sleep but respond readily to name spoken in normal tone	5
Appear alert and awake, response readily to name spoken in normal tone	6
Behaviour score	
Calm and cooperative	1
Anxious but reassurable	2
Anxious and not reassurable	3
Crying or resisting	4
Wake-up behaviour scores	
Calm and cooperative	1
Not calm but could be easily calmed	2
Not easily calmed, moderately agitated or restless	3
Combative, excited, disoriented	4

difference between groups. However, intraoperatively, significantly higher values of MAP and HR were seen in Group A at 30, 45 and 60 min [Figures 1 and 2]. Oxygen saturation was comparable between the groups except at 30 min.

The median sedation scores were higher in Group A at separation (5 vs. 2) and at the time of induction (6 vs. 3) which was statistically significant ($P < 0.001$). Compared to Group A, more patients in Group B were satisfactorily sedated at the time of separation (93.3% vs. 26.7%) and induction [83.3 vs. 23.3%, Table 3 and Figure 3].

The median behaviour score in Group A was higher than Group B at separation and induction (2 vs. 1). They were both in the range considered satisfactory (≤2) and were not significantly different between the groups at separation and induction [Table 3 and Figure 3].

The median wake up score at the time of extubation was similar in both groups. 73.3% of patients of Group A and 80.0% of Group B had satisfactory scores and were comparable among groups [Table 3 and Figure 3].

DISCUSSION

Premedication is an integral component in the practice of paediatric anaesthesia. Fear of painful or unpleasant procedures and separation from parents may result in untoward psychological effects. Although oral premedication is effective, the bitterness may cause retching and vomiting resulting in inadequate drug dosing.

Midazolam has been established as an effective oral premedication in children.[1-3] In doses of 0.5 mg/kg, it has been found to offer adequate sedation at separation and induction. It does not prolong recovery from anaesthesia or discharge from day care procedures. Yuen *et al*.[5] had concluded that an oral dose of 0.5 mg/kg midazolam was satisfactory as a premedicant

Table 2: Comparison of demography and types of surgery

Variables	Group A	Group B	*P*
Age (years), mean±SD	5.5±1.7	6.4±2.3	0.092
Weight (kg), mean±SD	17.5±6.8	20.2±7.2	0.162
Sex, *n* (%)			
Female	11 (36.7)	15 (50.0)	0.297
Male	19 (63.3)	15 (50.0)	
Type of surgery			
Adenotonsillectomy	5 (16.7)	4 (13.3)	0.568
Circumcision	4 (13.3)	-	
Hypospadias	3 (10.0)	2 (6.7)	
Syndactyly release	2 (6.7)	3 (10.0)	
Tonsillectomy	4 (13.3)	2 (6.7)	
Examination under anaesthesia	2 (6.7)	3 (10.0)	
Cystoscopy	3 (10.0)	5 (16.7)	
Hernia repair	2 (6.7)	4 (13.3)	
Lymph node biopsy	1 (3.3)	-	
Orchidopexy	2 (6.7)	2 (6.7)	
Abscess drain	2 (6.7)	2 (6.7)	
Myringotomy	-	1 (3.3)	
Nasal polypectomy	-	2 (6.7)	

SD – Standard deviation

Table 3: Comparison of sedation, behaviour and wake up scores

Variables	Scores	Group A, *n* (%)	Group B, *n* (%)	*P*
Sedation score at separation	≤4	8 (26.7)	28 (93.3)	<0.001
	≥5	22 (73.3)	2 (6.7)	
Sedation score at induction	≤4	7 (23.3)	25 (83.3)	<0.001
	≥5	23 (76.7)	5 (16.7)	
Behaviour score at separation	≤2	30 (100.0)	27 (90.0)	0.237
	≥3	0	3 (10.0)	
Behaviour score at induction	≤2	28 (93.3)	27 (90.0)	1.000
	≥3	2 (6.7)	3 (10.0)	
Wake up score at extubation	≤2	22 (73.3)	24 (80.0)	0.542
	≥3	8 (26.7)	6 (20.0)	

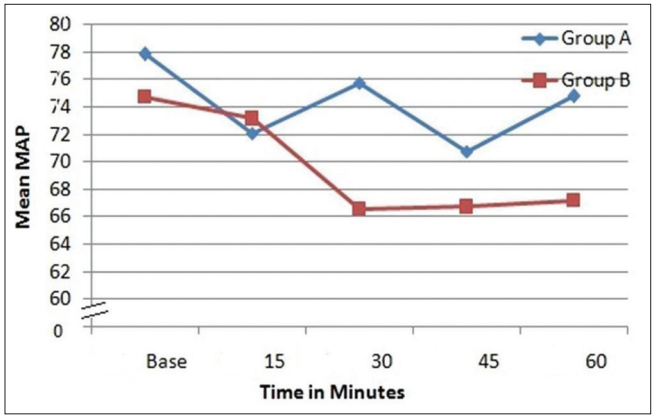

Figure 1: Distribution of mean arterial pressure

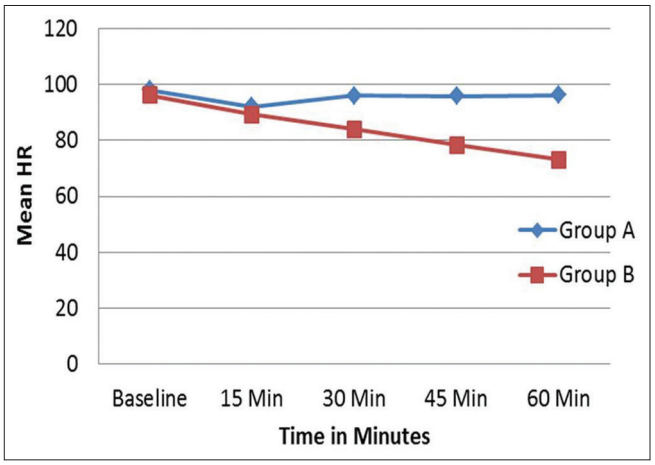

Figure 2: Distribution of mean heart rate

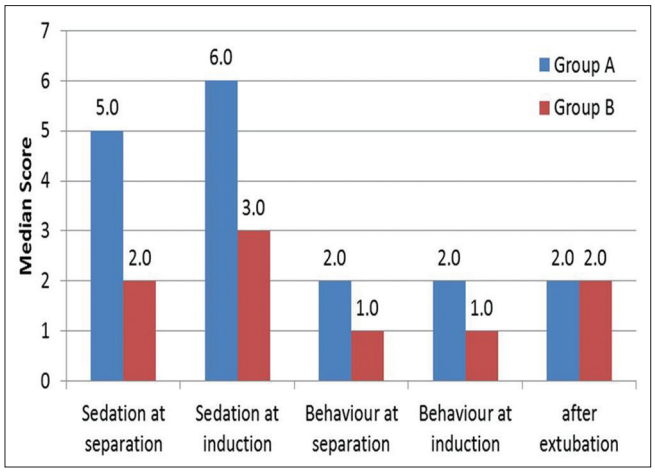

Figure 3: Distribution of sedation and behaviour scores

and that the effect correlated more closely with 1 μg/kg dexmedetomidine rather than with 0.5 μg/kg dexmedetomidine intranasally. Akin *et al*.[6] compared the effects of intranasally administered midazolam versus dexmedetomidine administered intranasally on premedication in children undergoing elective adenotonsillectomy. They concluded that both drugs were equally effective in decreasing separation anxiety in children although mask induction appeared to be superior in the midazolam group.

Dexmedetomidine is a newer selective alpha-2 agonist with a site of action at the locus coeruleus. It inhibits presynaptic release of norepinephrine that is responsible for its sedative and hypnotic effects.[7] The analgesic effects occur on account of activation of alpha-2 adrenoceptor in the descending medulla-spinal noradrenergic pathway. Bradycardia and hypotension occur on account of post-synaptic activation of alpha-2 receptors in the central nervous system. The finding of electroencephalogram activity similar to natural sleep supports the easy arousability from its effects. While there is sufficient literature supporting the use of oral midazolam, less information is available on the use of dexmedetomidine.

We found that a dose of 1 μg/kg dexmedetomidine resulted in better sedation scores and behavioural scores at separation and induction in comparison to oral midazolam. However, the recovery characteristics were comparable between both dexmedetomidine and midazolam groups.

Dexmedetomidine has limited bioavailability administered orally as compared to the nasal route; hence, we chose to compare the nasal administration of dexmedetomidine with the oral midazolam which has been accepted as a standard premedicant.[8] Although dexmedetomidine has good bioavailability through the mucosal route allowing the use of oral preparation, the effects would be manifested only if the patient made an effort to retain the drug in the mouth without swallowing. The nasal route of dexmedetomidine is not associated with irritant side effects as with intranasal midazolam. The advantages of dexmedetomidine are the absence of respiratory depression and analgesic effects; however, the drawback could be a longer onset time for sedation in comparison with midazolam.

A number of studies have compared the analgesic effects of oral midazolam with hydroxyzine[9] and chloral hydrate.[10] The utility of midazolam has been well established although some workers have observed better sedation with chloral hydrate in comparison with midazolam. We evaluated a lower dose of dexmedetomidine versus an accepted dose of oral midazolam to assess its applicability in paediatric premedication.

The average time from drug administration to induction in our study group was 45 min in two-third of our patients. This is similar to the study by Yuen *et al*.[11] who concluded that at 1 μg/kg dose intranasal dexmedetomidine produced satisfactory sedation scores at 30, 45 and 60 min after administration. They had found a median time of 25 min for the onset of sedation. We found a similar profile in our patients; although we did not measure the onset of sedation, the haemodynamic responses showed lowering of HR and blood pressure at 30 min after drug administration that correlated with the onset of sedation in our patients.

Yuen *et al*.[12] evaluated the efficacy of intranasal dexmedetomidine in two doses 1.0 and 1.5 μg/kg in 18 healthy adult volunteers and compared to a placebo. They concluded that the nasal route is convenient and safe for use and sedation occurred in 45 min with peak effect between 90 and 150 min after administration.

Our study was designed to primarily evaluate the efficacy of dexmedetomidine in comparison to midazolam as a premedicant in the profile of paediatric patients presenting to us for surgery. The objectives were the safety, comfort and ease of separation of the child in the holding area and behaviour at induction. We did not focus on the recovery characteristics and did not control the type and duration of surgery and anaesthesia. We also did not assess the analgesic benefits resulting in lesser fentanyl or propofol usage

during anaesthesia.[13] The scoring scales for sedation, behaviour and wake up were incorporated from the study by Yuen *et al*.[5]

In this study, we found that children receiving dexmedetomidine had significantly lower HR and blood pressure at 30, 45 and 60 min after drug administration in comparison with children receiving midazolam. A previous study comparing the additive effects of dexmedetomidine versus fentanyl with propofol showed that significant lowering in HR and MAP from baseline occurred in both groups.[13] A study using intranasal dexmedetomidine premedication in obese adults found that dexmedetomidine reduced the HR but not MAP in comparison to alprazolam.[14]

The fall in HR due to dexmedetomidine has been explained by its effect on sympathetic outflow and reducing levels of epinephrine and norepinephrine. The fall in blood pressure and HR was within acceptable limits for the age of the child and did not require the use of chronotropic agents, fluids or inotropes.

Study drugs were administered at a time presumed to be 45 min before anaesthesia. This could not be controlled most of the time; however, the dexmedetomidine group appeared to be sedated from 30 min after drug administration.

Dexmedetomidine has synergistic effects on analgesic requirements during the surgery. Schmidt *et al*.[15] have documented decreased sympathetic stimulation and decreased post-operative pain in the groups receiving dexmedetomidine. Mariappan *et al*.[16] have shown an anaesthetic sparing effect of dexmedetomidine in patients who received infusions of dexmedetomidine undergoing spine surgery. We did not assess opioid-sparing effects of dexmedetomidine and did not analyse the surgical requirements of analgesic. The management of intraoperative conditions was at the discretion of the anaesthesiologist who managed the case. It is possible that intraoperative requirements of fentanyl and propofol were lesser in the dexmedetomidine group. All children in both groups had an uneventful recovery, and wake up scores were not different between the groups.

Cardiovascular stability of dexmedetomidine has been documented in several studies; doses of 2 μg/kg intranasally in children undergoing non-complex cardiac surgeries have been shown to be safe.[17] Oral dexmedetomidine was also found to have better mask acceptability in children undergoing cardiac surgery.[18] Although the MAP and HR were lower in the dexmedetomidine group, this was still within acceptable limits for the age of the child.

The limitations in the study included failure to correlate the effects of dexmedetomidine premedication on the analgesic and anaesthetic requirements during surgery. The drugs were administered at 45–60 min before surgery; however, scheduling could not take place at the time proposed in some instances. We also did not monitor the time to onset of sedation in our study group, and the types of surgeries included were variable. The inclusion of a similar profile of surgeries along with monitoring analgesic requirements can document the additional intraoperative effect of the premedicant drugs.

CONCLUSIONS

Intranasal dexmedetomidine at a dose of 1 μg/kg produces superior sedation and behavioural scores at separation and induction but normal wake up scores in comparison to oral midazolam in paediatric patients.

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Conflicts of interest
There are no conflicts of interest.

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