Original Article

A comparison of oral midazolam and oral dexmedetomidine as premedication in pediatric anesthesia

ABSTRACT

Context: Oral premedication is widely used in pediatric anesthesia to provide preoperative anxiolysis and ensure smooth induction. Midazolam is currently the most commonly used premedicant, but newer drugs such as the α2-agonists have emerged as alternatives for premedication in children.

Aims: The aim of this study was to compare clinical effects of oral midazolam and oral dexmedetomidine on preanesthetic sedation and postoperative recovery profile in children.

Settings and Design: Randomized controlled trial.

Materials and Methods: We performed a prospective, randomized, controlled study in 60 children, aged 1-7 years undergoing elective, minor, lower abdominal surgeries under general anesthesia. Patients were randomly assigned to receive either oral midazolam 0.75 mg/kg (Group M, $n = 30$) or oral dexmedetomidine 4 μg/kg (Group D, $n = 30$) 40 min prior to mask induction. Preoperative sedation and anxiolysis, the response at parental separation, quality of mask acceptance and recovery profile were compared for the two groups.

Statistical Analysis Used: Results were analyzed using unpaired Student's *t*-test and Chi-squared test. $P < 0.05$ was considered statistically significant.

Results: There was no significant difference in the levels of preoperative sedation and anxiolysis between the two groups, but the onset of sedation was significantly faster with midazolam (18.90 ± 3.68 min) than with dexmedetomidine (30.50 ± 4.44 min). Response to parental separation and quality of mask acceptance was comparable between two groups ($P > 0.05$). The incidence of postoperative agitation was significantly less in the dexmedetomidine group ($P < 0.05$).

Conclusions: In this study, premedication with oral dexmedetomidine produced equally effective preoperative sedation and a better recovery from anesthesia in children in comparison to oral midazolam.

Key words: Dexmedetomidine; midazolam; pediatric anesthesia; premedication

Introduction

Almost 50% of children show signs of significant preoperative anxiety and fear.[1] In order to alleviate physiological and psychological effects of preoperative anxiety, most anesthesiologists use either the parental presence or sedative premedication.

In children, the issues of premedication are made more difficult as intravenous (IV) access is frequently absent and the child may view the placement of an IV cannula or administration of intramuscular medication as more invasive than the procedure itself. Therefore, routine clinical practice frequently makes use of oral administration

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Jannu V, Mane RS, Dhorigol MG, Sanikop CS

Department of Anesthesiology, J. N. Medical College, Belagavi, Karnataka, India

Address for correspondence: Dr. Vinayaka Jannu, Department of Anesthesiology, J. N. Medical College, Belagavi - 590 010, Karnataka, India. E-mail: drvinayakjannu84@gmail.com

of a sedative agent for premedication prior to anesthesia induction.[2,3]

Oral midazolam is currently the most commonly used sedative drug for premedication in children. It has been attributed to several beneficial effects such as anxiolysis, amnesia, rapid onset and offset of action. Nevertheless, a bitter taste has been described after its oral administration. Secondary and adverse effects to midazolam may include a paradoxical effect with behavioral changes and agitation and hiccups.[4]

Recently, α2-agonists have emerged as alternatives for premedication in children. Dexmedetomidine is a centrally acting selective α2-agonist, which has an anxiolytic and sedative effect and is devoid of respiratory depression.[5] Few preliminary studies suggest that dexmedetomidine shows promise as a premedicant for children to reduce anxiety and potentially reduce the occurrence and/or severity of emergence delirium.[6]

We conducted a prospective, randomized clinical trial to compare characteristics of oral dexmedetomidine and oral midazolam as premedication in children. Effects of premedication were assessed with regard to preoperative sedation and anxiolysis, the response at parental separation, quality of mask acceptance and postoperative agitation.

Materials and Methods

After obtaining approval of Ethical Committee, this prospective, randomized study was carried out on 60 pediatric patients (American Society of Anesthesiologists [ASA] I and II) aged 1-7 years, undergoing elective, minor, lower abdominal surgeries under general anesthesia. Children were excluded from the study if they were hemodynamically unstable, had mental retardation or neurobehavioral disorders, were under treatment with sedatives or anticonvulsants. Patients were allocated in a randomized manner by sealed envelope method into two groups (a) Group M (midazolam, $n = 30$) and (b) Group D (dexmedetomidine $n = 30$).

An informed and written consent was obtained from the parents or legal guardian during preanesthetic check-up 1 day prior to the surgery. Groups M and D were received an oral administration of 0.75 mg/kg of midazolam (up to a maximum of 15 mg) and 4 μg/kg of dexmedetomidine, respectively mixed with apple juice to make a final volume of 3-5 ml, in the preoperative holding area 40 min prior to anesthesia induction. An injectable preservative-free 5 mg/ml preparation of midazolam was used thus limiting the total volume administered and the IV formulation of dexmedetomidine (100 μg/ml) was given orally in its undiluted form. All study drugs were prepared by an independent investigator not involved in the observation or administration of anesthesia for the children. Observers and attending anesthesiologists were blinded to the study drug given. The child's response to drug administration was recorded. All children who refused to take the premedication or spat it out were excluded from the study protocol.

Sedation status was assessed before the drug administration and thereafter every 10 min for a maximum of 60 min after premedication. The onset of sedation was defined as the minimum time interval necessary for the child to become drowsy or asleep. Peak sedative effect was defined as the time interval from drug administration to reach the maximum level of sedation. The level of sedation was assessed by using a 4-point scale: 1 = anxious, depressed/agitated/crying, 2 = awake, calm, quiet, 3 = drowsy, responds to verbal commands/gentle stimulation, 4 = asleep. When a sedation score of >1 was reached, the child was transferred to the induction room. If no satisfactory sedation level was achieved for parental separation after the maximum time interval of 60 min, anesthesia induction was still performed. The response of the child at parental separation was recorded. It was graded as 1 = crying, cannot be reassured, 2 = awake, anxious, can be easily reassured, 3 = good separation, awake, calm, 4 = asleep.

After placement of routine monitoring (electrocardiogram, pulse oximetry, capnogram, and noninvasive blood pressure), anesthesia was initiated with sevoflurane 8% in oxygen-nitrous oxide mixture via a face mask. If the child came to the induction room already asleep, a steal induction was performed. Mask acceptance was assessed using a 5-point scale: 1 = combative, crying, 2 = moderate fear of mask, not easily calmed, 3 = cooperative with reassurance, 4 = calm, cooperative, and 5 = asleep, steal induction. Mask induction scores of 1 and 2 were considered unsatisfactory while a score of 3-5 was regarded as a successful response to premedication.

After the establishment of IV access, glycopyrrolate 5 μg/kg and fentanyl 2 μg/kg were injected. The airway was maintained with a facemask or laryngeal mask airway throughout the surgery. Anesthesia was maintained with sevoflurane in a 40-60% mixture of oxygen-nitrous oxide and analgesia was provided by caudal neuraxial block. At the end of the surgery as soon as a patent airway was maintained, the child was placed in the recovery position and allowed to wake up naturally in the postanesthesia care unit (PACU).

In the PACU, agitation was assessed as 1 = agitated, crying, 2 = crying, but easily consoled, and 3 = calm. Any episode of hypoxemia (SpO_2 <90%) or any other adverse hemodynamic events were recorded.

Statistical analysis

All values were reported as mean ± standard deviation (SD). Data analysis for numerical data was performed using unpaired Student's *t*-test to detect differences between the groups. Data analysis for categorical data was performed by Chi-squared test to detect differences in the scores. $P < 0.05$ was considered statistically significant.

Results

A total of 60 pediatric patients were enrolled in the study, with 30 children in each group. The two groups were similar with respect to age, gender, weight and ASA physical status [Table 1]. None of the children who accepted the premedication spat it out.

All children in both groups were reached the desired level of sedation prior to induction. However, the onset of sedation was 18.90 ± 3.68 min in Group M and 30.50 ± 4.44 min in Group D. This difference was statistically significant ($P < 0.05$). Peak sedative effect was achieved at 23.4 ± 4.92 min for midazolam and at 40.3 ± 3.93 min for dexmedetomidine ($P < 0.05$). The cumulative number of children with a sedation score of ≥2 at different time intervals is depicted in Table 2.

There were no significant differences in response at parental separation and quality of mask acceptance between the two groups ($P > 0.05$). The induction scores were comparable between the two groups ($P > 0.05$). In the PACU, children in Group D showed significantly lower agitation scores compared to Group M [Figure 1].

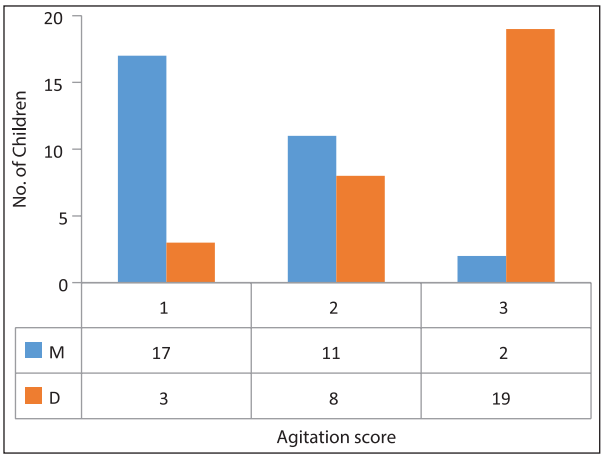

Figure 1: Postoperative agitation scores

Table 1: Demographic data

	Group M	Group D
Age (years)	2.9±1.21	3.03±1.16
Gender: Male/female	15/15	13/17
Weight (kg)	11.9±1.32	12.2±1.15
ASA status: I/II	28/2	29/1

ASA: American Society of Anesthesiologists

Table 2: Preoperative sedation; midazolam compared with dexmedetomidine

Time interval since oral premedication (min)	Group M	Group D
10	2 (6.66)	0
20	18 (59.94)	1 (3.33)
30	8 (26.64)	12 (39.96)
40	2 (6.66)	14 (46.62)
50	0	3 (9.99)
Onset of sedation (min)	18.9±3.68	30.5±4.44*
Peak sedative effect (min)	23.4±4.92	40.3±3.93*

Data are reported as a number of patients (frequency %) with a sedation score of ≥2; The onset of sedation and peak sedative effects are reported as mean ± SD; *$P < 0.05$ between groups; SD: Standard deviation

Discussion

Premedication is often required in children to lessen the adverse psychological effects of hospitalization, operative procedure and parental separation. An ideal premedicant should provide anxiolysis and sedation so as to allow a smooth anesthesia induction. It should be free from side effects such as respiratory depression, hemodynamic disturbances and emergence delirium.

Oral midazolam is the commonly used drug for premedication in pediatric anesthesia and has shown to be more effective in allaying child's anxiety than the parental presence.[7] The combination of the sedative and anxiolytic characteristics is believed to create a calming effect which makes children less anxious when they are separated from their parents and during mask placement.[8] It facilitates gamma amino butyric acid receptor-mediated chloride conductance, which has an inhibitory effect on neurons in the cerebral cortex. The dose of 0.75 mg/kg of injectable midazolam given orally as premedication is acceptable, effective and safe.[9]

Recently, α2-receptor agonists such as dexmedetomidine have also been found to be useful for premedication in children.[10-12] These drugs act on central α2-receptors located at the locus ceruleus causing inhibition of release of noradrenaline and create electroencephalogram activity similar to normal sleep. This results in anxiolytic effects, sedation and analgesia without respiratory depression.[13] In one study Mountain *et al*. postulated that 4 μg/kg of oral dexmedetomidine resulted in no adverse events, including the

two most common reported side effects of hypotension and bradycardia. In fact, there were no differences between the midazolam and dexmedetomidine groups in hemodynamic stability or oxygenation prior to, during or after surgery.[6]

Following oral administration midazolam is completely and rapidly absorbed. Maximum plasma levels are reached within 30 min. The amount of conjugated alpha-hydroxy metabolite excreted in the urine after oral and IV is practically constant. The oral bioavailability ranged from 31% to 72%.[14] After oral administration, the maximum dexmedetomidine concentration in serum was achieved in 2.2 ± 0.5 h after a lag time of 0.6 ± 0.3 h. Bioavailability of dexmedetomidine after oral administration is 16% as compared to 82% for buccal preparations probably due to extensive first pass metabolism.[15] This would explain the basis for slow onset of action of oral dexmedetomidine in comparison to oral midazolam. Our study results confirm that onset of sedation and peak sedative effect was significantly slower after oral dexmedetomidine compared with oral midazolam. Oral dexmedetomidine needs to be administrated at least 40 min prior to induction to achieve optimum sedation whereas satisfactory sedation can be achieved 20 min after ingestion of oral midazolam as evident from previous studies.[16,17] However, there are obvious disadvantages to use a premedicant with a long onset time especially in busy surgical centers.

The occurrence of emergence agitation (EA) in children after sevoflurane anesthesia is common, with a reported incidence up to 80%. The etiology for EA is not fully elucidated, but possible risk factors include intrinsic characteristics of an anesthetic, rapid emergence from anesthesia, postoperative pain, preschool age, preoperative anxiety and child temperament. Although the severity of agitation varies, it often requires additional nursing care as well as treatment with analgesics or sedatives, which may delay discharge from hospital.[18] We observed a lower incidence of EA in children premedicated with dexmedetomidine. These results are consistent with previous studies as shown by the effective use of either single dose 0.3 μg/kg or continuous perioperative infusion 0.2 μg/kg/h of IV dexmedetomidine for reduction of postoperative agitation in children treated with sevoflurane.[11,19] However, children premedicated with midazolam had a higher incidence of EA consistent with few published data.[20,21]

Limitations of the study include (1) as oral formulations of midazolam and dexmedetomidine were not available, IV preparations of drugs were used, (2) uptake and bioavailability of drugs varies markedly among the study population depending on gastrointestinal and metabolic constitutions of the individual and (3) there are no clinical studies establishing the safety and efficacy of dexmedetomidine in children, however, preliminary case studies discussing the use of dexmedetomidine in children have been published.

Conclusion

In this study, premedication with oral dexmedetomidine produced equally effective preoperative sedation and a better recovery from anesthesia in children in comparison to oral midazolam.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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