A comparison of oral dexmedetomidine and oral midazolam as premedicants in children

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Abstract

Background and Aim: Midazolam has been the most popular oral premedicant in children despite its side effects. Dexmedetomidine with its favorable clinical profile is a suitable alternative, but with limited research. The aim of this study was to compare the effectiveness of dexmedetomidine and midazolam as oral premedicants in children.

Material and Methods: Eighty children of the American Society of Anesthesiologist physical status I scheduled for elective herniotomy were included in this prospective randomized double-blind study. Patients were randomly assigned to receive either dexmedetomidine 4 µg/kg (Group A, n = 40) or midazolam 0.5 mg/kg (Group B, n = 40) orally 40 min before induction. Pre-operative sedation, response to parental separation and venepuncture, emergence agitation, recovery nurse satisfaction, and side effects were compared between the two groups. Quantitative data were compared using unpaired Student’s t-test and categorical variables with Chi-square test.

Results: Pre-operative sedation and response to parental separation and venepuncture were similar between the two groups. Group A had a significantly lower incidence and severity of emergence agitation (P = 0.000). Recovery nurse satisfaction was significantly higher in Group A (P = 0.002). However, incidence of hypotension and bradycardia was found to be more in Group A (P = 0.04).

Conclusion: Premedication with oral dexmedetomidine is as effective as oral midazolam in providing sedation and anxiolysis in children. Dexmedetomidine in addition reduces the incidence and severity of emergence agitation.

Keywords: Dexmedetomidine, midazolam, oral premedication, pediatric

Introduction

Apprehensive, crying, and uncooperative children are not rare sights in operation theaters. Incidence of preoperative anxiety is about 60%–70% in pediatric population.[1] This is associated with an increased risk of negative effects such as difficult induction, postoperative agitation, and increased postoperative pain.[2] Delayed psychological and behavioral changes such as night-time crying, enuresis, separation anxiety, anorexia, and temper tantrums can also result from excessive perioperative anxiety.[2] Sedative premedication is an effective method to allay anxiety and provide a calm and cooperative child.[3] Being atraumatic, oral premedication is easily accepted by children. Midazolam, a benzodiazepine, is one of the commonest sedative premedication prescribed.[4] Although midazolam has a strong record of safety and efficacy, it has no analgesic effect. Several untoward effects such as restlessness, paradoxical reaction, respiratory depression, and negative postoperative behavior have been described with midazolam.[2,5] So the search for a better alternative is always on.

Dexmedetomidine is a highly specific α2 agonist with sedative, analgesic, and anxiolytic properties and minimal respiratory depression.[2,6,7] Use of dexmedetomidine in...
pediatric anesthesia is increasing because of its favorable safety profile. However, there is limited literature regarding its use as an oral premedicant in children although preliminary studies have shown promising results.\[^2,^8\] We hypothesized that dexmedetomidine is a suitable alternative to midazolam for oral premedication in children.

This prospective randomized double-blind study was conducted to compare the efficacy of dexmedetomidine and midazolam as oral premedicants in children undergoing herniotomy. The effects of premedication were assessed with regard to preoperative sedation, response to parental separation, response to venepuncture, and the incidence and severity of postoperative emergence agitation (EA). Secondary outcomes studied included hemodynamic stability and the incidence of the adverse effects of the drugs.

**Material and Methods**

After the approval from the Institutional Ethics Committee and written informed consent from a parent, this prospective randomized double-blind study (CTRI/2018/04/013062) was conducted in 80 children of either sex, age 1–6 years, belonging to the American Society of Anesthesiologist (ASA) physical status I, posted for herniotomy under general anesthesia. Patients with a known allergy to the study drugs, mental retardation, or neurobehavioral problems were excluded from the study. In a previous study, 21.9% patients in the midazolam group and 75% in the dexmedetomidine group had satisfactory sedation scores at separation.\[^9\] Targeting the same difference, with a 95% confidence level and 80% power, the minimum sample size was calculated as 17 in each group. We included 40 patients in each group in our study. The children were randomized using block randomization into two groups of 40 each. Blocks of two and four were used by the allocator, and the principal investigator was unaware of the block sizes. Group A received oral dexmedetomidine 4 mg/kg and Group B received oral midazolam 0.5 mg/kg, 40 min before induction.

Before giving premedication, heart rate (HR), systolic blood pressure (SBP), and oxygen saturation (SpO\(_2\)) were recorded. The emotional status of the children was assessed and graded using a 4-point scale (Grade 1: Calm; Grade 2: Apprehensive, not smiling, tentative behavior, withdrawn; Grade 3: Crying; Grade 4: Thrashing, resisting).\[^10\]

An injectable preservative-free preparation of the study drugs mixed in 5 mL of honey was administered by a nurse not involved in the observation or anesthetic care, in the preoperative holding area in the presence of a parent. All children who refused to take the premedication or spat it out or vomited were excluded from the study protocol. The patient/parent, observer, and the attending anesthesiologist were blinded to the study drug given.

The level of sedation was assessed 30 min after premedication using a 5-point grading system (Grade 1: Agitated; Grade 2: Oriented, calm, and cooperative; Grade 3: Drowsy, responding to verbal command; Grade 4: Not responding to verbal command, but to painful stimuli; Grade 5: Not responding to painful stimuli).\[^11\] Grades 1 and 2 were grouped as poor sedation, Grades 3 and 4 were considered as good sedation, and Grade 5 was taken as unresponsive.

Children were separated from the parent 40 min after premedication, and the behavior of the child on separation from the parents was assessed and graded using parental separation anxiety scale (PSAS):\[^12\] Grade 1: Easy separation; Grade 2: Whimpers, but is easily reassured, not cling; Grade 3: Cries and cannot be easily reassured, but not clinging; Grade 4: Crying and clinging to parents. A PSAS score of 1 and 2 was considered as acceptable separation from parents and Grades 3 and 4 were taken as not acceptable.

The child was taken inside the operating room and the response to venepuncture was graded using an empirical 4-point intravenous (IV) acceptability score. Grade 1: Asleep, not responsive to painful stimulus and IV cannulation; Grade 2: Calm, awake, but not crying, no withdrawal to painful stimulation or IV cannulation; Grade 3: Withdrawal to painful stimulus, but allows for IV cannulation; Grade 4: Crying and uncooperative, not able to start IV line. Grades 1 and 2 were considered as ideal and Grade 3 as acceptable condition for venepuncture. Grade 4 was taken as not acceptable.

After establishing standard monitoring, IV induction was done with thiopentone sodium and maintained on spontaneous ventilation through a face mask with 66% nitrous oxide in oxygen and a titrated concentration of isoflurane. All patients received fentanyl 1 µg/kg followed by caudal epidural block with 1 mL/kg of 0.25% bupivacaine. Throughout the procedure and in recovery, HR, SBP, and SpO\(_2\) were monitored. Side effects of drugs such as nausea, vomiting, respiratory depression, bradycardia, and hypotension were looked for. Bradycardia is defined by HR <80 bpm in 1–3 years and <70 bpm in 4–6 years, and hypotension by SBP <70 mmHg in 1–3 years and <80 mmHg in 4–6 years.\[^13\]

In the post anesthesia care unit (PACU), the occurrence and severity of EA were measured using Pediatric Anesthesia Emergence Delirium Scale (PAEDS).\[^14\] score at the time when the child was fully awake or at the pinnacle of
agitation. A score greater than 10 was taken as the presence of EA [Table 1].

Satisfaction of the recovery nurse who was blinded to the study groups was recorded using a 5-point scale (1 = very dissatisfied, 2 = somewhat dissatisfied, 3 = neutral, 4 = somewhat satisfied, 5 = very satisfied) before the patient was discharged to postoperative ward. [15]

Statistical analysis
The numerical data were compared using unpaired Student’s t-test and reported as mean ± standard deviation. The categorical variables were compared by Chi-square test and reported as median with interquartile range (IQR) and also numbers and percentages. A P value of 0.05 or less was set for assessing statistical significance. Analysis was done using PASW statistics for Windows, Version 18 (SPSS Inc., IBM Corp., Chicago, IL, USA; 2010).

Results
Eighty children scheduled for inguinal herniotomy were enrolled in the study and assigned to Group A (n = 40) and Group B (n = 40). There was no statistically significant difference among the groups with respect to demographic characteristics and the duration of surgery [Table 2]. All patients included in the study were ASA class I. Emotional status assessed before premedication was comparable in both groups (P = 0.514) [Table 2].

The sedation score after 30 min of premedication, the parental separation anxiety score, and IV acceptability score were comparable between the two groups [Table 3]. Four patients in Group A developed bradycardia and hypotension, but none in Group B had these side effects (P = 0.04).

EA was significantly less in Group A than Group B (P = 0.000) [Figure 1]. Higher Nurse Satisfaction Scores were seen in Group A (P = 0.002) [Figure 2].

Discussion
Children aged 1–5 years are at maximum risk of experiencing severe preoperative anxiety and have highest incidence of EA. [14,16] This not only causes suffering in children but also negatively affects their recovery and necessitates utilization of additional resources too. The rational use of premedication makes the patient’s surgical experience better, safer, and more pleasant without increasing the cost of health care. [13,16] Midazolam is considered as the gold standard in premedication by many. [2] It is an effective sedative, anxiolytic with a fast onset of action and provides anterograde amnesia. But many authors consider it suboptimal for premedication in children. They advocate the use of α2 agonists with additional analgesic effect in children. [2] α2 agonists produce sedation that is similar to normal sleep and do not affect memory. [2]
Our study involved 80 children in the age group of 1–6 years with a high risk of preoperative anxiety. The two groups had a comparable demographic profile in addition to a similar baseline emotional status and duration of surgery. Dexmedetomidine was used in a dose of 4 µg/kg to circumvent poor bioavailability after oral administration as recommended by Zub et al. and Mountain et al. This also explains the delay in the onset of action of dexmedetomidine necessitating it to be administered at least 40 min before induction as evident from previous studies. The parenteral preparation of dexmedetomidine is colorless, odorless, and tasteless unlike midazolam which is bitter to taste. However, none of our children spat out the drug mixed in honey.

In our study, the sedation score at 30 min was similar in both the groups. About 45% of children in the dexmedetomidine group and 57.5% in the midazolam group were very well sedated at 30 min. This is contrary to the findings of Kumari and colleagues who found faster onset and higher mean sedation scores at 30, 45, and 60 min with oral midazolam. Jannu et al. also confirmed an early onset of sedation and a faster achievement of peak sedative effect in the midazolam group compared with oral dexmedetomidine. Although we did not study the onset of sedation, both the drugs were found to be equally effective in producing sedation at 30 min. No patient in either group became unresponsive. We found satisfactory sedation with both the drugs as early as 30 min, although a long onset time was one of the disadvantages quoted in many studies against dexmedetomidine.

Aware IV placement, parental separation, and induction are the time points of maximum anxiety in children during the preoperative period. We observed no significant difference in the parental separation anxiety score at 40 min between the two groups akin to Jannu et al. Acceptable parental separation was found in 92.5% and 95% of children belonging to dexmedetomidine and midazolam groups, respectively (P = 0.644). In contrast to our findings, Kumari and coworkers found oral midazolam to be superior to dexmedetomidine in providing easy separation from parents. Mountain et al., however, could not find any significant difference with regard to acceptable behavior at parent separation or mask acceptance in children receiving these two premedicants 30 min before induction.

Children in both the study groups had similar IV acceptability scores; 17.5% children in dexmedetomidine group and 20% in midazolam group resisted venepuncture. Zub and colleagues reported easy IV cannulation in children with neurobehavioral disorders premedicated with oral dexmedetomidine in whom previous attempts at sedation had failed. Prabhu and Mehandale observed three times better mask acceptance and induction environment in the dexmedetomidine group unlike findings of Kumari et al.

EA is a common problem encountered in pediatric anesthesia (20%–30%). An agitated child disrupts the controlled environment of PACU. It not only inflicts harm to the patient but also puts a strain on healthcare personnel and increases resource utilization. Postoperative pain is an important aggravating and confounding factor for EA. We ensured good pain relief with fentanyl and caudal epidural block. PAEDS score was used to identify and assess severity of EA. PAEDS score was significantly lower in the dexmedetomidine group (P = 0.000). Prabhu and Mehandale reported a reduction in the incidence and severity of EA with oral dexmedetomidine premedication compared with oral midazolam; similar to Jannu et al. Mountain et al., however, could not demonstrate any advantage of dexmedetomidine over midazolam. Zhu et al. undertook a meta-analysis involving 20 randomized controlled trials of dexmedetomidine on EA and found that use of dexmedetomidine reduced the occurrence of EA when compared with placebo regardless of the route of administration or surgical procedure, but prolonged discharge from recovery. They did not find significant difference in the incidence of EA between patients receiving dexmedetomidine, fentanyl, or midazolam, but cautioned against that interpretation as only three studies were included. Recovery nurse satisfaction was found to be better in dexmedetomidine group (P = 0.002).

In our study, the incidence of bradycardia and hypotension was significantly more in the dexmedetomidine group, possibly an exaggeration of its physiological effects; but they were amenable to treatment. Prabhu and Mehandale observed consistently lower HR in dexmedetomidine group which required treatment with atropine in 4 among 45 subjects. They also reported lower mean arterial pressure which was not clinically significant in patients receiving oral

Figure 2: Nurse Satisfaction Score

1. Sajid, et al.: Oral dexmedetomidine vs oral midazolam as premedicants in children
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Oral dexmedetomidine is as effective as oral midazolam in providing sedation and anxiolysis in the pediatric age group. In addition, dexmedetomidine reduced the occurrence and severity of EA making recovery more pleasant.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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