Dexmedetomidine as a Pediatric Anesthetic Premedication to Reduce Anxiety and to Deter Emergence Delirium

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Presurgery anxiety in children may result in preoperative and postoperative complications. Emergence delirium (ED) is a mental disturbance common in children during recovery from general anesthesia. This study investigated the role of preoperative dexmedetomidine on parental separation anxiety and acceptance of wearing an anesthesia mask, and its effectiveness in reducing the incidence and severity of ED. A double-blind study was conducted in 41 children, aged 1 to 6 years, undergoing dental restoration and/or extractions. Subjects received 4 µg/kg of dexmedetomidine or 0.5 mg/kg of midazolam orally prior to anesthesia induction. Subjects’ anxiety over parental separation, acceptance of anesthesia masks, and presence and severity of ED were evaluated.

There were no statistically significant differences in parental separation anxiety or mask acceptance between the 2 groups. There were also no significant differences in ED occurrence. In this study, dexmedetomidine produced no common side effects (blood pressure and heart rate fluctuation), which may indicate that oral administration with a 16% bioavailability versus 82% in buccal preparations results in fewer side effects but requires higher dosing to gain therapeutic effects. Future studies should examine the use of higher doses of oral dexmedetomidine in reducing presurgical anxiety and postsurgical ED.

Keywords: Dexmedetomidine, emergence delirium, oral premedication.

Anxiety associated with operative procedures is distressful for children and families and has been reported to be as high as 60%. Preoperative anxiety, which is often displayed in several ways, including difficulty separating from parents or difficulty accepting an anesthesia mask, can lead to negative responses postoperatively. Kain et al. demonstrated that 54% of their subjects had negative behavior patterns at 2 weeks and 20% continued these patterns up to 6 months. In a follow-up study, Kain et al. found that children with preoperative anxiety had a higher excitement score in the postanesthesia care unit (PACU) and negative behaviors at home, such as bad dreams, waking up crying, separation anxiety, and temper tantrums. Furthermore, Kain demonstrated that preoperative anxiety may be linked to emergence delirium (ED), which is a postoperative negative behavior that may include symptoms such as combative movements, thrashing, excitability, disorientation, and inconsolable crying.

Patients experiencing ED, commonly interchanged with emergence agitation or postanesthetic excitement, frequently require temporary restraint for longer than 3 minutes. Studies have reported that the incidence of ED in children ranges from 20% to 30%. During ED, children risk injuring themselves by dislodging intravenous tubing or drains, losing a skin graft, bleeding from the operative site, increasing their pain, and injuring their caregivers. The child’s behavior can be disruptive to the PACU and often requires increased nursing supervision, which strains nursing resources. Several factors influence the severity and occurrence of ED, such as receiving sevoflurane, perioperative medications, and pain. Sevoflurane is the agent often used in pediatric anesthesia because of its safety and efficacy for mask induction. Many studies have documented increased occurrence of ED after the use of sevoflurane despite the absence of pain in children who had regional blocks. There are, however, some reports of both isoflurane and desflurane having a similar incidence of ED in pediatrics.

The most commonly used medication to reduce anxiety in the pediatric population preoperatively is midazolam. It has been shown to be more effective than parental presence or a placebo. Dexmedetomidine, an α2 adrenergic agonist that provides sedation as well as analgesia, has been shown to reduce ED when given intravenously during the intraoperative period. It has been administered preoperatively to reduce ED and...
postoperative negative behaviors such as aggression.\(^\text{18}\) According to Isik and colleagues,\(^\text{19}\) dexmedetomidine decreases ED after sevoflurane anesthesia in the nonsurgical pediatric patient as well. Because of the relationship between preanxiety and postoperative responses, this study examined the effects of oral dexmedetomidine and midazolam in reducing anxiety and ED in children aged 1 to 6 years receiving dental restoration.

- **Background.** In 2006, Schmidt et al\(^\text{20}\) concluded that when comparing midazolam and dexmedetomidine, levels of preoperative anxiety in both groups were similar. However, they also found that the subjects given dexmedetomidine had less postoperative pain than those given midazolam. Shukry et al\(^\text{17}\) studied the efficacy of continuous intravenous administration of dexmedetomidine in decreasing ED in 50 children aged 1 to 10 years who were undergoing sevoflurane-based general anesthesia. This double-blind study randomly assigned children to receive either dexmedetomidine or placebo (normal saline) as a continuous intravenous infusion that was initiated after securing the airway. The total infusion averaged 2 to 5 μg/kg and was maintained for 15 minutes following the admission to the PACU, where a blinded observer evaluated ED scores. The authors’ findings suggest that the incidence of ED was significantly higher (61%) in the placebo group (P = .036) compared with the dexmedetomidine group (26%).

Zub et al\(^\text{18}\) investigated the use of oral dexmedetomidine in 13 patients who received dexmedetomidine in a range between 1.0 and 4.2 μg/kg orally. Their data suggested that intravenous preparations of dexmedetomidine may be an effective oral premedicant. Many children undergo anesthesia without intravenous access, and therefore, an oral route of premedication is desirable. The intravenous preparation of dexmedetomidine was used orally, and all patients tolerated the medication with no complaints about palatability. Four subjects received dexmedetomidine as an anesthetic premedication, with only 1 patient, who received 1 μg/kg and who was not sedated sufficiently upon parental separation and acceptance of mask. Of the 9 patients receiving oral dexmedetomidine for procedural sedation, only 1 had moderate distress when the intravenous cannula was inserted. Ray and Tobias\(^\text{21}\) continued the work of Zub et al by altering the recommended dosing of oral dexmedetomidine to 2.9 to 4.4 μg/kg for sedation prior to intravenous catheter insertion in children with autism, pervasive developmental disorders, and seizure disorders. The results indicated that 2.9 to 4.4 μg/kg of orally administered dexmedetomidine was an effective premedicant in the pediatric population.

These studies suggest that dexmedetomidine shows promise as a premedicant for children to reduce anxiety and potentially reduce the occurrence and/or severity of ED. Studies conducted on dexmedetomidine use in children have been limited and, in general, restricted to intravenous route of administration, which limits its use. Reducing preoperative anxiety may reduce aggressive behaviors, such as ED in the postoperative stage.

The research questions in this study were twofold. First, is oral dexmedetomidine as effective as midazolam in reducing anxiety, as measured by a tool assessing separation from the parent and an acceptance of mask scale, prior to dental restoration surgery? Second, does oral dexmedetomidine reduce the incidence and severity of ED in children aged 1 to 6 years undergoing dental restoration surgery?

**Methods**

This study used a randomized, prospective, double-blinded design. First the study was approved by both an affiliated university and the hospital institutional review board. Children were recruited to participate in this study by receiving a packet of information from 4 participating dentists when their dental restoration procedure was scheduled. Families who received information about the study were contacted by phone to determine their interest in participating in the study and to answer questions about the study. Once the child and family arrived at the hospital the day of the procedure, a research team member obtained consent from those interested in participating in the study. The study sample included 41 children aged 1 to 6 years undergoing dental restoration and possible tooth extraction. Exclusion criteria were as follows: (1) known allergies to midazolam and/or dexmedetomidine; (2) developmental delay or mental retardation, as reported by parents; (3) history of ED; (4) ASA classification greater than II; or (5) any known previous reactions to anesthesia. Subjects were randomly assigned to 1 of 2 groups; the experimental group received 4 μg/kg of oral dexmedetomidine, and the control group received 0.5 mg/kg of oral midazolam. According to the manufacturer, the most common side effects of dexmedetomidine include nausea and vomiting, bradycardia, hypotension, and fever. According to the manufacturer of midazolam, the most common side effects include amnesia, headache, drowsiness, confusion, blood pressure changes, nausea and vomiting, and coughing.

The dexmedetomidine dosing was selected based on the first study by Zub et al,\(^\text{18}\) who administered intravenously prepared dexmedetomidine orally. At the time of our study, the study by Ray and Tobias\(^\text{21}\) had not been published. The midazolam dosing in this study followed standard hospital protocol. The hospital pharmacy staff kept a log of the subjects and prepared the medications based on study protocol. All other staff and members of the research team were blinded to the group assignments and the medication administered. To prevent staff from identifying study drugs based on the volume or color of the drug in the syringes, both drugs were packaged so that the volume of medication in the prepared syringes...
was the same regardless of the study drug administered. Both midazolam and dexmedetomidine were prepared with cherry-flavored syrup.

- **Instruments.** Three instruments were used in this study. The Parental Separation Anxiety Scale (PSAS) is a 4-point scale as follows: 1 = easy separation; 2 = whimpers, but is easily reassured, not clinging; 3 = cries and cannot be easily reassured, but not clinging to parents; and 4 = crying and clinging to parents. This instrument was used despite the tool not having published psychometric data, because the PSAS has been used in a previous study and no other similar tool exists. Weldon and colleagues recommend the following scoring criteria, which were used in this study: a PSAS score of 1 or 2 was classified as an acceptable separation, whereas scores of 3 or 4 were considered difficult separations from the parents.

The subject’s ability to accept the anesthesia mask was measured using the Mask Acceptance Scale (MAS). The MAS scale is a 4-point Likert scale: 1 = excellent (unafraid, cooperative, accepts mask readily), 2 = good (slight fear of mask, easily reassured), 3 = fair (moderate fear of mask, not calmed with reassurance), and 4 = poor (terrified, crying, or combative). Subjects who received a score of 1 or 2 were considered “satisfactory” acceptance of the anesthesia mask; scores of 3 or 4 were considered “unsatisfactory.” This tool was used by both Shukry and Weldon et al, although no psychometric data are available on this tool.

The occurrence and severity of ED were measured using the Pediatric Anesthesia Emergence Delirium Scale (PAEDS). According to Sikich and Lerman, who developed the PAEDS, the presence of ED is evaluated based on 5 criteria: (1) makes eye contact with caregiver, (2) actions are purposeful, (3) aware of his or her surroundings, (4) restless, and (5) inconsolable. Of 20 possible points, a score greater than 10 indicated the presence of the anesthesia mask; scores of 3 or 4 were considered “unsatisfactory.” In this study, the PAEDS had an internal consistency reliability of \( \alpha = .892 \). In addition to the scale score, several other items were recorded to detect any relationships that may exist. These items included demographic data, vital signs, time of medication administration, operative procedures, anesthesia delivery time, extubation time, time of admission to postsurgical unit, and opioid administration.

To ensure interrater reliability of rating scales for each tool used, all research team members were trained in data collection and how to score each tool. The training was performed by 1 of the principal investigators (B.W.M.) and included video simulation with 7 case studies and practice scoring the tools based on the case studies. Differences in scoring during training were discussed. To ensure consistency of scoring during data collection, 2 research team members independently scored the 20th and 40th subject enrolled. No differences in scoring occurred. All data were entered into a secure electronic database and recorded on a hard copy. Data in both sources were compared and verified for each subject, to identify and correct recording errors.

- **Procedures.** After consent was obtained, demographic data were collected from parents and the medical chart. The designated study medication was then prepared by the pharmacists and administered by the staff nurse on call from the operating room, which was 30 minutes prior to transport to the operating room. Pulse oximetry and blood pressure monitoring were recorded every 15 minutes until the patient left the outpatient unit. The research team member accompanied the child to surgery, and the PSAS was scored at this time, approximately 30 minutes after medication administration. The research assistant then accompanied the patient to the operating room, reviewed study anesthesia protocol with the Certified Registered Nurse Anesthetist, and calculated the patient’s MAS score.

The study anesthesia protocol consisted of the following:

1. Mask induction was performed with sevoflurane, oxygen and nitrous oxide.
2. Induction anesthesia was changed over to isoflurane for maintenance as soon as possible.
3. Spontaneous ventilation was maintained if possible.
4. If ventilatory support was required, muscle relaxants were avoided if possible.
5. Drugs with anticholinergic properties such as atropine, glycopyrrolate (Robinul), meperidine hydrochloride (Demerol), and pancuronium bromide (Pavulon) were avoided to help prevent any confusion between ED and anticholinergic toxicity.
6. In retrospect, no subjects in the study needed to receive any anticholinergic agents during the study. Anesthetic was to be maintained with isoflurane, oxygen, and nitrous oxide.
7. The patient was to receive ondansetron hydrochloride (Zofran, 0.2 mg/kg) and dexamethasone (Decadron, 0.25 mg/kg) as soon as convenient at the beginning of the case for antiemesis.
8. Fentanyl (1 to 2 \( \mu \)g/kg) was used for narcotic analgesia.
9. The oral surgeon was asked to provide local anesthetic blocks for all root canals and extractions, and such data were recorded on the anesthetic record.
10. All the preceding steps were to be abandoned if needed for the safety of the patient, and study personnel were to be notified.

Following surgery, the patient was taken to the PACU, where the patient was monitored according to unit protocol. Subjects were observed by the research team member during the entire PACU stay or up to 1 hour even if discharged to the outpatient surgery unit. A PAEDS score was determined at either the point when the subject was...
fully aroused or at the pinnacle of the ED episode.

Data were stored on a password-protected database accessed from handheld computers with a secure wireless Internet connection. The handheld computers were stored in a locked file cabinet in the office of 1 of the authors (L.S.). To prevent permanent loss of data, the online database was exported to a statistical software package (SPSS 15.0, SPSS Inc, Chicago, Illinois) on a weekly basis. The SPSS dataset was stored on a secure server. Data were downloaded to a computer disk for permanent storage at the completion of the study and stored in a locked file cabinet.

- **Analysis.** A Pearson $\chi^2$ analysis was performed to determine differences between the control and experimental groups with respect to separation anxiety and acceptance of the anesthesia mask. An independent sample t test was used to determine differences between the occurrence and severity of ED in the experimental and control groups. The level of significance was set at $P = .05$.

**Results**

Of the 41 subjects recruited (between May 2006 and June 2007), 21 (51%) were males and 20 (49%) were females. The mean age was 4 years, with more 3- and 6-year-old subjects than any other age group. Twenty-seven subjects (65%) were white, 9 (22%) were African American, and 5 (12%) were of Hispanic origin. None of the subjects reported previous complications such as postoperative nausea and vomiting, malignant hyperthermia, or difficult intubations related to surgery or anesthesia. Blood pressure and oxygen saturation levels for each subject were also collected at baseline and every 5 minutes for the duration of the surgical procedure. To determine differences between blood pressure levels in the experimental and control groups, the mean blood pressure was calculated and compared between the 2 groups. There was no statistically significant difference between mean blood pressure values in the 2 groups ($t = 0.852, P = .399$). The 95% confidence interval for the difference in mean blood pressure was −7.68 to 3.13. There was no statistical difference between mean pulse oximetry values in the 2 groups ($t = 0.459, P = .649$). The 95% confidence interval for the mean difference in pulse oximetry was −0.746 to 0.471.

To determine difficulties with parent separation, the categories in the scale were collapsed. A score of 1 and 2 reflected no difficulties, and scores 3 and 4 on the parent separation scale were collapsed into 1 category representing difficulties separating from parents (Table 1). There were no statistically significant differences ($\chi^2 = 0.478, P = .489$) in separation from parents between the experimental and control groups. Acceptance of the anesthesia mask was measured (Table 2), and again, there were no statistically significant differences ($\chi^2 = 0.602, P = .438$) between the control and experimental group. The effects of dexmedetomidine versus midazolam on the severity and occurrence of ED were measured using the PAEDS tool. Of the 41 subjects, 8 children (20%) experienced ED; 3 of the 8 were in the experimental (dexmedetomidine) group and 5 were in the control (midazolam) group. The mean scores (± SD) on the PAEDS were 7.42 (SD, 5.210) in the midazolam group and 5.62 (SD, 5.861) in the dexmedetomidine group. There were no statistically significant differences between the mean PAEDS scores in the midazolam and dexmedetomidine groups ($t = 1.023, P = .313$). The 95%
improve the preoperative experience for patients and reducing preoperative anxiety is desired not only to improve the preoperative experience for patients and families but also because Kain et al.1,3,4 determined that a patient’s anxiety level influences their immediate postoperative outcomes as well as long-term outcomes after discharge. Zub et al.18 examined anesthesia records to determine the most effective anxiety-reducing anesthesia premedicant for children prior to surgical procedures. Based on their retrospective review, Zub and colleagues recommended 3 to 4 μg/kg of oral dexmedetomidine to reduce anxiety. This study used the oral dosing that Zub et al recommended, yet there were no significant differences between dexmedetomidine and midazolam in reducing anxiety as evidenced by mask acceptance scores or parental separation scores. It should be noted, however, that children receiving dexmedetomidine were less likely to experience ED.

In this limited sample size, 4 μg/kg of oral dexmedetomidine resulted in no adverse events, including the 2 most common reported side effects of hypotension and bradycardia. In fact, there were no differences between the midazolam and dexmedetomidine groups in blood pressure stability or oxygenation prior to, during, or after surgery. The absence of fluctuations in blood pressure and heart rate, which is a common side effect of dexmedetomidine, may indicate that the 4 μg/kg of oral dexmedetomidine dosing was too low to be clinically effective in reducing preoperative anxiety. However, the drug’s potential effectiveness in reducing preoperative anxiety and ED may improve with higher dosing. Of course, with an increase in dose, there may be an increase in side effects. Furthermore, this study used an oral administration of dexmedetomidine and the bioavailability in oral administration is 16% compared with 82% in buccal preparations.23 This may suggest that the more common side effects of dexmedetomidine occur with more uptake and better absorption of the medication, as would be seen in intravenous or buccal administration.

Currently, dexmedetomidine is not approved by the US Food and Drug Administration for children, and it is not available in an oral or buccal preparation. One clear advantage of using the intravenous preparation is that it lacks the bitter taste reported with midazolam, which becomes an important factor in children. It would be difficult to ask a child to hold liquid or a tablet under their tongue, but a quickly dissolving strip might deliver the medication more efficiently. With more child-friendly dexmedetomidine preparations, future studies can examine appropriate dosing and the efficacy of dexmedetomidine at reducing anxiety and ED.

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