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ORIGINAL RESEARCH

The Effect of Intranasal Dexmedetomidine on Emergence Delirium Prevention in Pediatric Ambulatory Dental Rehabilitation Under General Anesthesia: A Randomized Clinical Trial

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Purpose: Sevoflurane is the preferred anesthetic agent for induction and maintenance of ambulatory surgery due to its property of fast onset and recovery. However, it has been recognized as one of the major contributors of emergence delirium. The aim of this study was to evaluate the preventive effect of intranasal dexmedetomidine on the occurrence of emergence delirium in pediatric patients under general anesthesia with sevoflurane.

Patients and Methods: Ninety pediatric patients undergoing dental rehabilitation under sevoflurane anesthesia were enrolled in this study. The patients were divided into three groups (n=30 each in the 2 μg/kg dexmedetomidine, 1 μg/kg dexmedetomidine, and control with saline groups). The same volume (0.02mL/kg) of the mixed solution was dropped into the nasal cavity of the children 30 minutes before surgery. We used the Pediatric Anesthesia Emergence Delirium Scale (PAED) to assess the level and incidence of delirium in the post-anesthesia care unit.

Results: Compared with the control group, prophylactic use of different dosages of intranasal dexmedetomidine significantly reduces the incidence of ED and severe ED in PACU (P<0.001). Intranasal administration of 2 μg/kg dexmedetomidine was associated with a better acceptance of mask induction and a better tolerance of separation with parents.

Conclusion: Both 2 μg/kg and 1 μg/kg intranasal dexmedetomidine can achieve ED preventive effects in PACU in dental rehabilitation under general anesthesia. A dosage of 2 μg/kg is more effective in preventing severe ED and providing better mask acceptance.

Keywords: intranasal dexmedetomidine, emergence delirium, sevoflurane anesthesia, pediatric patients, dental rehabilitation

Introduction

Emergence delirium (ED) is a common complication after pediatric anesthesia, which may cause injury to the child, requiring extra nursing care, and may delay patient discharge from hospital.[1] The incidence of ED ranges from 10% to 50% but may be as high as 80%.[1] Volatile anesthetics are among the proposed contributors to ED, and sevoflurane has relatively greater propensity.[2,3] Although ED can be reversed in a short period of time after recovery from general anesthesia, additional nursing care and analgesics may be needed. ED is also associated with prolonged abnormal neurobehavioral performance after sevoflurane anesthesia.[4]

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Children's fear about dental treatment may lead to behaviour management problems for the dentist, which can be a barrier to the successful dental treatment.[5] Despite reports of an overall decrease in caries, severe decay is still a prevalent disease in early childhood, and thus the demand for treatment under general anesthesia increases.[6] Since a majority of this population cannot tolerate awake treatment in outpatient environment, general anesthesia is an important option for successful dental treatment.[7]

Sevoflurane is a volatile anesthetic widely used for induction and maintenance of ambulatory anesthesia because of its property of fast onset and recovery.[8] Dexmedetomidine is a selective α2-adrenergic agonist, which is widely used in perioperative sedation. It has pharmacologic properties including greater ability to induce arousal, anti-inflammatory and analgesic actions, lack of respiratory suppression, and improved sleep.[9] Intranasal dexmedetomidine can provide safe and satisfying sedation at parent separation. Previous studies of preoperative sedation in pediatric dental rehabilitation under general anesthesia are few.[10,11] In the present study, we aim to evaluate the preoperative use of two different doses of intranasal dexmedetomidine in the prevention of ED in children undergoing dental rehabilitation. The incidence of ED and severe ED in postanesthesia care unit (PACU) was considered as the primary outcome and MAS score and postoperative pain, as the second outcomes.

Materials and Methods

Study Design, Ethics Approval, and Consent to Participate

This research is an investigator-initiated, double-blind trial with parallel design and superiority outcomes. The protocol of the study was approved by the Ethics Committee of Shanghai Stomatological Hospital, Fudan University. Patients scheduled for dental rehabilitation under general anesthesia were enrolled. The trial was registered at chictr.org.cn (ChiCTR2100042575) before the first patient was enrolled. There were no substantive changes to the protocol after initiation of patient enrolment. Written informed consent was obtained from one of the legal guardians of the participants at outpatient clinics or during preoperative visits before surgery. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Enrollment Criteria

From February 2021 to April 2022, 92 children scheduled for full mouth dental rehabilitation under general anesthesia in ambulatory setting were chosen as the study subject. The children who need dental treatment under general anesthesia are determined by pediatric dentists and are arranged to undergo preoperative assessment at an anesthesia evaluation clinic. Patients undergoing dental treatment with ASA status I or II under general anesthesia were included in this study. All patients were between 3 and 7 years of age and were excluded from the study if they met any of the following criteria: congenital organic diseases, growth retardation, liver and kidney dysfunction, attention deficit hyperactivity disorder and autism, allergic to dexmedetomidine, and refusal from the parents.

Randomization and Blinding

In total, 90 children were randomly allocated (1:1:1 ratio) into three groups according to a computer-generated table: Group D2 to receive 2 μg kg^{-1} intranasal dexmedetomidine, Group D1 to receive 1 μg kg^{-1} intranasal dexmedetomidine, and Group C to receive intranasal saline.

All children included were fasted for 8h and deprived of clear fluids for 2h before surgery. The child entered the anesthesia preparation room 30 minutes before induction of anesthesia accompanied by one of the parents. A 1mL tuberculin syringe containing 100 μg or 50 μg dexmedetomidine was prepared for Group D2 or Group D1. A 1mL tuberculin syringe containing 0.9% saline was prepared for Group C. All the drugs for each subgroup were diluted with 0.9% saline to a final volume of 1mL. Patients in Group D2 and Group D1 received intranasal drop of dexmedetomidine, respectively, at the concentration of 100 $\mu g.mL^{-1}$ and 50 $\mu g.mL^{-1}$. Patients in Group C received intranasal drop of saline. A numbered sealed envelope was used for group allocation. Dexmedetomidine or saline was prepared by an anesthetic nurse who was not involved in data collection or patient's care. All parents, attending anesthesiologists, caring nurses and dentists involved in the study were blinded to the group assignments. The study drug was administered through two nostrils by one anesthesiologist 30 minutes prior to being transferred to the operating room. A total volume of 0.02mL/kg drug mixture is used regardless of whether drugs or normal saline is used. Vital signs including heart rate and SpO_2 were

recorded by a portable pulse oxygen saturation monitor (model: YX303, Jiangsu Yuyue Medical Equipment & Supply Co., Ltd), and respiration rate was counted by the anesthesiologist. During the stay in the anesthesia preparation room, scales including Ramsay sedation score (RSS) and pediatric separation anxiety scale (PSAS) were evaluated by the same anesthesiologist.

Anesthesia and Perioperative Care

After patients entered the operation room, electrocardiography, noninvasive arterial blood pressure (BP), pulse oximetry, and bispectral index (BIS, America, Covidien IIc Co.) were monitored. Anesthesia induction was performed using 8% sevoflurane in oxygen ($8L \cdot min^{-1}$) via a face mask. During the inhalation induction, the mask acceptance scale (MAS) was evaluated. Propofol ($1.5\ mg.kg^{-1}$), rocuronium ($0.6\ mg.kg^{-1}$) and sufentanil ($0.3\ \mu g.kg^{-1}$) were administered after intravenous line placement was achieved. Ringer's acetate (RA) was used as balanced crystalloid solutions and was infused at a rate of 5–7 $mL.kg^{-1}h^{-1}$. Nasal fiberoptic intubation technique was used in all the patients to secure safe and effective airway control. Dentists may use regional anesthetic (Articaine hydrochloride and epinephrine tartrate injection) on their own decision to minimize bleeding of gingiva. The baseline inspiratory gas was a mixture of 60/40% oxygen/air. Anesthesia was maintained with sevoflurane (2.5–3%) and remifentanil (0.05 μg/kg/min). The BIS values were maintained between 40 and 60 for appropriate anesthesia depth. The patient's body temperature was monitored by an axillary temperature sensor probe and maintained between 35.5 °C and 37.0 °C.

Remifentanil infusion and sevoflurane inhalation were terminated when dentists finished their procedure. No extra analgesic or antagonist was given postoperatively. Extubation was done after confirming regular breathing with sufficient tidal volume (> 5 mL/kg) and purposeful movement.

After extubation, the patient was transferred to the post-anaesthetic care unit (PACU). Their ED and pain conditions were recorded by subjective scales including PAED,[12] Watcha,[13] and Flacc[14] scales. The PAED scale containing five aspects of child behavior (eye contact, purposeful movement, evidence of awareness of surroundings, restlessness, and inconsolability). Ratings are summed to produce a total score ranging from 0 to 20; greater scores indicate greater severity. The Watcha scale has four levels (1: calm; 2: crying, but can be consoled; 3: crying, cannot be consoled; and 4: agitated and thrashing around). Face, Legs, Activity, Cry and Consolability (FLACC) pain scale was used to assess pain severity. All patients should be observed in the post-anesthesia care unit for at least 30 minutes after extubation.

Sample Size and Statistical Analysis

The sample size was estimated as a minimum of 25 subjects in each study group based on a previous study,[15] at a significance level of 5% and a power of 80%. The final sample size in present study was determined to be 30 patients per group, when considered a 10% dropout rate.

Statistical analyses were performed using the IBM SPSS 26.0 (IBM Corp, Armonk, New York, USA) for Windows. Continuous variables with normal distribution were expressed as mean ±SD, nonparametric data were shown as median [range], and categorical data were reported as number (%). Normally distributed data were analyzed using analysis of variance (ANOVA) followed by a Bonferroni test. Nonparametric data were analyzed using the Kruskal–Wallis test. Categorical data, including the incidence of emergence agitation, were analyzed using the χ^2 test or Fisher's exact test as appropriate.

Results

A total of 92 children were initially enrolled in this study. Of these, 2 were excluded from analysis owing to infection of COVID-19 or severe laryngeal spasm. Complete data sets were available from the remaining 90 participants (30 in the 2 $\mu g\ kg^{-1}$ dexmedetomidine group, 30 in the 1 $\mu g\ kg^{-1}$ dexmedetomidine group, and 30 in the normal saline group). The details of patient recruitment are shown in the CONSORT flow diagram (Figure 1). Table 1 provides a detailed overview of participant demographics and general clinical history, which were similar among groups.

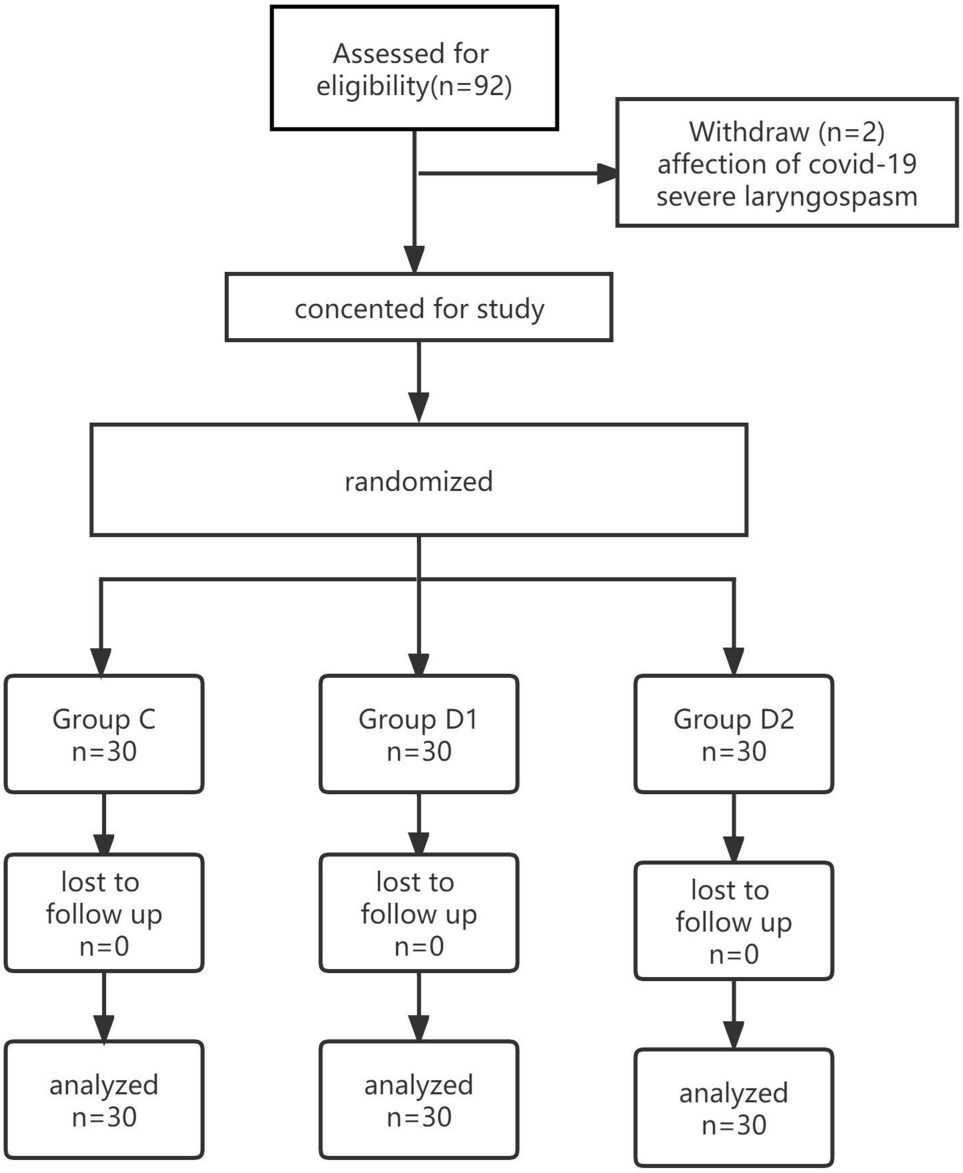

Figure 1 Consolidated Standards of Reporting Trials (CONSORT) flow diagram illustrating the patient progress through the study.

Primary Outcome

Table 2 shows the recovery status in the post-anesthesia care unit. We used PEAD score ≥10 as the diagnostic threshold of ED.[15,16] Patients with PEAD score ≥15 were diagnosed as severe ED.[17] We found that compare with control group, prophylactic use of different dosages of intranasal dexmedetomidine significantly reduce the incidence of ED and severe ED in PACU (P<0.001, Table 2). Group comparison analyses indicate that Group D2 is more effective than Group D1 in preventing ED, but these two groups show no significance difference in preventing severe ED (Bonferroni correction for multiple comparisons, P>0.016667).

Secondary Outcomes

The peak FLACC pain score was 5.0 (IQR, 4.8–7.0) in Group C, 4.0 (IQR, 2.8–5.0) in Group D1 and 2.0 (IQR, 1.0–3.0) in Group D2 (P<0.001, Table 2).

Table 3 details the immediate status after entering the operating room. Intranasal administration of 2 μg/kg dexmedetomidine was associated with a better acceptance of mask induction (higher MAS score) and a better tolerance

Table 1 Patient Characteristics and Operation-Related Data for Each Group

Variable	Control	Group D1	Group D2	*P* values
Age (m)	58.0±9.0	57.2±10.2	56.2±10.2	0.785
Male/female	20/10	15/15	14/16	0.249
Weight (kg)	19.1±3.8	18.6±3.4	18.8±3.3	0.852
BMI (kg/m^2)	15.8±2.4	15.9±2.4	15.7±2.8	0.925
ASA 1/2	30/0	30/0	30/0	NS
Duration of anesthesia (min)	197.0±44.1	196.7±69.7	201.3±56.3	0.941
Teeth treated	12.10 ±2.54	12.87 ±2.64	12.53 ±2.74	0.336
Teeth treated (fore)	4.30 ±1.86	5.13 ±1.66	4.57 ±2.53	0.079
Teeth treated (back)	7.80 ±1.19	7.80 ±1.47	8.03 ±1.25	0.754

Notes: Data are presented as mean ± SD or number.
Abbreviations: ASA, American Society of Anesthesiologists; NS, no significance.

Table 2 Recovery Status in the Post-Anesthesia Care Unit

Study Group	Group Control	Group D1	Group D2	*P* value
PAED score max	13.0 [8.0–16.0]	8.0 [5.8–11.3]	5.0 [3.0–7.0]	<0.001
Watcha score	3.0 [2.0–3.0]	2.0 [2.0–3.0]	1.0 [1.0–2.0]	<0.001
FLACC score	5.0 [4.8–7.0]	4.0 [2.8–5.0]	2.0 [1.0–3.0]	<0.001
Incidence of ED	21 (70%)	11 (36.7%)	3 (10%)[ab]	<0.001
Incidence of severe ED	11 (36.7%)	1 (3.3%)	0 (0%)[a]	<0.001

Notes: [a]P < 0.017 vs the Group C. [b]P < 0.017 vs the Group D1. Data are presented as median [IQR], or number (%).
Abbreviations: PAED, pediatric anesthesia emergence delirium; Watcha, FLACC, the Face, Legs, Activity, Cry, and Consolability scale; ED, emergence delirium.

Table 3 Patients' Status After Entering the Operating Room

Study Group	Group Control	Group D1	Group D2	*P* value
Ramsay score	2[1–2]	2[2–2]	2[2–2]	0.229
PSAS score	2[1–3]	1[1–2]	1[1–1]	0.004
MAS score	3[2–4]	3.5[3–4]	4[3–4]	0.005
Heart rate 0min	105[97–111]	102[94–107]	99[89–107]	0.250
Heart rate 10min	105[97–111]	100[94–103]	93[87–107]	0.024
Heart rate 20min	103[97–109]	94[88–102]	89[82–97]	0.001
Heart rate 30min	105[97–112]	95[85–101]	86[79–99]	0.001

Notes: Data are presented as median [IQR].
Abbreviations: PSAS, parental separation anxiety scale; MAS, mask acceptance scale.

of separation with parents compared with normal saline. There was a significant difference in heart rate immediately after entering the operating room. There was no significant difference in Ramsay score between 3 groups.

Discussion

The data in our study indicate that intranasal administration of 2 μg/kg or 1 μg/kg dexmedetomidine significantly decreases the incidence of emergence delirium under the threshold of both PAED score over 10 or 15 in post-anesthesia care unit. Besides, 2 μg/kg is a better intranasal dosage in preventing severe ED and providing better mask acceptance.

Previous studies on the role of intranasal dexmedetomidine in emergence delirium mainly focused on relatively short surgery like inguinal hernia repairs, tonsillectomy, adenoidectomy, and ophthalmic surgeries,[18] while dental rehabilitation is relatively more time consuming compared with the previous surgeries. This protective effect of ED may be due to the residual effect of intranasal dexmedetomidine. Recent research about the pharmacokinetics of intranasal dexmedetomidine show that

the dose at 2 μg/kg could achieve a preset therapeutic threshold of mild to moderate sedation that lasted for up to 2 hours.[19] In pediatric patients requiring sedation for magnetic resonance imaging (MRI), 2–3 μg/kg intranasal dexmedetomidine was quickly absorbed, its peak concentration achieved in a median time of 37 minutes, and the maximal sedative effect observed 45 minutes after dosing.[20] They also report the individual concentration–time curves after intranasal 2–3 μg/kg dosing of dexmedetomidine as nasal spray, indicating that at the time of 210min, most children had a plasma concentration of dexmedetomidine more than 0.2ng/mL. In our study, the majority of pediatric dental treatments can be completed within 210 minutes (Table 1), which is also consistent with clinical practice. We suggest that plasma concentration of dexmedetomidine is significant at the end of most dental rehabilitation surgeries, but whether or not this plasma concentration can prevent pediatric emergence delirium is unknown and needs proven.

Another possible explanation may be due to the relieved preoperative anxiety directly decreasing the rate of ED.[21] We found that children who were premedicated with 2 μg/kg of intranasal dexmedetomidine had a significantly improved compliance rate during anesthesia inhalation induction than those premedicated with 1 μg/kg of intranasal dexmedetomidine or merely saline. Preoperative anxiety is one of the factors that may increase the likelihood of emergence delirium in pediatric patients. Many non-pharmacological methods have been applied to mitigate children's preoperative anxiety —such as clown doctors, cartoon videos, virtual reality glasses, and comical information leaflets,[22–24] some children may still resist the inhalation induction procedure, which may cause delirium at emergence. A study has shown that children with parental presence at induction of anesthesia (PPIA) have lower PAED score compared with control group.[25] These research indicate that relieved preoperative anxiety may independently decrease the incidence of emergence delirium.

Dexmedetomidine was initially approved for intravenous use for up to 24 h in the adult intensive care unit population only and was additionally approved by the US Food and Drug Administration in 2003 for procedural sedation. Dexmedetomidine has appeared useful in multiple off-label applications such as pediatric sedation, intranasal, or buccal administration.[26] Compared with intravenous administration of dexmedetomidine, intranasal administration has the advantages of rapid absorption, rapid onset, avoidance of liver first-pass effect, and can achieve a certain depth of sedation before setting up intravenous line. A previous study found that the ED95 of intranasal dexmedetomidine for preventing emergency agitation was 1.78 μg/kg in children aged 3 to 10 years.[27] This may indicate that 2 μg/kg may be a better choice than 1 μg/kg for prophylactic usage. Meanwhile, dexmedetomidine has a moderate analgesic effect[28] and has been proven to be effective in postoperative pain relief in pediatric maxillofacial surgery. It is consistent with the lower FLACC scores in the dexmedetomidine groups in our research results.

Children who require dental rehabilitation under general anesthesia are often difficult to cooperate within the outpatient setting. Due to health economic considerations, dentists and parents usually have higher expectations for fast anesthesia recovery and early discharge from hospital. Public acceptance of GA in pediatric dentistry has also evolved in recent years, with an increase in preference for its use in parents when compared with negative behavioral management.[29] The American Dental Association recognizes dental treatment under GA as a viable option because of its low rates of post-operative complication.[30] In order to maximize conservation of health care resources and aim for same-day discharge, rigorous preoperative examinations are often performed in the anesthesia clinic. ED is an important factor affecting the early postoperative outcome of patients, increasing unnecessary medical risks and labor costs. The promotion of ambulatory surgery make it possible for such children to be discharged early.

In 1996, Welborn and Lerman in United States reported emergence agitation with sevoflurane and compared to other volatile agents.[31,32] Pediatric dental rehabilitation usually does not require deep muscle relaxation. Although sevoflurane anesthesia is reported to be a significant risk factor for postoperative delirium in children,[21] we still use it as the main component for anesthesia induction and maintenance in this study, since it has the character of providing stable anesthesia, fast recovery, and low rate of intraoperative awareness. Common options of pediatric sedation include atomised intranasal midazolam or oral midazolam. However, some research show that intranasal midazolam used for premedication was associated with increased incidence of perioperative respiratory adverse events.[33] Combined usage of pharmacological and non-pharmacological approaches may be more effective in ambulatory setting.[34]

There are a few limitations in our work. First, we found that the individual differences of the children themselves were obvious, which may be related to the education level of the parents. In this trial, we did not evaluate the education

status of parents. Secondly, no further follow-up was performed after patients' discharge to home; we could miss the information of long-term effect on the children's behavior and cognition.

Conclusion

In conclusion, both 2 μg/kg and 1 μg/kg intranasal dexmedetomidine can achieve ED preventive effects in PACU. Dosage at 2 μg/kg is better in preventing severe ED and providing better mask acceptance.

Data Sharing Statement

The datasets generated and/or analyzed during the current study are available from the corresponding author (Yun Shao) on reasonable request.

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Disclosure

The authors declare no conflicts of interest in this work.

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