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Original Article

Effect of intravenous nalbuphine on emergence agitation in children undergoing dental surgery under sevoflurane anesthesia

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Abstract: Background: Nalbuphine may relieve postoperative pain and decrease emergence agitation (EA) in children after seveflurane anesthesia. Aims: This study evaluated the effectiveness of intravenous nalbuphine 0.1 mg/kg for EA in pediatric patients undergoing dental surgery under sevoflurane anesthesia. Methods: A total of 84 pediatric patients (3-6 years) scheduled for dental surgery under sevoflurane for induction and maintenance of anesthesia with a laryngeal mask airway (LMA) were randomized to receive intravenous nalbuphine 0.1 mg/kg (Group N; n = 42) or saline 0.1 mg/kg (Group S; n = 42) 30 minutes before the end of surgery. Primary outcomes were the incidence and severity of EA in the PACU. Secondary outcomes were postoperative pain and the incidence of postoperative nausea and vomiting (PONV) in the PACU. Results: In the PACU, the incidence of EA (Aono's scale ≥ 3: 21.43% vs. 57.14%; Pediatric Anesthesia Emergence Delirium [PAED] scale ≥ 10: 21.43% vs. 54.76%; both $P < 0.01$), the percentage of patients with severe EA (PAED score ≥ 15; 7.69 % vs. 40.48%; $P < 0.01$), and peak pain score (2.60 ± 2.07 vs. 4.10 ± 2.49; $P = 0.004$) were significantly lower in the Group N compared to the Group S. Emergence time was significantly longer in the Group N, but there was no difference in time to discharge from the PACU. Conclusions: Compared to placebo, 0.1 mg/kg nalbuphine administered intravenously 30 minutes before the end of surgery significantly decreased the incidence and severity of EA in the PACU but did not delay discharge in pediatric patients undergoing dental surgery under sevoflurane anesthesia.

Keywords: Sevoflurane, children, emergence agitation, nalbuphine

Introduction

Sevoflurane is a commonly used anesthetic for pediatric patients as induction can be achieved quickly and safely by inhalation using a mask, sevoflurane does not cause substantial hemodynamic changes, and return to the preoperative level of consciousness following anesthesia is rapid. However, sevoflurane can result in emergence agitation (EA). The incidence of EA after sevoflurane anesthesia is estimated at 80%. EA occurs most frequently in preschool children during the early stage of emergence from anesthesia [1-3]. EA is characterized by inconsolable crying, agitation, restlessness, delusion, and disorientation [4]. Although EA resolves spontaneously, it is considered a potentially serious postoperative complication that can result in physical harm and removal of intravenous catheters. As such, EA is a source of dissatisfaction for the parents of pediatric patients [5] and their healthcare providers.

Various pharmacological agents administered pre-, intra-, and post-operatively including propofol [6], α2-adrenoreceptor agonists [7], ketamine [8], and midazolam [9] have been utilized to reduce the incidence of EA in pediatric patients. In particular, opioids [10] are considered a safe and efficacious intervention to reduce the rate of EA after seveflurane anesthesia. Nalbuphine is a semi-synthetic, agonist-antagonist opioid analgesic agent. Nalbuphine acts as a partial agonist at kappa receptors and an antagonist at μ receptors, has minimal side effects, and exhibits a ceiling effect for respiratory depression [11, 12]. Nalbuphine should effectively relieve postoperative pain and decrease the rate of EA in pediatric patients after seveflurane anesthesia. This double-blinded randomized prospective study was conducted to evaluate the efficacy and safety of intravenous nalbuphine 0.1 mg/kg for EA in pediatric patients undergoing dental surgery under sevoflurane anesthesia.

Table 1. Pediatric anesthesia emergence delirium scale (PAED)

	Score
The child makes eye contact with the caregiver	4 = not at all
The child's actions are purposeful	3 = just a little
The child is aware of the surroundings	2 = quite a bit
	1 = very much
	0 = extremely
The child is restless	0 = not at all
The child is inconsolable	1 = just a little
	2 = quite a bit
	3 = very much
	4 = extremely

Table 2. Modified Children's Hospital of Eastern Ontario Pain Scale (mCHEOPS)

Score	0	1	2
Cry	No cry	Crying, moaning	Scream
Facial	Smiling	Composed	Grimace
Verbal	Positive	None or other complaints	Pain complaint
Torso	Neutral	Shifting, tense, upright	Restrained
Legs	Neutral	Kicks, squirm, drawn-up	Restrained

Patients and methods

Study population

Pediatric patients undergoing dental surgery at the Comfort Dental Center, Stomatology Hospital Affiliated ChongQing Medical University, ChongQing, China between April 2017 and July 2017 were eligible for this study. Inclusion criteria were: 1) age between 3 and 6 years; 2) American Society of Anesthesiologists (ASA) score I or II; 3) scheduled for a surgical root canal procedure with no extractions; and 4) receiving sevoflurane anesthesia. Exclusion criteria were 1) psychiatric disease; 2) fever, cough, or reactive airway diseases such as asthma or upper respiratory tract infection (URI); 3) anticipated difficult airway; 4) hearing defect; 5) neurological disorder; 6) history of malignant hyperthermia; or 7) contraindications to the use of any investigational product.

Institutional approval for this study was obtained from the Stomatology Hospital Affiliated ChongQing Medical University Ethics Committee (#2013-012-131). Written informed consent was obtained from the parents/legal guardians of the pediatric patients.

Anesthesia and study design

Pediatric patients were consecutively enrolled into the study and randomly assigned 1:1 to a nalbuphine group (Group N) or a saline control group (Group S) using the sealed-envelope system, whereby a computer-generated, random allocation sequence with a block size of two, four, or six was placed in each envelope. The randomization procedure was implemented by an independent healthcare provider. The anesthesiologist that managed the patients in the operating room was not blinded to the group allocation. The nurse responsible for the patients in the post-anesthetic care unit (PACU) and the anesthesiologist that evaluated EA in the PACU were kept blinded.

Pediatric patients were fasted for ≥ 6 hours before anesthesia and did not receive any premedication. In our institution, in pediatric dental surgery, sevoflurane is used for induction and maintenance of anesthesia with a laryngeal mask airway (LMA). Each patient was accompanied into the operating room by their parents/legal guardians, who remained until their child lost consciousness. Pulse oximetry (SpO_2), heart rate, respiratory rate, tidal volume (VT), noninvasive blood pressure (NBP), and end-tidal carbon dioxide ($EtCO_2$) monitoring were applied. Sevoflurane concentrations and bispectral index (BIS) Philips MP40; Philips Medical, Boebingen, Germany) were monitored.

Induction of anesthesia was performed using 8% sevoflurane in 100% oxygen. The LMA (LMA Classic™) was inserted when the jaw was relaxed after the pediatric patient lost consciousness. Ten ml/kg of glucose and sodium chloride solution was infused through a peripheral venous catheter followed by standard maintenance fluids. No anticholinergics, sedatives, muscle relaxants, or narcotics were administered during the procedure.

The LMA was lubricated with water soluble jelly and placed according to the manufacturer's instructions; the cuff was inflated. LMA size 1.5, 2, 2.5, and 3 were used for pediatric patients weighing 5-10, 10-20, 20-30, and >

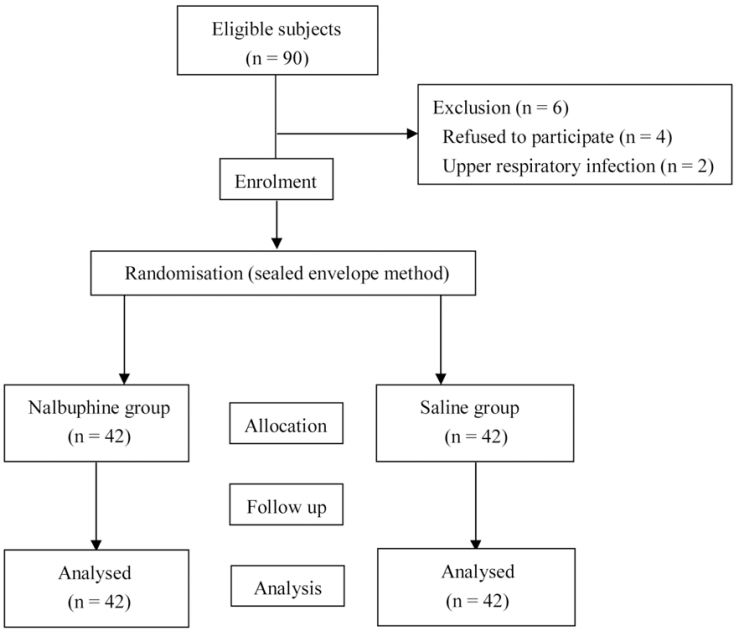

Figure 1. Consort flow diagram.

30 kg, respectively. Anesthesia was maintained with 3% sevoflurane through a semi-closed circuit (Fabius GS; Drager Medical, Lübeck, Germany). Spontaneous respiration was permitted if $EtCO_2$ remained < 50 mmHg. Assisted respiration was provided if $EtCO_2$ exceeded 50 mmHg. In these cases, patient data were excluded from the analyses. The BIS value was maintained between 40 and 60.

Pediatric patients in the Group N received 0.1 mg/kg nalbuphine 30 min before the end of surgery. Patients in the Group S received an equal volume of saline 0.1 mg/kg. Both investigational products were contained in the same volume of clear liquid in identical vials. At completion of the surgical procedure, sevoflurane were discontinued, oropharyngeal suction was performed, the LMA cuff was deflated, and the LMA was removed while the patient was unconscious. Patients were transferred to the PACU for recovery and were provided a warm environment without any stimuli.

Postoperative assessments

Parents were allowed access to the PACU. Primary outcomes were the incidence and severity of EA in the PACU. Secondary outcomes were postoperative pain and the incidence of postoperative nausea and vomiting (PONV) in the PACU. Other assessments included: duration of surgery, duration of sevoflurane anesthesia (from induction to discontinuation of the inhaled anesthetic), emergence time (from discontinuation of sevoflurane to eye opening), and time to discharge (duration in the PACU).

The incidence and severity of EA were evaluated upon admission to the PACU, and every 5 minutes thereafter. The highest EA score for each child was recorded as the outcome.

Incidence of EA was assessed using Aono's four point scale, where: 1 = calm; 2 = not calm but could be easily consoled; 3 = moderately agitated or restless and not easily calmed; and 4 = combative, excited, or disoriented, thrashing around. Absence of EA was defined as a score of ≤ 2; presence of EA was defined as a score ≥ 3.

The incidence and severity of EA was assessed using the pediatric anesthesia emergence delirium (PAED) scale [4] (**Table 1**). EA was defined as a PAED score ≥ 10 points, and a score ≥ 15 was classified as severe EA.

Postoperative pain was assessed according to the modified Children's Hospital of Eastern Ontario Pain Scale (mCHEOPS) (**Table 2**).

The incidence of PONV was assessed according to a 4 point scale [13], where: 0 = absence of nausea and vomiting; 1 = nausea only; 2 = one single emetic episode; and 3 = multiple emetic episodes.

Statistical analysis

Statistical analyses were performed using SPSS 17.0. Sample size was calculated using a power analysis based on a previous study [14] where a sample size of 80 (40 patients per study group) was required to detect a clinically significant difference of 30% in the incidence of EA between two groups of pediatric patients undergoing strabismus surgery under sevoflu-

Table 3. Patients' demographic and clinical characteristics

	Group N (n = 42)	Group S (n = 42)	*P* value
Age (years)	4.48 ± 1.31	4.38 ± 1.19	*P* = 0.728
Weight (kg)	19.26 ± 4.34	17.88 ± 3.64	*P* = 0.118
Height (cm)	102.21 ± 6.24	101.19 ± 5.98	*P* = 0.445
Male: female	26/16	29/13	*P* = 0.576
Duration of anesthesia (min)	124.43 ± 14.09	128.00 ±16.75	*P* = 0.293
Duration of surgery (min)	114.33 ± 13.98	118.29 ±16.41	*P* = 0.237

Data presented as mean ± SD or number of the groups.

Table 4. Primary and secondary outcomes

	Group N (n = 42)	Group S (n = 42)	*P* value
Time to eye opening (mins) (mean ± SD)	19.12+5.41	10.40+4.16	*P* < 0.01
Aono's scale			
Agitated n (%)	9 (21.43%)	24 (57.14%)	*P* < 0.01
Non-agitated n (%)	33 (78.57%)	18 (42.86%)	*P* < 0.01
Patients with PAED ≥ 10 n (%)	9 (21.43%)	23 (54.76%)	*P* < 0.01
Patients with PAED ≥ 15 n (%)	3 (7.69%)	17 (40.48%)	*P* < 0.01
Pain score peak (mean ± SD)*	2.60 ± 2.07	4.10 ± 2.49	*P* = 0.004
Time to discharge (mins) (mean ± SD)	32.50 ± 5.24	30.76 ± 5.40	*P* = 0.138

PAED, pediatric anesthesia emergence delirium. *Pain score was measured with the modified Children's Hospital of Eastern Ontario Pain Scale.

rane anesthesia (alpha value, 0.05 [one-sided]; beta-value, 0.80).

Continuous variables are reported as mean ± standard deviation (SD), and categorical variables are reported as number and percentage. Continuous variables were compared using the independent two sample t-test and Mann-Whitney U-test. The incidence of adverse events during the intra-operative period and in the PACU were analyzed using the Chi-squared test. $P < 0.05$ was considered statistically significant.

Results

A total of 90 pediatric patients were eligible for this study. Six patients were excluded, and among these, 4 refused to participate and 2 had a URI. The remaining 84 patients were included in the analyses, with 42 patients randomized to Group N (26 boys and 16 girls) and 42 patients (29 boys and 13 girls) randomized to Group S. **Figure 1** shows the disposition of subjects for the two treatment groups.

The demographic and clinical characteristics of all pediatric patients are summarized in **Table 3**. There were no significant differences in age, weight, height, sex, and the duration of anesthesia or the surgical procedure between the two groups. Surgery was performed successfully in all patients.

Primary outcomes

Primary outcome data are shown in **Table 4**. The incidence of EA in the PACU was significantly lower in the Group N compared to the Group S (Aono's scale: Group N, 21.43% vs. Group S, 57.14%; PAED scale: Group N, 21.43% vs. Group S, 54.76%; both $P < 0.01$). The percentage of patients with severe EA (7.69% vs. 40.48%, $P < 0.05$) was significantly lower in Group N compared to Group S.

Secondary outcomes

Secondary outcome data are shown in **Tables 4** and **5**. Mean mCHEOPS score was significantly lower in Group N compared to Group S (Group N, 2.60 ± 2.07 vs. Group S, 4.10 ± 2.49; $P = 0.004$). Emergence time was significantly longer in Group N compared to Group S (Group N, 19.12 + 5.41 vs. Group S, 10.40 + 4.16 min; $P < 0.01$). There was no significant difference in time to discharge between the two groups.

There was no significant difference in the incidence of PONV between the two groups, with 3 patients in Group N and 2 patients in Group S experiencing nausea without vomiting. No other clinically relevant adverse events were observed.

Discussion

This study demonstrates that a single dose of intravenous nalbuphine 0.1 mg/kg reduces the incidence and severity of EA in pediatric

Table 5. Adverse effects

	Group N (n=42)	Group S (n=42)	*P* value
Nausea	3	2	0.645
Vomiting	0	0	ns
Desaturation	0	0	ns

Ns, not significant.

patients undergoing root canal treatment under sevoflurane for induction and maintenance of anesthesia with a LMA. In addition, nalbuphine reduced postoperative pain. Although emergence was delayed in patients treated with nalbuphine, length of stay in the PACU was not prolonged. There were no significant differences in the incidence of PONV or other adverse events between the nalbuphine and control groups.

In the current study, there were no clinically significant postoperative complications such as respiratory depression, hypotension, or bradycardia, and the incidence of PONV was low. Nalbuphine exhibits antagonist activity at μ receptors, which may explain the decreased tendency of nalbuphine to cause nausea, vomiting, and psychomimetic effects when compared with morphine [15].

Root canal treatment under general anesthesia in children requires a duration of 90 to 150 minutes. Therefore, large doses of sedatives are needed to maintain a pharmacodynamic effect until the end of surgery. However, ventilation may be required, and there are potential complications. Small doses of nalbuphine have the ability to induce analgesia and sedation and are recommended for postoperative pain management in children > 3 years of age [16]. In our study, the incidence and severity of EA were significantly lower in pediatric patients administered nalbuphine 0.1 mg/kg vs. saline 30 minutes before the end of root canal treatment under sevoflurane anesthesia. In accordance with these findings, previous reports show that nalbuphine 0.1 mg/kg administered to pediatric patients following MRI under sevoflurane anesthesia reduced EA more effectively than ketamine [17]. Likewise, nalbuphine 0.1 mg/kg administered to children 5 minutes before the end of cochlear implant surgery under sevoflurane anesthesia was more effective than propofol 1 mg/kg in decreasing the incidence and severity of EA [18]. Furthermore, nalbuphine 0.1 mg/kg administered at the end of strabismus surgery under sevoflurane anesthesia decreased EA in pediatric patients, but propofol did not [19].

These previous studies investigated the effect of caudally administered nalbuphine on the incidence and severity of EA following sevoflurane anesthesia in children. In these studies, nalbuphine had variable effects on emergence time, which was significantly increased [19] or unchanged [20]. In an attempt to eliminate inconsistent effects of caudally administered nalbuphine on emergence time, in the current study, nalbuphine was administered intravenously 30 minutes before the end of surgery. Although emergence was delayed in patients treated with nalbuphine, length of stay in the PACU was not prolonged.

Despite the clinical utility of sevoflurane in pediatric patients, there are concerns about quality of recovery after anesthesia [20, 21]. The etiology of EA remains to be elucidated, and various anesthetic-, surgical-, patient- and medication-related factors may play a role in its initiation. These include type of surgery, intrinsic characteristics of the anesthetic, preschool age, temperament of the child, preoperative anxiety, postoperative pain, and rapid emergence from anesthesia. However, confounding evidence suggests that prophylactic or postoperative analgesia does not prevent EA following sevoflurane anesthesia in children [22, 23], there is an increased incidence of EA after sevoflurane compared to halothane anesthesia independent of any painful stimulus [24], and delayed emergence from sevoflurane anesthesia does not reduce the incidence of EA [25].

Distinguishing the symptoms of postoperative pain, including anxiety, crying and screaming, from those of EA is difficult, especially in young children. Postoperative pain may lead to EA [23]. However, EA can occur in children in the absence of a painful stimulus [26, 27]. Previous studies show that EA occurred in 48% of pediatric patients after sevoflurane anesthesia for MRI [28], there were no correlations between the efficacies of ketamine, α2-agonists, or fentanyl for postoperative pain relief and prevention of EA [21], and fentanyl had a protective effect against EA after sevoflurane anesthesia

in pediatric patients that received additional analgesia [29]. These findings suggest that post-operative pain is not the only contributing factor to EA, and that the analgesic properties of interventions are not solely responsible for the prevention of EA. In contrast, the sedative effect may also play a role. In the current study, nalbuphine was administered to reduce post-operative pain, and the postoperative pain score was lower in Group N compared to Group S. However, we speculate that postoperative pain is not a major contributor to EA in pediatric patients after dental surgery under sevoflurane anesthesia, as few children complained of postoperative pain after EA had spontaneously resolved.

Several theories have been proposed that explain the mechanism of postoperative EA. Cohen et al. [30] suggested that patients receiving sevoflurane have variable neurological recovery that results in a dissociative state and an increased sensitivity to stimuli in the surrounding environment. Lindemayer attributed EA to dysfunction in the dopaminergic, serotonergic, noradrenergic, and GABAergic systems [31].

Our study has several limitations. First, preoperative anxiety may contribute to or exacerbate EA. However, we did not assess pediatric patients' anxiety levels preoperatively. Evidence suggests that preoperative anxiety is closely associated with EA and postoperative maladaptive behavioral changes [32], and that the severity of EA may be decreased by parental presence during anesthetic induction [33]. In the current study, a parent/legal guardian was present during anesthetic induction and at emergence which minimized the effect of preoperative anxiety on our findings. Second, nalbuphine is an opioid agonist/antagonist, which may lead to PONV. Patients were allowed to go home after fulfilling the discharge criteria. Therefore, we could not assess the incidence of delayed PONV.

In conclusion, the results of this double-blinded randomized prospective study show that compared to saline, 0.1 mg/kg nalbuphine administered intravenously 30 minutes before the end of surgery significantly decreased the incidence and severity of EA in the PACU in pediatric patients undergoing dental treatment under sevoflurane anesthesia. Administration of 0.1 mg/kg nalbuphine was not associated with adverse effects. Emergence was significantly delayed in patients administered 0.1 mg/kg nalbuphine, but stay in the PACU was not prolonged.

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Disclosure of conflict of interest

None.

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