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Clinical Research Paper

Co-administration of sufentanil and dexmedetomidine prevents emergence agitation in pediatric patients

Li-Ting Hou[1], Yong-Hong Bi[1], Xiao-Guang Cui[1], Zhi-Jia Feng[1] and Yan-Zhuo Zhang[1]

[1]Department of Anesthesiology, China and Heilongjiang Key Laboratory for Anesthesia and Critical Care, The Second Affiliated Hospital of Harbin Medical University, Harbin, China

Correspondence to: Yan-Zhuo Zhang, **email:** zhangyanzhuo625@sina.com

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ABSTRACT

We compared the effectiveness of dexmedetomidine alone and combined with sufentanil for preventing emergence agitation in children under sevoflurane anesthesia. Eighty children scheduled for tonsillectomy or adenotonsillectomy under sevoflurane anesthesia were randomized into four groups: control, dexmedetomidine, dexmedetomidine with 0.1 μg/kg sufentanil (Dex+Suf1), and dexmedetomidine with 0.2 μg/kg sufentanil (Dex+Suf2). The incidence and severity of emergence agitation was evaluated based on Aono's scale and the pediatric anesthesia emergence delirium scale. The incidence of agitation was 45% in the control group, 20% in the dexmedetomidine group, 5% in Dex+Suf1 group, and 0% in Dex+Suf2 group. The Aono's and pediatric anesthesia emergence delirium scores in the Dex+Suf1 and Dex+Suf2 groups were lower than in the control or dexmedetomidine group during the tracheal extubation ($P < 0.05$). In the Dex+Suf1 and Dex+Suf2 groups, the time of tracheal extubation was longer than in the control or dexmedetomidine group ($P < 0.05$). The Dex+Suf2 group had longer tracheal extubation and awaken times than the other groups ($P < 0.05$). Thus dexmedetomidine with 0.1 μg/kg sufentanil was the optimal dose combination that reduced emergence agitation without prolonging awaken time.

INTRODUCTION

Sevoflurane has been widely used in pediatric surgery for general anesthesia induction and maintenance. The main disadvantage of sevoflurane is the agitation during emergence. The incidence of emergence agitation (EA) for children after sevoflurane anesthesia can be as high as 80% and presents potential risks such as falling out of bed, removal of the surgical dressings and intravenous catheters, and increased medical expenses [1–4].

Prophylactic pharmaceutical interventions such as α_2-agonist [5–7], μ-opioid agonists [8–9], and propofol [10] are effective for preventing EA. Dexmedetomidine, a selective α_2-adrenoceptor agonist, significantly reduced the incidence of EA in children [11, 12]. Sato M [13] showed that intravenous dexmedetomidine after induction of anesthesia at a dose of 0.3 μg/kg reduced sevoflurane-associated EA from 68% to 24%. Sufentanil, a synthetic opioid, can decrease the incidence of EA [8]. Li et al. [14] revealed that administration of sufentanil after induction of anesthesia at 0.2 μg/kg reduced EA in children receiving sevoflurane anesthesia from 71% to 13%. Liang et al. [15] concluded that the single dose of 0.1μg/kg sufentanil could reduce EA from 63.33% to 30% in children anesthetized with sevoflurane.

The lowest incidence of EA after administration of dexmedetomidine and sufentanil is 24% and 13%, which we considered suboptimal. Dexmedetomidine is a safer option for sedation when used in conjunction with opioids because it causes sedation with minimal respiratory depression. We hypothesized that the dexmedetomidine and sufentanil have a synergistic effect and that co-administration can decrease EA to a satisfactory degree in children receiving sevoflurane anesthesia.

We investigated the efficacy of co-administration of dexmedetomidine with sufentanil for preventing EA in children undergoing sevoflurane anesthesia and identified the optimal dosage of sufentanil.

RESULTS

There were no significant differences among four groups ($P > 0.05$) regarding age, gender, surgery type, weight, or duration of surgery and anesthesia (Table 1).

Dexmedetomidine (Dex) alone reduced the incidence of emergence agitation from 45% (control group) to 20%. Combination with sufentanil (Suf) further decreased the occurrence rate to 5% in the Dex+Suf1 (0.1 μg/kg) group and 0% in the Dex+Suf2 (0.2 μg/kg) group (Table 2).

Time to extubation was not influenced by dexmedetomidine alone but was sufentanil prolonged the time from 12.32 ± 3.99 min in the dexmedetomidine group to 15.34 ± 4.88 min in Dex+Suf1 group and 16.76 ± 4.67 min in the Dex+Suf2 group ($P < 0.05$). There is no significant difference among the control group, the dexmedetomidine group, or the Dex+Suf1 group in awaken time. However, the awaken time of the Dex+Suf2 group was significantly longer ($P < 0.05$).

The Aono's score was not significantly different between the control and dexmedetomidine groups during extubation. Administration of sufentanil decreased the Aono's score at doses of 0.1 μg/kg or 0.2 μg/kg ($P < 0.05$; Table 3).

During extubation, the pediatric anesthesia emergence delirium (PAED) scale score was comparable between control and dexmedetomidine groups. Administration of sufentanil at 0.1 μg/kg and 0.2 μg/kg with dexmedetomidine decreased the PAED score at the time of extubation (E0), 5 min after extubation (E5), and 10 min after extubation (E10) ($P < 0.05$; Table 4). No severe EA occurred in the Dex+Suf1 group or Dex+Suf2 group. Severe EA in the Dex+Suf1 and Dex+Suf2 groups was significantly lower than that in the control group or dexmedetomidine group at E5 ($P < 0.05$) (Table 5). There were no significant differences in Face, Legs, Activity, Cry, Consolability scale (FLACC) [16] scores among the groups at E0, E5 and E10.

During the late stage of intubation and the period of extubation, the heart rate (HR) increased gradually. Dexmedetomidine alone and co-administration of sufentanil at the doses of 0.1 μg/kg and 0.2 μg/kg inhibited the HR increase (Figure 1).

The mean arterial pressure (MAP) was kept stable during anesthesia and was not influenced by administration of dexmedetomidine and sufentanil (Figure 2).

DISCUSSION

We demonstrated that intravenous administration of 0.4 μg/kg dexmedetomidine alone or in combination with intravenous sufentanil at the induction of anesthesia reduced sevoflurane-associated EA in children undergoing adenotonsillectomy surgery. The Aono's score and PAED scores of the Dex+Suf1 and Dex+Suf2 groups were significantly lower than those of control group and dexmedetomidine group. There was no difference between the Aono's and PAED scores in the Dex+Suf1 and Dex+Suf2 groups. No severe EA occurred in the Dex+Suf1 or Dex+Suf2 groups. The awaken time of the Dex+Suf2 group was longer than that of Dex+Suf1 group. Co-administration of dexmedetomidine and sufentanil prevented EA more effectively than dexmedetomidine alone. Intravenous administration of 0.4 μg/kg dexmedetomidine with 0.1 μg/kg sufentanil was the optimal dose to prevent EA after sevoflurane anesthesia and did not prolong the awaken time.

EA is a common challenge in pediatric surgery after sevoflurane anesthesia. Several risk factors may be involved in EA development, including age, pain, type of surgery, inhalation agents, fast emergence and anesthetic technique [17]. Children aged 7 years or less were more likely to experience EA [18]. We enrolled children 3–7 years old who were prone to EA. The incidence of EA was 45% in our study, which was similar to that of 44% in the study by Przybylo [18] with children of similar age. EA is associated with tonsil, thyroid, middle ear, head, and neck surgery [1, 19], so we enrolled children who underwent tonsillectomy and adenoidectomy surgery that were at high risk of EA.

The prophylactic analgesic approach has successfully reduced EA in previous studies, suggesting that pain may be the primary cause of EA [20]. However, post-anesthetic EA has been observed with effective pain control [21] or in the absence of pain [22]. Pre-emptive tramadol at 2 mg/kg and local anesthesia demonstrated positive effects, and there was no significant difference in the pain scores or rescue fentanyl among the groups, although rescue fentanyl use was increased in the control group and dexmedetomidine group. We concluded that pain was not the primary cause of post-anesthetic EA.

The sedative, analgesic and anxiolytic properties of dexmedetomidine may prevent EA in children undergoing tonsillectomy and adenoidectomy [12, 23, 24]. Both a single dose and continuous infusion of dexmedetomidine have been shown to reduce EA after sevoflurane anesthesia in children [11]. In our study, a single dose of dexmedetomidine was administrated during induction of anesthesia and reduced postoperative EA from 45% to 20% without prolonging awaken time. For prevention of EA after desflurane anesthesia, the 50% and 95% effective doses of dexmedetomidine were 0.25 μg/kg and 0.38 μg/kg, respectively, in children undergoing tonsillectomy or adenoidectomy [25]. Ibacache et al. [26] and Guler et al. [27] reported no hemodynamic effects at a 0.3–0.5 μg/kg bolus dose of dexmedetomidine to prevent EA. Although many studies have suggested that dexmedetomidine could be safely used in pediatrics, a recent study indicated that dexmedetomidine could cause a variety of hemodynamic changes in children [28]. We administered a 0.4 μg/kg bolus dose of dexmedetomidine, which prevented EA without side effects.

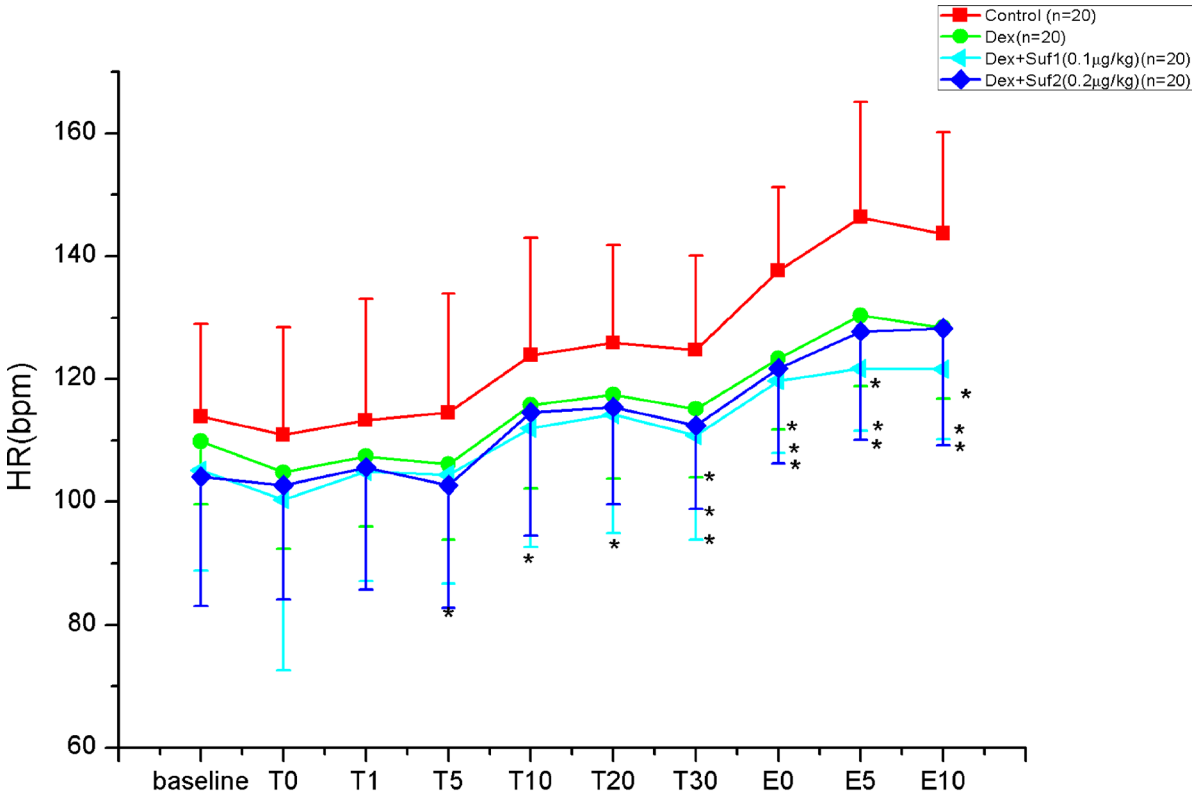

Figure 1: Heart rate of patients during anesthesia among groups $^{*}P < 0.05$, Significant difference compared with control group.

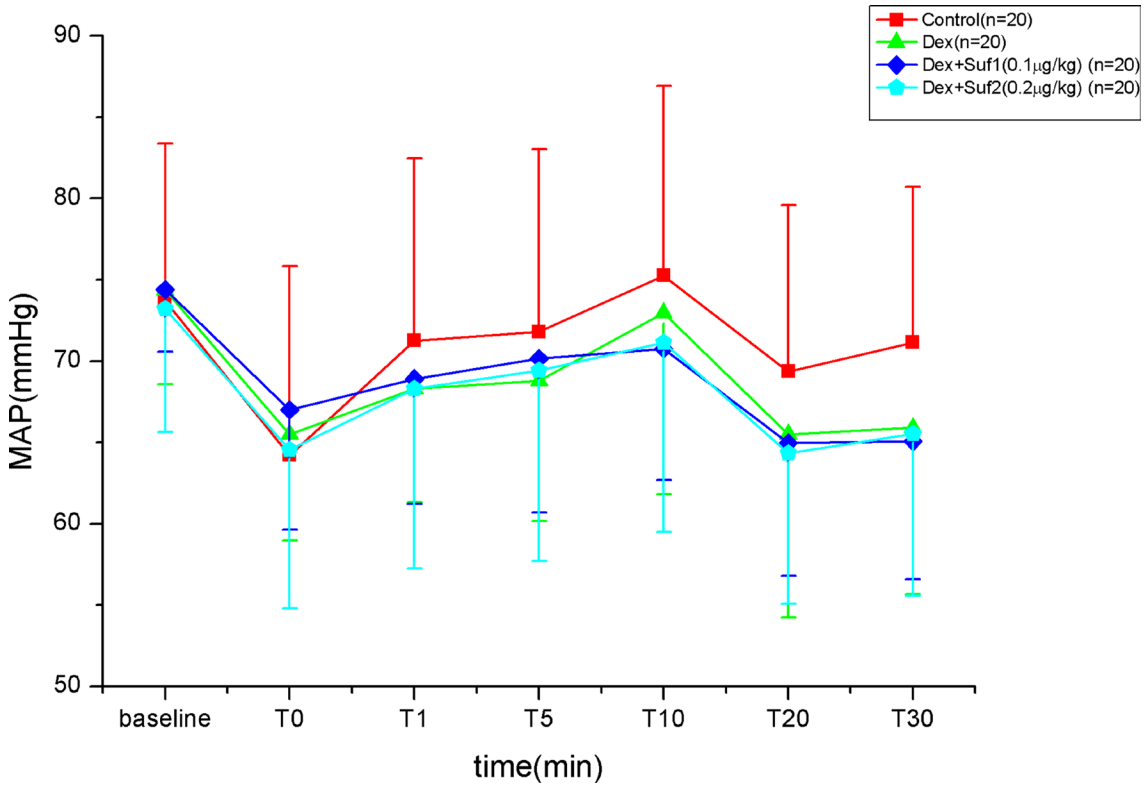

Figure 2: MAP of patients during anesthesia among groups $^{*}P < 0.05$, Significant difference compared with control group.

Table 1: Demographic and surgical characteristics (n = 20)

	Control	Dex	Dex+Suf1 (0.1 μg/kg)	Dex+Suf2 (0.2 μg/kg)
Age (year)	4.65 ± 1.38	4.90 ± 1.11	5.20 ± 1.38	5.21 ± 1.38
Gender (M/F)	11/9	13/7	11/9	12/8
Weight (kg)	22.35 ± 9.87	21.90 ± 5.32	26.15 ± 7.81	24.11 ± 8.42
Tonsillectomy/ Adenotonsillectomy	1/19	2/18	2/18	1/19
Anesthesia duration (min)	60.81 ± 5.52	62.96 ± 12.67	63.08 ± 10.11	61.46 ± 11.74
Surgery duration (min)	36.99 ± 4.80	38.26 ± 10.73	36.16 ± 11.03	34.18 ± 12.71

Dex, dexmedetomidine; Suf, sufentanil; M, male; F, female.

Table 2: EA and the time of extubation and awaken (mean ± SD, n = 20)

	Control	Dex	Dex+Suf1 (0.1 μg/kg)	Dex+Suf2 (0.2 μg/kg)
Emergence agitation	9 (45%)	4 (20%)	1 (5%)*	0 (0)*
Time of extubation (min)	11.11 ± 3.49$^{\Delta}$	12.32 ± 3.99$^{\Delta}$	15.34 ± 4.88$^{*\#}$	16.76 ± 4.67$^{*\#}$
Awaken Time (min)	12.95 ± 3.46	14.56 ± 3.91	15.50 ± 4.76	19.26 ± 3.73$^{*\#\Delta}$

$^{*}P < 0.05$, Significant difference compared with control group; $^{\#}P < 0.05$, Significant difference compared with Dex group; $^{\Delta}P < 0.05$, Significant difference compared with Dex+Suf1 group; Dex, dexmedetomidine; Suf, sufentanil.

Table 3: Aono's four point scale of different groups (mean ± SD, n = 20)

	Control	Dex	Dex+Suf1 (0.1 μg/kg)	Dex+Suf2 (0.2 μg/kg)
E0	1.80 ± 1.05 $^{\Delta}$	2.00 ± 0.72$^{\Delta}$	1.20 ± 0.52$^{*\#}$	1.00 ± 0$^{*\#}$
E5	1.95 ± 0.94 $^{\Delta}$	1.85 ± 0.98$^{\Delta}$	1.20 ± 0.52$^{*\#}$	1.00 ± 0$^{*\#}$
E10	1.60 ± 0.68	1.40 ± 0.59	1.20 ± 0.52	1.00 ± 0$^{*\#}$

$^{*}P < 0.05$, Significant difference compared with control group; $^{\#}P < 0.05$, Significant difference compared with Dex group; $^{\Delta}P < 0.05$, Significant difference compared with Dex+Suf1 group; Dex, dexmedetomidine; Suf, sufentanil.

Table 4: The scale of PAED in different groups (mean ± SD, n = 20)

	Control	Dex	Dex+Suf1 (0.1 μg /kg)	Dex+Suf2 (0.2 μg/kg)
E0	12.50 ± 2.58$^{\Delta}$	12.05 ± 1.70$^{\Delta}$	11.17 ± 1.72$^{*\#}$	10.95 ± 1.70$^{*\#}$
E5	10.35 ± 4.52$^{\Delta}$	9.00 ± 4.19$^{\Delta}$	6.61 ± 2.46$^{*\#}$	6.85 ± 3.73$^{*\#}$
E10	6.65 ± 4.08$^{\Delta}$	5.20 ± 3.46$^{\Delta}$	4.35 ± 2.41*	4.25 ± 3.47*

$^{*}P < 0.05$, Significant difference compared with control group; $^{\#}P < 0.05$, Significant difference compared with Dex group; $^{\Delta}P < 0.05$, Significant difference compared with Dex+Suf1 group; Dex, dexmedetomidine; Suf, sufentanil.

Intravenous sufentanil at dosages of 0.1 μg/kg and 0.2 μg/kg have been demonstrated to decrease the incidence of EA [14–15]. We combined these dosages with dexmedetomidine. Opioid drugs have a slight sedative effect, which may be associated with the mechanism of sufentanil in preventing EA after sevoflurane anesthesia [15]. The analgesic effect might also be one of the reasons that it can prevent the EA, but the effect of pain on EA

Table 5: The number of patients that suffered severe agitation

	Control	Dex	Dex+Suf1 (0.1 μg/kg)	Dex+Suf2 (0.2 μg/kg)
E0	3	3	0	0
E5	5	2	0*	0*
E10	1	0	0	0

*$P < 0.05$, Significant difference compared with control group; Dex, dexmedetomidine; Suf, sufentanil.

is unclear [20–22]. There was no significant difference in FLACC scores among the groups, so this result did not support this proposed mechanism of EA prevention. Opioids can also cause postoperative nausea and vomiting, and Li et al. [29] found that the incidence of vomiting was significantly higher in the fentanyl group than in the sufentanil group after sevoflurane anesthesia. In our study, prophylactic dexamethasone had an antiemetic effect and we did not observe postoperative nausea or vomiting. The anti-inflammatory effects may also decrease postoperative edema and improve subsequent oral intake after tonsillectomy [30].

Sufentanil had a mild effect on respiratory depression, while dexmedetomidine was sedative and had a minimal effect. Subjects did not demonstrate respiratory depression during extubation or in the PACU. No hypoxemia was found upon return to the ward. The MAP was stable during extubation and in the PACU, and no hypotension occurred. The sedative effect of dexmedetomidine and sufentanil prevented HR increase. The combination of dexmedetomidine and sufentanil demonstrated a synergistic effect to prevent EA after sevoflurane anesthesia without severe side effects.

MATERIALS AND METHODS

This study was approved by the institutional ethics committee (ethics number: ChiCTR-IIR-17010413). After obtaining informed consent from the parents of all children, 92 children between 3 and 7 years with an ASA physical status I or II and scheduled for either a tonsillectomy alone or both an adenoidectomy and tonsillectomy, were enrolled in this prospective, randomized, double-blind, controlled study. The enrolled patients presented with repeated infection of tonsils, tonsil enlargement more than II degree, and snoring. Patients with cardiac disease, developmental delay, abnormal upper airway, asthma, obstructive sleep apnea syndrome (OSAS), a history of sleep-disordered breathing or sleep apnea or a history of upper respiratory tract infection in the preceding 4 weeks were excluded. 12 children were excluded: 1 child with myocarditis, 1 child with developmental delay, 1 child with abnormal upper airway, 2 children with asthma, 2 children with OSAS, and 5 children have a history of upper respiratory tract infection in the preceding 4 weeks. 80 children were randomly allocated to four groups: the control group received normal saline; the dexmedetomidine group received 0.4 μg/kg dexmedetomidine for 10 min beginning at the onset of induction; the Dex+Suf1 group received 0.4 μg/kg dexmedetomidine for 10 min beginning at the onset of induction and 0.1 μg/kg sufentanil at induction; and the Dex+Suf2 group received 0.4 μg/kg dexmedetomidine for 10 min beginning at the onset of induction and 0.2 μg/kg sufentanil at induction.

Upon arrival at the operating room, the children were monitored with electrocardiography (ECG), pulse oximetry (SpO_2), and noninvasive blood pressure (NIBP). The bispectral index (BIS) was recorded. The anesthesia induction drugs 3% sevoflurane with 5 L/min oxygen, lidocaine 1 mg/kg, propofol 2-2.5 mg/kg, atracurium 0.3 mg/kg, and the study drugs were administrated. The trachea was intubated 3 minutes later if intubating conditions were adequate. The study drug was prepared and administered by an investigator uninvolved in data collection and assessment. Anesthesia was maintained with 2–3% sevoflurane in approximately 50% oxygen with a total inflow of 2 L/min. The concentration of sevoflurane was adjusted to a BIS range of 40–60. A 3 ml 0.5 % lidocaine and epinephrine mixture (ratio of 1:200 000) was injected into the mucosa surrounding each tonsillar fossa for local anesthesia and vasoconstriction. Intravenous tramadol (2 mg/kg) and dexamethasone (0.1 mg/kg) were administrated after induction of anesthesia for postoperative analgesia, nausea and vomiting. The mean noninvasive blood pressure (MAP), heart rate (HR) and SpO_2 were recorded on arrival in the operating room (baseline), intubation time (T0), and 1 min (T1), 5 min (T5), 10 min (T10), 20 min (T20), and 30 min (T30) after intubation. The HR was recorded at the tracheal extubation (E0), 5 min after tracheal extubation (E5), and 10 min after tracheal extubation (E10). Sevoflurane was discontinued upon removal of mouth gag, and tracheal extubation was performed when the patients began breathing spontaneously and coughed or had body movement.

Time of tracheal extubation was defined by discontinuation of sevoflurane until the tracheal tube was extubated. Awaken time was defined by discontinuation of sevoflurane until the children acted on command. The incidence of EA was evaluated using Aono's [31] four point scale; 1 = calm; 2 = not calm but easily consoled; 3 = moderately agitated or restless and not easily calmed; 4 =

combative, excited or disoriented, thrashing around. Scores of 1 and 2 were considered an absence of EA, and scores of 3 and 4 indicated presence of EA. The severity of EA was evaluated using the pediatric anesthesia emergence delirium (PAED) scale devised by Sikich et al. [32], which consisted of 5 items: (1) the child makes eye contact with the caregiver, (2) the child shows purposeful actions, (3) the child is aware of his or her surroundings, (4) the child is restless, and (5) the child is inconsolable. Items 1-3 are scored as follows: 4 = not at all, 3 = just a little, 2 = quite a bit, 1 = very much, and 0 = extremely. Items 4 and 5 are scored as: 0 = not at all, 1 = just a little, 2 = quite a bit, 3 = very much, and 4 = extremely. The score for each item was summed up to get a total PAED scale score, and the highest scores were recorded. According to the scoring standard, a comprehensive score greater than 15 was considered severe agitation. Then 0.5 mg/kg propofol was given. Postoperative pain was assessed with the Face, Legs, Activity, Cry, Consolability scale (FLACC) [16] upon PACU arrival and at 5 min and 10 min after arriving the PACU. When children showed FLACC scores no less than 4, 0.5 μg/kg fentanyl was administered. The incidence and severity of EA and pain were measured at E0, E5, and E10.

Statistical analyses were performed using the statistical package, SPSS 20.0 for windows. Demographic data including age, gender, weight, type of surgery, and duration of anesthesia and surgery were compared with unpaired Student's *t* tests. Differences in the incidence of EA and severe EA among the groups were analyzed using a χ^2 test with Fisher's exact test correction. Intra- and postoperative hemodynamic and respiratory variables of the subjects were compared by use of the Bonferroni test after repeated-measures analysis of variance. $P < 0.05$ was considered to be of statistically significance.

CONCLUSIONS

Co-administration of sufentanil and dexmedetomidine reduced EA in children anesthetized with sevoflurane. Administration of 0.1 μg/kg sufentanil with 0.4μg/kg dexmedetomidine at induction of sevoflurane anesthesia reduced EA in pediatric patients undergoing adenotonsillectomy surgery.

Author contributions

Yan-zhuo Zhang and Li-ting Hou designed experiments and carried out experiments; Yong-hong Bi, Xiao-guang Cui and Zhi-jia Feng Collected the data; Yong-hong Bi and Xiao-guang Cui analyzed experimental results; Yan-zhuo Zhang and Li-ting Hou wrote the manuscript.

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CONFLICTS OF INTEREST

None.

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