



ORIGINAL INVESTIGATION

The effect of two different doses of dexmedetomidine to prevent emergence agitation in children undergoing adenotonsillectomy: a randomized controlled trial

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KEYWORDS

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Abstract

Objective: To evaluate different doses of dexmedetomidine for the prevention of emergence agitation in children undergoing adenotonsillectomy.

Method: One hundred and thirty children aged 3–10 years scheduled for adenotonsillectomy were randomly assigned to two groups. Anesthesia was induced with 0.5 $\mu\text{g}\cdot\text{kg}^{-1}$ dexmedetomidine (DEX 0.5 group) or 1 $\mu\text{g}\cdot\text{kg}^{-1}$ dexmedetomidine (DEX 1 group) at the beginning of surgery. Observers who recorded the data in the postanesthesia care unit were blinded to the allocation. The primary outcome was the percentage of emergence agitation. The times to spontaneous breath, awake, extubate, and postanesthesia care unit stay were also recorded.

Results: One hundred twenty four children were randomized into two groups. Five children were excluded because of adverse events and dropout (DEX 0.5 group, $n = 58$; DEX 1 group, $n = 62$). No significant differences were noted in the percentage of emergence agitation between the two groups. The times to extubation ($p = 0.003$), awake, and postanesthesia care unit stay in DEX 0.5 group were shorter than those in DEX 1 group ($p < 0.0001$). There was no significant difference between the two groups in the time to spontaneous breath. Approximately 8% of patients in DEX 0.5 group and 18% patients in DEX 1 group presented low SpO_2 , showing a significant difference between the two groups ($p = 0.043$).

Conclusions: A dose of 0.5 $\mu\text{g}\cdot\text{kg}^{-1}$ dexmedetomidine was equally effective as 1 $\mu\text{g}\cdot\text{kg}^{-1}$ dexmedetomidine in preventing emergence agitation.

Trial registration: : The trial is currently completed recruitment, registered in ClinicalTrials.gov (ID:NCT03760809). Inclusion began on 4 January, 2019.

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Introduction

Adenotonsillectomy is one of the most common surgeries in children. Emergence agitation (EA), which is characterized by non-purposeful restlessness, thrashing, crying, disorientation, and incoherence, often occurs during extubation in pediatric surgeries.¹ It may result in severe consequences, such as bleeding, airway obstruction, and a prolonged stay in the post anesthesia care unit (PACU).² Multiple factors are associated with EA, including temperament, adaptability and pain. The incidence of EA in younger children undergoing otorhinolaryngology is as high as 42%,³ especially after receiving inhaled anesthesia.^{2,4}

Dexmedetomidine (DEX) has a specific affinity for α_2 -adrenergic receptors and can induce a satisfactory sedative effect by primarily acting on the α -adrenergic receptor of the brainstem nucleus to inhibit norepinephrine release. The property of analgesia without respiration depression is also the reason for its prevalent use in children. DEX ($0.5 \mu\text{g}\cdot\text{kg}^{-1}$) has been reported to have the same effect as morphine ($50 \mu\text{g}\cdot\text{kg}^{-1}$) in reducing the pain scores in children undergoing adenotonsillectomy,⁵ and it is commonly administered intraoperatively to prevent EA in tonsillectomy and adenoidectomy.^{6–10} Knowing that many adverse events following agitation also occur frequently after extubation, DEX is a suitable choice for pediatric anesthesia, and 1 and $0.5 \mu\text{g}\cdot\text{kg}^{-1}$ DEX are the most commonly used doses for surgery. The aim of this study was to compare those two doses of DEX to prevent the occurrence of EA in adenotonsillectomy.

Methods

Ethical statement and patients

The registration number of the study on www.clinicaltrials.gov is NCT03760809, and the study protocol was approved by the ethics committee of our hospital. Children undergoing adenotonsillectomy between January and April 2019 were included. The primary inclusion criteria were children between 3 and 10 years of age with an American Society of Anesthesiologists (ASA) physical status I–II and body weight of 12–30 kg. The exclusion criteria were children with respiratory problems, circulatory or nervous system/hepatic dysfunction, known adverse reactions to hydromorphone and DEX, preoperative sedation or medical treatment during PACU stay. All participants were randomly assigned to 1 of 2 treatment groups by computer-generated allocation: a $0.5 \mu\text{g}\cdot\text{kg}^{-1}$ DEX (DEX 0.5) group and a $1 \mu\text{g}\cdot\text{kg}^{-1}$ DEX (DEX 1) group. The investigator handed the envelope that concealed the sequential number to the anesthesia provider. An observer who only stayed in the PACU was blinded to the allocation and was responsible for recording the data.

Anesthetic management

Children were permitted to have solid food until 6 hours prior to entering the operating room and to drink clear

liquids until 2 hours prior to the procedure. No medication was administered before the operation, and intravenous access was set in the preoperative waiting room. Electrocardiography plus oximetry and noninvasive monitoring of arterial blood pressure were applied on arrival in the operating room. Anesthesia was induced with intravenous $3 \text{ mg}\cdot\text{kg}^{-1}$ propofol, cisatracurium besylate $0.1 \text{ mg}\cdot\text{kg}^{-1}$ and hydromorphone $0.03 \text{ mg}\cdot\text{kg}^{-1}$ as a bolus. After intubation, children in the DEX 0.5 group received DEX $0.5 \mu\text{g}\cdot\text{kg}^{-1}$, and those in the DEX 1 group received DEX $1 \mu\text{g}\cdot\text{kg}^{-1}$, both diluted in 100 ml normal saline (NS) dripped within 10 minutes.

Anesthesia was maintained using 1.0 MAC sevoflurane with 50% oxygen flow of $2 \text{ L}\cdot\text{min}^{-1}$. All patients were ventilated with pressure-regulated volume control at a tidal volume of $6\text{--}8 \text{ ml}\cdot\text{kg}^{-1}$, a rate of $15 \text{ breaths}\cdot\text{min}^{-1}$, an I:E ratio of 1:1.5, and end-tidal CO_2 of 35–45 mmHg. Both groups received $0.25 \text{ mg}\cdot\text{kg}^{-1}$ dolasetron to prevent nausea and vomiting. If noninvasive blood pressure or heart rate increased to 20% of the value in the operation, remifentanyl ($0.1 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) was administered immediately. Normal saline at $15 \text{ ml}\cdot\text{kg}^{-1}$ was administered if systolic blood pressure was decreased by 30% from baseline.

Sevoflurane was discontinued once the operation was over. The children were escorted to the PACU immediately after surgery. Neostigmine ($0.05 \text{ mg}\cdot\text{kg}^{-1}$) and atropine ($0.01 \text{ mg}\cdot\text{kg}^{-1}$) were prescribed to reverse muscle relaxation. The pharyngeal airway tube was inserted with the patient lying in a lateral position. If children had spontaneous breathing, the ventilation was converted to the CPAP mode until the tube was removed.

All the data were recorded. The primary outcome measures are the evaluation of EA. EA was evaluated by the EA score and the PAED scale.¹¹ The EA score is a 5-point agitation scale designed by Cole.¹² An EA score ≥ 4 or a PAED score ≥ 10 is defined as agitation. The EA and PAED scores were measured every 5 minutes in the PACU. Propofol ($2 \text{ mg}\cdot\text{kg}^{-1}$) was given for PAED scores > 15 or EA scores ≥ 4 . The second measures are the Oucher scale, coughing and the times to spontaneous breath, awake, tracheal extubation and stay in the PACU. The Oucher scale, accessed at oucher.org, was adopted to evaluate pain. In our study, we used the Asian version of the Ocher scale, the validity of which was confirmed by Yeh in 2005.¹³ The Oucher scale was recorded at 0 (the time of trachea extubation), 4, 12, and 24 hours after surgery. When the Oucher score was > 5 , hydromorphone $0.005 \text{ mg}\cdot\text{kg}^{-1}$ was administered. The time to spontaneous breath was recorded from the arrival in the PACU to the advent of spontaneous breath. The time to awake was defined as opening eyes spontaneously or on command from the arrival in the PACU. The time of extubation was recorded from the arrival in the PACU to tracheal extubation. Coughing was evaluated on a 9-point scale (1 = no coughing, 2 = minimal coughing, one or two times, 3–4 = moderate coughing, 3–4 times, 5–6 = moderate coughing, more than 5 times, 7–8 = severe coughing, more than 10 times, 9 = laryngospasm) after extubation. Patients who developed retching, breath holding, coughing, bronchospasm, or $\text{SpO}_2 < 95\%$ in the PACU were observed and analyzed as the second measures.

Statistical analysis

EA scores and the time to awake were powered for the study. Based on preliminary experiments, 16 patients in each group were required to reduce the incidence of EA by 50%. Fifty seven patients were warranted to determine a significant level of 5% and 80% power to detect a difference in the time to awake. Because a larger sample size gives more reliable results with greater precision and power if the resource allows, the number of patients in each group was set at approximately 62, for a 10% loss of subjects.

SPSS software (version 16, Chicago, Illinois) was used to analyze the data. Depending on the distribution of the data, Student's t-test was used to compare the differences in anesthesia time, weight and age between the groups, and the Mann-Whitney U test was applied for nonparametric data, such as the Oucher, coughing, EA, and PAED scores. Nominal (gender) and percentage data were subjected to Pearson's χ^2 test or Fisher's exact test. $p < 0.05$ was considered a statistically significant difference.

Results

In total, 130 children undergoing adenotonsillectomy were identified as candidates. Six of the children were excluded because they were anxious and received preoperative sedation. The remaining 124 children were equally assigned to two groups. In the DEX 0.5 group, four children were excluded from the study because of administration of propofol or naloxone in the PACU, and one child was lost to follow-up analysis. Finally, the DEX 0.5 group contained 58 patients, and the DEX 1 group contained 62 (Fig. 1). The mean ages of occurrence of desaturation were 5.33 years old in the DEX 1 group and 5.5 years old in the DEX 0.5 group ($p = 0.537$).

The recovery profile of the patients is delineated in Table 1 and Figure 2. The PAED and EA scores were measured for EA evaluation. Patients with EA scores ≥ 4 were defined as exhibiting EA. No significant difference was found in the percentages of EA scores at the four time points after extubation (Fig. 2A). However, the maximum EA score in the DEX 0.5 group was slightly higher than that in the DEX 1 group ($p = 0.019$) (Table 1).

After children arrived at the PACU, the times of extubation were 48.37 minutes in the DEX 1 group and 40.05 minutes in the DEX 0.5 group, showing a statistically significant difference between the two groups ($p = 0.003$). The time to awake in the DEX 0.5 group was 52.38 minutes, which was significantly shorter than the 66.67 minutes in the DEX 1 group. The time of PACU stay in the DEX 0.5 group was 58.58 minutes, which was shorter than the 72.78 minutes in the DEX 1 group ($p < 0.001$). There was no difference in the time to spontaneous breath between the two groups ($p = 0.095$) (Table 2).

There was no significant difference in the percentage of Oucher scores > 3 between the two groups (Fig. 2B). No patient had a pain score > 5 when they stayed in the PACU. However, there were patients with severe pain from 4 hours after surgery in ward. Cough was evaluated during EA evaluation, also showing no significant difference in the percentage of patients with moderate coughing at the four

time points (Fig. 2C). No respiratory complication events, such as postoperative pulmonary edema, laryngospasm, bronchospasm or pneumonia, occurred in this study. A statistically significant difference was observed in the number of patients with SpO₂ below 95% in the PACU between the DEX 1 and DEX 0.5 groups (18 (29%) vs. 8 (13.8%), $p = 0.043$). All patients with desaturation needed to receive oxygen inhalation in the PACU to maintain a normal level of SpO₂.

Discussion

In this study of children undergoing adenotonsillectomy, 0.5 $\mu\text{g}\cdot\text{kg}^{-1}$ dexmedetomidine in the anesthesia induction have an equal effect on the incidence of EA, in comparison with 1 $\mu\text{g}\cdot\text{kg}^{-1}$ group. Additionally, it significantly decreased time of extubation, awake, and PACU stay.

Sevoflurane is often used in pediatric patients for general anesthesia, but the incidence of sevoflurane-related EA ranges from 10–80%.¹⁴ DEX with sedative and analgesic actions plays a pivotal role in preventing agitation in children under sevoflurane anesthesia. Compared to midazolam, fentanyl, or propofol, DEX was as high as 90.04% effective in reducing the incidence of EA.¹⁵

Various doses of DEX (0.1–2 $\mu\text{g}\cdot\text{kg}^{-1}$), time points of administration (immediately after anesthesia induction or a few minutes before the end of surgery)^{6,16,17} or methods (single bolus or single bolus with continuous infusion)¹⁸ have been investigated in other studies. A bolus of 0.5 $\mu\text{g}\cdot\text{kg}^{-1}$ DEX given 5 minutes before the end of surgery could reduce the incidence of EA by 12% after sevoflurane anesthesia.⁶ No patient had EA after 1 $\mu\text{g}\cdot\text{kg}^{-1}$ or 2 $\mu\text{g}\cdot\text{kg}^{-1}$ DEX, as premedication was administered.¹⁹ We used a bolus of DEX immediately before the operation began because it could prevent procedure-associated stimuli that might result in hemodynamic changes, such as increased heart rate and high blood pressure. Considering the short half-life (1.8 hours) of DEX in children,²⁰ DEX can be partially metabolized during surgery, and the residual effect could suppress EA.

As the most effective method for evaluating EA, the PAED scale is widely used in pediatric patients.¹¹ However, the disadvantage of the PAED scale is that the subjectivity of the assessment is too strong, whereas the EA scale was developed based on the behavior of children and is notably easy to use. Therefore, we combined the PAED and EA scales to accurately evaluate agitation. We compared the median of scores on the EA scale at each time point, and both doses of DEX effectively reduced the occurrence of agitation. The medians of the highest scores on the EA scale of the two groups were below 3, which suggested that children were in a good state of sedation during the recovery time after intravenous DEX administration.

The different uses of DEX have an impact on the postoperative recovery profile. A high dose of DEX causes prolonged sedation and results in a difficulty in turnover in the PACU. Pediatric patients who received loading doses of DEX (1 $\mu\text{g}\cdot\text{kg}^{-1}$) over 10 minutes followed by 0.5 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ continuous infusion had lowered pain scores, but the waking time and the extubation time were lengthened.²¹ Similarly, our study showed that the times to extubation, awake and PACU stay in the DEX 1 group were longer than those in

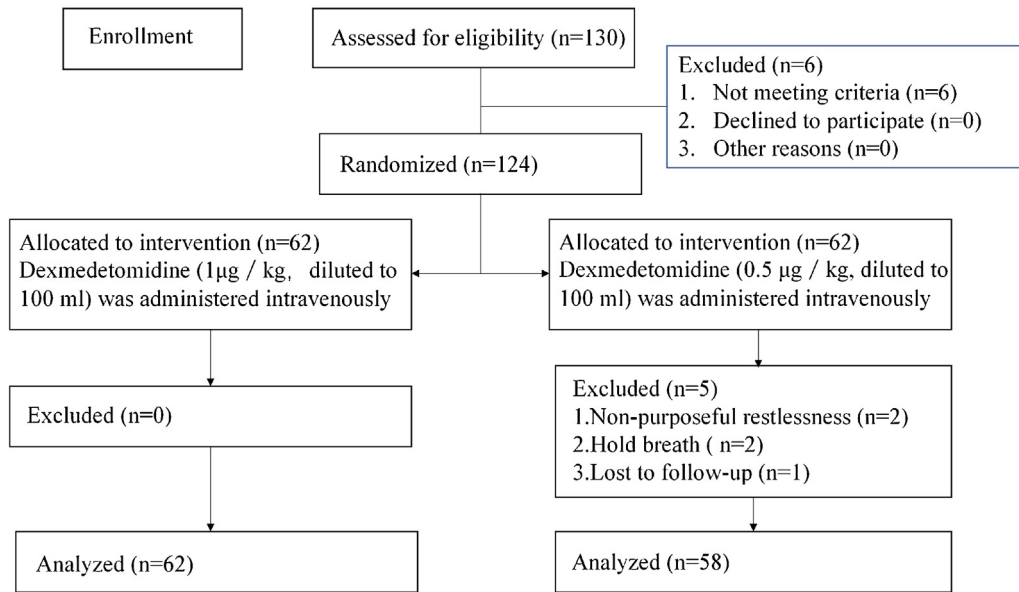


Figure 1 Randomization of patients into dexmedetomidine 1 µg.kg⁻¹ or dexmedetomidine 0.5 µg.kg⁻¹ groups.

Table 1 Data are expressed as median (IQR) (Mann-Whitney U test) and n (%) (Pearson’s χ^2 test). Group DEX 1 = dexmedetomidine 1 µg.kg⁻¹ group; Group DEX 0.5 = dexmedetomidine 0.5 µg.kg⁻¹ group.

	Group DEX 1 (n = 62)	Group DEX 0.5 (n = 58)	p-value
Oucher maximum	5 (3.25–6.75)	3 (2.25–4)	0.180
PAED score maximum	12 (12–12)	12 (12–12)	1
EA score maximum	1 (1–3.25)	2 (1.25–3.5)	0.019 ^a
Cough score maximum	1 (0–2.75)	6 (5–7)	0.350
SpO ₂ below 95%, n (%)	18 (29.03)	8 (13.79)	0.043 ^a

^a $p < 0.05$.

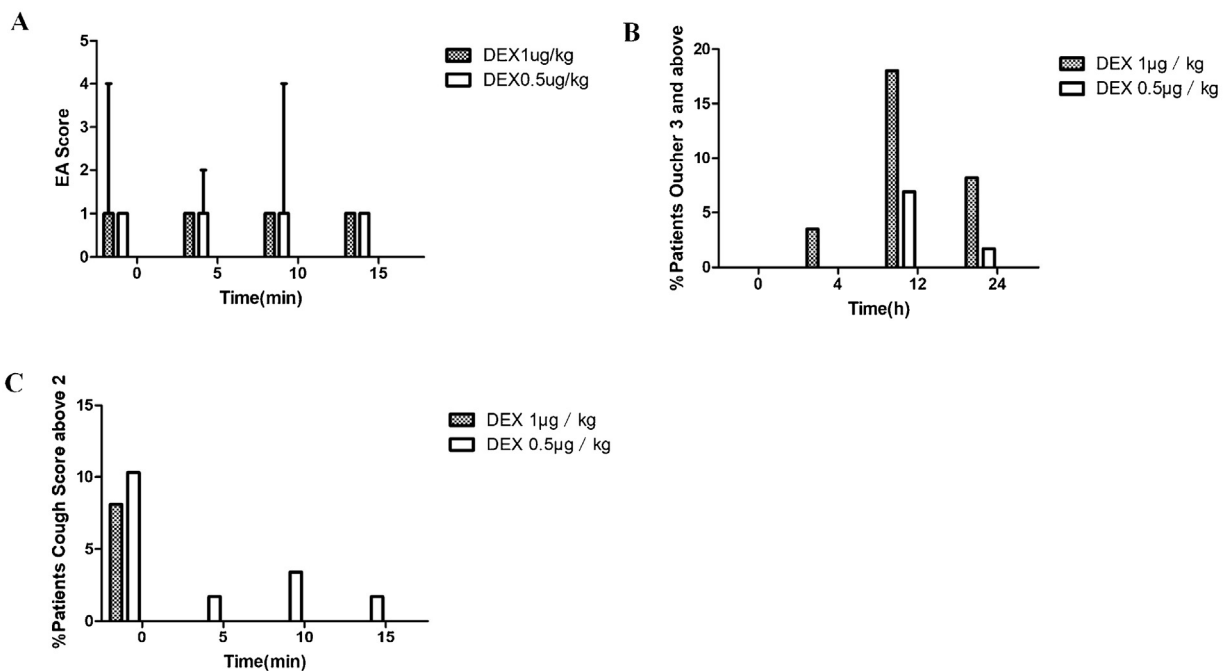


Figure 2 A, EA scores is expressed as median (upper and lower limit) (Mann-Whitney U test); B, Percentage of patients with Oucher score of 3 and above; C, Percentage of patients with cough score above 2.

Table 2 Data are expressed as mean \pm SD (Student's *t* test). Group DEX 1 = dexmedetomidine 1 $\mu\text{g}\cdot\text{kg}^{-1}$ group; Group DEX 0.5 = dexmedetomidine 0.5 $\mu\text{g}\cdot\text{kg}^{-1}$ group.

	Group DEX 1 (n = 62)	Group DEX 0.5 (n = 58)	p-value	Effect size (95% CI)
Age (years)	6.06 \pm 1.71	6.17 \pm 1.80	0.737	
Weight (kg)	23.28 \pm 7.42	23.03 \pm 6.74	0.848	
Gender (M/F)	39/23	38/20	0.914	
Anesthesia time (minutes)	38.92 \pm 8.06	38.93 \pm 7.934	0.994	
Time to spontaneous breath	24.48 \pm 7.11	22.31 \pm 7.03	0.095	0.15 (-0.38 to 4.73)
Time to awake (minutes)	66.67 \pm 16.12	52.38 \pm 15.33	<0.001 ^a	0.41 (8.58 to 20.01)
Time to extubate (minutes)	48.37 \pm 18.07	40.05 \pm 10.86	0.003 ^a	0.27 (2.88 to 13.76)
Time of PACU stay (minutes)	72.78 \pm 19.06	58.58 \pm 15.78	<0.001 ^a	0.37 (7.45 to 20.32)

^a $p < 0.05$.

the DEX 0.5 group, and the two regimes of DEX are equally beneficial for the prevention of EA.

Evaluation of agitation is easily disturbed by pain, which presents as restlessness and inconsolableness. In our study, no child required extra analgesic rescue in the PACU; thus, the impact of pain on agitation assessment can be completely ruled out. The Oucher scale, developed by Judith E. Beyer in 1980, is a valid and ideal tool for pain measurement in children aged 3–12 years.^{22,23} Its metric is consistent with other visual analog scale pain measures. The Oucher scale uses photographs of real children in pain or discomfort. With this specialization, children can select or report a photograph or number to express their amount of pain. Five versions of this scale already exist for different ethnic groups. Although the Oucher scale has been used extensively, additional evidence is still needed to demonstrate the validity and appropriateness for the use of the various versions.²⁴ Children who underwent adenotonsillectomy often experienced severe pain after surgery, and various opioid analgesics have been used, but none of them have been accepted as the best due to their adverse effects. To better investigate DEX, we used hydromorphone as the main analgesic for children. Because of its shorter plasma elimination (2–3 hours), hydromorphone rarely results in delayed fatal respiratory depression,²⁵ and it has a similar effect in attenuating stimulation during intubation compared with fentanyl.²⁶ Compared with morphine, hydromorphone was found to induce less nausea, vomiting and itching and showed a slightly better analgesic effect.²⁷ These advantages are beneficial to reducing the occurrence of postoperative agitation.

No severe adverse events occurred in the two groups. The incidence of low SpO₂ in the DEX 1 group was more than twice that of the DEX 0.5 group (8%), which would be related to the dose-dependent sedative effect of DEX. As we showed in our study, the median of EA score maximum in the DEX 1 group (1 = sleeping) was lower than that of the DEX 0.5 group (2 = awake, calm). Children after adenotonsillectomy still have the risk of respiratory distress, and deep sedation may increase the occurrence of upper airway obstruction. Age is risk factors of respiratory depression, especially age less than 3 years which was not included in this study.²⁸ Although there was no significant difference between two groups in ages, we further investigated the mean ages of children with low SpO₂ were 5.33 and 5.5 years old in two groups. These values are similar to those in the study by

Kou, who reported that the rate of respiratory complications among tonsillectomy patients was 6%, and the mean age was 5.2 years old.²⁹

A potential problem appeared in our study was that some of children who were agitated with receiving rating of 3 on the 5 items of the PAED scale, but could be consolable by gently patted for a while. Therefore we modified our treatment standard that propofol was administered if the PAED > 15, but not \geq 10. The limitation of our study is that the EA scale is not a validated scale, even it is easy to use to define the severe. The PAED scale is the only validated method for emergence delirium. We only use PAED score to run concomitantly to decided whether restless children should be treated. It would be better to use both of them in a study of EA.

We followed the patients after they were discharged from the PACU to the ward and found that the highest percentage of pain scores occurred 4 hours after surgery. These observations suggested that it is worthwhile for us to administer long-acting postoperative analgesia for children undergoing adenotonsillectomy.

Conclusion

In conclusion, compared with 1 $\mu\text{g}\cdot\text{kg}^{-1}$ DEX, intraoperative infusion of 0.5 $\mu\text{g}\cdot\text{kg}^{-1}$ DEX can supply the same effect in reducing EA, without delaying extubation and awakening in pediatric patients undergoing tonsillectomy and adenoidectomy.

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Conflict of interest

The authors declare no conflicts of interest.

Acknowledgements

WJY and JL conducted the clinical trials, WJY wrote the manuscript, WXL and JEJ designed and analyzed the study,

and LCW and YZ recorded the data. All authors read and approved the final manuscript.

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