Observational Study

Medicine®

OPEN

# Effects of intraoperative dexmedetomidine with intravenous anesthesia on postoperative emergence agitation/delirium in pediatric patients undergoing tonsillectomy with or without adenoidectomy

## A CONSORT-prospective, randomized, controlled clinical trial

Jun-Li Cao, MD, PhD[a,b], Yu-Ping Pei, MD[a], Jing-Qiu Wei, MD[a], Yue-Ying Zhang, MD[a,*]

**Abstract**

Postoperative emergence agitation/delirium (POED) is a common complication in pediatric surgery patients, which increases the risk of developing postoperative airway obstruction and respiratory depression. This study aims to investigate the safety and efficacy of intraoperative infusion of dexmedetomidine (DEX) and its effects on POED in pediatric patients undergoing tonsillectomy with or without adenoidectomy.

Sixty patients scheduled for tonsillectomy with or without adenoidectomy, aged 2 to 8 years, were randomly allocated into 2 groups (n = 30). Pediatric patients in the group DEX received intravenous (IV) DEX 1 μg/kg over 10 minutes, followed by 0.5 μg/kg/h continuous infusion, and the same volume of 0.9% saline was administrated in the group control. Anesthesia was maintained with target-controlled infusion (TCI) of propofol and remifentanyl. Intraoperative heart rate (HR), noninvasive blood pressure (NIBP), blood oxygen saturation ($SPO_2$), recovery time, and extubation time were recorded. Pain level was evaluated using the objective pain score (OPS), pediatric anesthesia emergence delirium (PAED) scale and Cole 5-point scale (CPS) was used to evaluate POED when patients at 0, 5, 15 minutes, and then at intervals of 15 minutes for 60 minutes after parents arrival at postanesthesia care unit (PACU).

The results showed that intraoperative HR was significantly lower in group DEX ($P < 0.05$), mean diastolic and systolic NIBP was not statistically different between groups. Time to wake and time to extubation were lengthened in group DEX as compared with group control ($P < 0.05$). OPS and CPS were lower in group DEX at 15, 30, and 45 minutes time points ($P < 0.05$); however, there were no significantly differences in the PAED score at different time points in the PACU.

The present data suggested that intraoperative infusion of dexmedetomidine combined with intravenous anesthetics can provide satisfactory intraoperative conditions for pediatric patients undergoing tonsillectomy with or without adenoidectomy, without adverse hemodynamic effects, though the lower incidence of POED was not observed.

**Abbreviations:** AS = visual analog scale, ASA = American Society of Anesthesiologists, BIS = bispectral index, BMI = body mass index, CPS = Cole 5-point scale, DBP = diastolic blood pressure, DEX = dexmedetomidine, HR = heart rate, IV = intravenous, NIBP = noninvasive blood pressure, OPS = objective pain score, PACU = postanesthesia care unit, PAED = pediatric anesthesia emergence delirium, PCA = patient-controlled analgesia, POED = postoperative emergence agitation/delirium, SBP = systolic blood pressure, $SPO_2$ = blood oxygen saturation, TCI = target controlled infusion.

**Keywords:** adenotonsillectomy, dexmedetomidine, intravenous anesthesia, postoperative emergence agitation/delirium

*Editor: Kazuo Hanaoka.*

*J-LC and Y-PP contributed equally to this work.*

*J-LC and Y-YZ conceived this study, Y-PP and Y-YZ conducted the clinical trials, J-LC, J-QW, and Y-YZ analyzed the results and wrote the manuscript. All authors reviewed the manuscript.*

*This study was supported by the "Xing-Wei" Project of Jiangsu Province Department of Health (RC2007094, XK201136), the Key Project of Nature Science Foundation of Jiangsu Education Department (11KJA320001), and the Priority Academic Program Development of Jiangsu Higher Education Institutions. No additional external funding was received for this study. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.*

*The authors have no conflicts of interest to disclose.*

*[a] Department of Anesthesiology, The Affiliated Hospital of Xuzhou Medical University, [b] Jiangsu Province Key Laboratory of Anesthesiology and Jiangsu Province Key Laboratory of Anesthesia and Analgesia Application Technology, Xuzhou Medical University, Xuzhou, Jiangsu, P.R. China.*

*[*] Correspondence: Yue-Ying Zhang, Department of Anesthesiology, The Affiliated Hospital of Xuzhou Medical University, No. 99 Huaihai Western Road, Xuzhou, Jiangsu 221002, P.R. China (e-mail: zyy0218@126.com).*



*Medicine (2016) 95:49(e5566)*

*Received: 10 October 2016 / Received in final form: 2 November 2016 / Accepted: 7 November 2016*

*http://dx.doi.org/10.1097/MD.0000000000005566*

## 1. Introduction

Postoperative emergence agitation/delirium (POED) in pediatric surgery patients is a cluster of postoperative disturbing behaviors occurring in the early period of postanesthetic recovery, characterized by a variety of presentations, including crying, excitation, and agitation, and is one of the major causes of dissatisfaction among parents and healthcare workers.[1–4] Pediatric patients undergoing tonsillectomy and adenoidectomy usually have a high incidence of POED, which increases the risk of developing postoperative airway obstruction and respiratory depression due to anatomical characteristics of operative location and increased susceptibility to opioid analgesics. Although several factors, such as anesthetics, patient, surgical, and medication-related procedures, associated with POED have been reported,[5] the etiology of POED remains to be further characterized. With the help of various drugs and techniques, anesthesiologists recently endeavor in reducing the incidence of POED and improving the quality of pediatric patients' postoperative condition.

Although different drugs, including opioids analgesics,[6] benzodiazepines,[7] $\alpha_2$-adrenergic receptor agonists such as clonidine,[8] and propofol,[9] have been used in clinic for the prevention or treatment for the established POED, the effects of these treatment regimens have been variable. Dexmedetomidine (DEX), with its potent and specific affinity of $\alpha_2$-adrenergic receptors,[10] has properties of sedation, antianxiety, and analgesic effects,[11–15] and can reduce the incidence of POED in pediatric patients undergoing inhalation anesthesia.[11,12,14,16–18] However, the impact of DEX on the incidence of POED in pediatric patients after intravenous anesthesia is unknown. In the present study, we observed the safety of intraoperative combination of DEX with intravenous anesthesia in pediatric patients undergoing tonsillectomy with or without adenoidectomy, and validity for the prevention of POED.

## 2. Methods

### 2.1. Study protocol

This prospective, randomized, controlled clinical trial was conducted at the Affiliated Hospital of Xuzhou Medical University, Xuzhou, Jiangsu, P.R. China, and the protocol of this study was approved by the Institutional Medical Ethics Committee of Xuzhou Medical University, in accordance with the approved guidelines. Written informed consent for participation in this study was obtained from parents or guardians of all the participants before the start of the study. The sample size of the study was calculated according to the previous studies[11,9–21] and was based on a pilot study.

### 2.2. Patients

Pediatric patients, aged between 2 and 8 years, of American Society of Anesthesiologist physical status I or II, and scheduled for tonsillectomy with or without adenoidectomy under general anesthesia were enrolled. Exclusion criteria included: previous general anesthesia or recent administration of sedatives or analgesics, any known allergy to the study drugs preoperative cardiovascular diseases, mental disease, nervous system disease, or developmental delay.

### 2.3. Anesthesia

All pediatric patients were not administrated any preoperative medication. Parents or guardians accompanied their children to the operating room. Anesthesia induction was carried out using 8% sevoflurane in oxygen inhaled via a face mask by pediatric patients in both groups. Standard monitoring (noninvasive blood pressure [NIBP], blood oxygen saturation [$SPO_2$], and electrocardiogram) was applied, and a peripheral intravenous cannula insertion was performed when adequate anesthetic depth was obtained. Intravenous injection of 0.5 mg/kg dexamethasone (maximum dose not more than 10 mg), 0.01 mg/kg penehyclidine hydrochloride, 0.5 mg/kg etomidate, 1 μg/kg fentanyl, and 0.2 mg/kg cisatracurium was used for anaesthesia induction, endotracheal tube was inserted through the mouth and connected to anesthetic machine with volume-controlled ventilation mode and aiming at end-tidal carbon dioxide value of 4.6 to 5.9 kPa. Plasma target concentration of 3 μg/mL propofol and remifentanyl 2 to 3 ng/mL was set for anesthesia maintenance using the target-controlled infusion pump in the pediatric patients of both 2 groups. Intraoperative blood pressure or heart rate of pediatric patients increased ≥30% above the preoperative basic value, and lasted for 5 minutes, 0.5 μg/kg fentanyl was IV injected. Intraoperative blood pressure or heart rate of pediatric patients decreased ≥30% above the preoperative basic value, and lasted for 5 minutes, 10 mL/kg Ringer solution or 0.01 mg/kg atropine was intravenously infused, respectively.

### 2.4. Randomization and blinding

All pediatric patients were assigned by dint of a computer-generated random number table into 1 of 2 groups (n = 30): group control and group DEX. The children in the group DEX received intravenous 1 μg/kg DEX diluted into 0.9% saline and administered over 10 minutes, and then continuous pump infusion of 0.5 μg/kg/h DEX until to 5 minutes before the end of surgery, while pediatric patients in the group control only received the same pump infusion rate of IV 0.9% saline served as control.

### 2.5. Postoperative care

After completion of surgery, the anesthetics were taken off, and endotracheal tube was removed after resumption of adequate spontaneous breathing. All pediatric patients were transferred into the postanesthesia care unit (PACU) once they had a regular respiratory pattern, facial grimacing and appropriate limb movement, and vital signs and $SpO_2$ was monitored.

### 2.6. Outcome measures

Another anesthetist not directly involved in anesthesia for the patient collected all related data. The heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and $SpO_2$ of pediatric patients was recorded during the operation at intervals of 5 minutes. Recovery time (defined as the time from the end of operation to spontaneous eye opening or response to verbal command) and extubation time (defined as the time from the completion of operation to extubation) was evaluated and recorded. Objective pain score (OPS) (as shown in Table 1)[22,23] was used for the evaluation of pain degree, and the PAED scale (as shown in Table 2)[24–27] and CPS (as shown in Table 3)[28–30] was employed to assess POED at the time points of 0, 5, 15, 30, 45, and 60 minutes after transfer into the PACU. One parent or guardian met the child on arrival in the recovery area and the child was allowed to regain consciousness undisturbed. Morphine 0.05 to 0.1 mg/kg was intravenously given under the condition of pain score values ≥3, and propofol 1 mg/kg was

**Table 1**

**The objective pain score (OPS).**

| Parameter | Criteria | Score |
|---|---|---|
| Systolic | Increase <20% of preoperative blood pressure | 0 |
| blood | Increase 20% to 30% of preoperative blood pressure | 1 |
| pressure | Increase >30% of preoperative blood pressure | 2 |
| Crying | Not crying | 0 |
| | Responds to age appropriate nurturing (tender loving care) | 1 |
| | Does not respond to nurturing | 2 |
| Movements | No movements, relaxed | 0 |
| | Restless, moving about in bed constantly | 1 |
| | Thrashing (moving wildly) | 2 |
| | Rigid (stiff) | 2 |
| Agitation | Asleep or calm | 0 |
| | Can be comforted to lessen the agitation (mild) | 1 |
| | Cannot be comforted (hysterical) | 2 |
| Complains of pain | Asleep | 0 |
| | States no pain | 0 |
| | Cannot localize | 1 |
| | Localizes pain | 2 |

administered intravenously to treat severe POED (score values ≥4 and lasting for 5 minutes), if the patient was assessed to be pain-free and when the parent or guardian could not console their child. The same dose of medicine was repeated at the 10 minutes intervals if necessary.

### 2.7. Statistical analysis

Data analyses first entailed characterization of participants using descriptive and summary statistics (mean ± SD for HR, SBP, DBP, recovery time, and extubation time; percentages for incidence of severe POED, median for OPS, PAED, and Cole 5-point scale [CPS]). Data between 2 groups were compared using Student *t* test, Fischer test, or Mann–Whitney *U* test. Statistical analyses of data were generated using Statistical Package for Social Science, version 11.0 (SPSS 11.0). All *P* values given are based on 2-tailed tests and a *P* value of $<0.05$ was considered statistically significant.

## 3. Results

Figure 1 shows the CONSORT flow diagram for pediatric patients in the present study. A total number of 68 pediatric patients were enrolled in this study, 8 patients were eliminated from data analysis, and the data for 60 patients were analyzed.

Pediatric patient demographic data are shown in Table 4. There were no significant differences between the 2 groups in demographic data, anesthesia duration, and operation duration of all pediatric patients. Compared with the control group, extubation, and recovery times were significantly prolonged in the DEX group ($P<0.05$).

Table 5 shows hemodynamic changes of pediatric patients in the 2 groups at time point of baseline before study drug administration and from 5 to 30 minutes after study drug administration at 5 minutes intervals. Both groups were comparable in values of baseline DBP, SBP, and HR. Compared with the group control, the group DEX displayed a significant decrease in HR for all time points ($P<0.05$) after study drug injection, except for at the time point of 20 minutes; however, none of the patients need treatment for bradycardia. After injection of the study drug, neither DBP nor SBP differed between the group DEX and group control, although DBP and SBP in the group DEX were slightly higher than that in the group control for all time points.

The variables of pediatric patients measured in the PACU in both groups at 5 minutes intervals from 0 to 60 minutes after awakening are shown in Table 6. On the CPS, severe POED was defined as a score of 4 to 5. Although severe POED was not found in the 2 groups, the median (range) POED scores were significantly higher in the group control (3 [1–4], 2 [1–4], and 2 [1–3]) than that in the group DEX (2.5 [0–6], 2 [0–6], and 2 [0–6], from 15 to 45 minutes after awakening ($P<0.05$, $P<0.05$, and $P<0.05$, respectively); however, most episodes of POED in the group control were self-limiting and did not require any treatment. The median (range) OPS scores from 15 to 45 minutes after awakening were statistically lower in the group DEX (0 [0–9], 0 [0–5], and 0 [0–7]) compared with the group control (2.5 [0–6], 2 [0–6], and 2 [0–6], ($P<0.05$, $P<0.05$, and $P<0.05$, respectively). On arrival in the PACU until 60 minutes after awakening, there was no statistical difference in PAED score between the group control and group DEX.

## 4. Discussion

DEX, selectively binding to postsynaptic $\alpha_2$ adrenergic receptor located in the central nucleus of solitary tract, inhibits nervous impulse from sympathetic neurons in anterior horn of the spinal cord and reduces systemic sympathetic nervous tension, and inhibits the release of norepinephrine from sympathetic nerve endings through activating presynaptic $\alpha_2$ adrenergic receptor. Its sedative effect is similar to physiological sleep, with less respiratory depression, and decrease of HR or blood pressure (BP). A study found that IV injection of DEX with single small dose of 0.5 μg/kg over 5 minutes, combined with 1 minimum alveolar concentration (MAC) of sevoflurane or desflurane for anesthesia maintenance, significantly decreased HR of pediatric patients, likewise, no evident changes were found in the BP during

**Table 2**

**The pediatric anesthesia emergence delirium (PAED) scale.**

| Behavior | Not at all | Just a little | Quite a bit | Very much | Extremely |
|---|---|---|---|---|---|
| Makes eye contact with caregiver | 4 | 3 | 2 | 1 | 0 |
| Actions are purposeful | 4 | 3 | 2 | 1 | 0 |
| Aware of surroundings | 4 | 3 | 2 | 1 | 0 |
| Restless | 0 | 1 | 2 | 3 | 4 |
| Inconsolable | 0 | 1 | 2 | 3 | 4 |

**Table 3**

**The Cole 5-point scale (CPS) score.**

| Behavior | Score |
|---|---|
| Sleeping | 1 |
| Awake, calm | 1 |
| Irritable, crying | 3 |
| Inconsolable crying | 4 |
| Severe restlessness, disorientation | 5 |

the study period.[31] Patel et al[28] showed that children with obstructive sleep apnea syndrome received IV DEX with load dosage of 2 μg/kg over 10 minutes, followed by continuing infusion at the rate of 0.7 μg/kg/h, under anesthesia maintenance with 1 MAC sevoflurane, had significantly lower BP and HR almost the entire duration of the anesthetic compared with the control group, but none of the patients needed intervention for bradycardia or hypotension on the basis of study criteria. However, it has not been reported in the literature that DEX combined with propofol and remifentanil was used for anesthesia maintenance in pediatric patients. Because remifentanil has an obvious inhibitory effect on HR, the hemodynamic changes should be carefully monitored, when DEX is used in combination with remifentanil. In the present study, HR in the group DEX was significantly lower than that in the group control, but it did not require any treatment, and no evidence was found for changes in the DBP or SBP during the study episode. Consistent with other earlier studies, the authors did not found the bidirectional changes of BP observed in adult patients, in the pediatric patients, when dexmedetomidine was administrated.

Because pediatric patients undergoing tonsillectomy with or without adenoidectomy, often accompanied by obstructive sleep apnea syndrome, are sensitive to opioids and at high risk for respiratory depression, and on account of rapid metabolism of propofol and remifentanil in body and severe pain induced by withdrawal of both drugs, fentanyl in small doses of 1 μg/kg was given for anesthesia induction in the pediatric patients of this study. Although the same anesthesia was used in both 2 groups, compared with the control group, the extubation and recovery times were significantly prolonged in the dexmedetomidine group. Guler et al[32] found that 5 minutes before the end of operation, intravenous injection of a single dose of 0.5 μg/kg DEX could increase the extubation and recovery times. However,

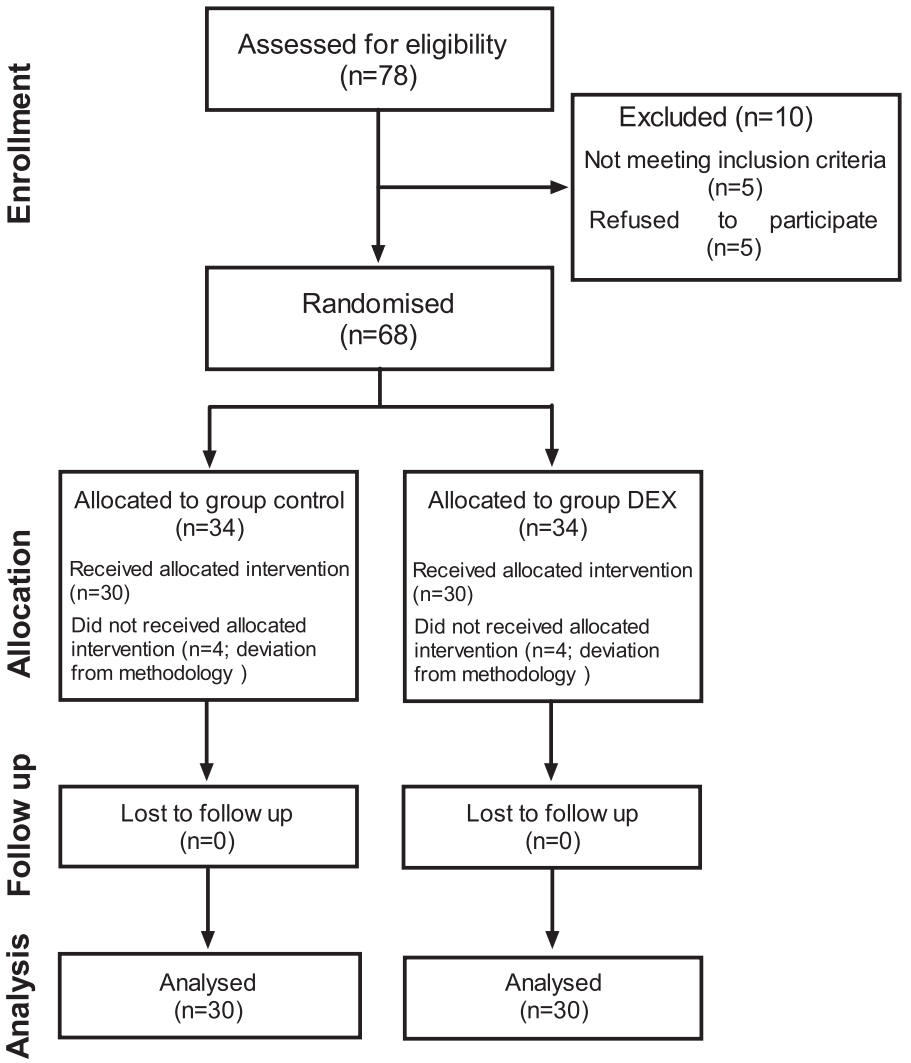


**Figure 1.** CONSORT flow diagram of patients included in the study.

**Table 4**

**Pediatric patient demographic data, anesthesia duration, operation duration, extubation, and recovery times of pediatric patients included in the study.**

| | Group control | Group DEX |
|---|---|---|
| Age, y | 3.9±1.8 | 4.1±1.5 |
| Weight, kg | 21.7±7.9 | 20.9±5.8 |
| Gender; male:female | 20:10 | 18:12 |
| Operation duration, min | 60.6±15.2 | 58.9±12.9 |
| Anesthesia duration, min | 89.5±12.8 | 91.2±16.3 |
| Extubation time, min | 11.6±3.0 | 14.4±4.5* |
| Recovery time, min | 12.4±3.5 | 15.2±5.1* |

Data are presented as mean±SD, or number of patients.
DEX=dexmedetomidine.
* $P<0.05$ versus group control.

a number of studies have suggested that perioperative administration of dexmedetomidine decreases or has no effects on the extubation and recovery times.[28,33] The causes of conflicting data may attribute to different doses of intraoperative anesthetics: there was no significant difference in doses of intraoperative anesthetics between the 2 groups in this study, because there were no obvious changes in the DBP or SBP during the study episode. But the decreased intraoperative anesthetics were found in the above other studies.

Many reasons can cause POED, and it shows great variations in the incidence of POED among different studies, attributing to application of different evaluation criteria and evaluation time points.[34] PAED score is wildly accepted as an ideal, reliable, and valid rating scale to evaluate emergence agitation in pediatric patients in the current study.[25] To some extent, PAED score can distinguish the postoperative agitation from irritability caused by pain, except for the last 2 items, restless and inconsolable, being similar to the irritable behaviors caused by pain. Therefore, PAED score was employed in the present study. The development and evaluation of PAED rating scales in pediatric patients was first carried out 10 minutes after recovering from general anesthesia and keeping awake. However, we found that most pediatric patients were all in a state of sleep after extubation in the present study, the scores of first 3 items in PAED score: makes eye contact with caregiver, actions are purposeful, or aware of surroundings, were all 4 point respectively, which was not consistent with the actual condition that the pediatric patients being asleep did not possibly display any agitation. So we improved the PAED score, if only the pediatric patients were asleep, the scores of first 3 items in PAED score were all designated as 0 point. To avoid deviation in our improved PAED score, we also combined CPS score with PAED score. CPS score is conveniently used and easily distinguished between mild and severe POED. To elucidate the relation between POED and pain, we used OPS to estimate postoperative pain intensity in the pediatric patients at different time points. At the time point of 0 and 5 minutes after transfer into the PACU, all the pediatric patients in the 2 groups showed no significant differences in the 3 scores, only OPS and CPS scores significantly decreased in the group DEX as compared with the group control at 15, 30, and 45 minutes after their arrival at the PACU, indicating that pain is not consistent with postanesthesia ED in pediatric patients, despite pain being regarded as 1 reason causing POED. We also observed that there was no significant difference in incidence rate of severe POED between the group DEX (27%) and the group control (30%), which was inconsistent with the conclusions from other groups.[28,33] The causes of the different data from the present and other studies might be due to propofol used for anesthesia maintenance in the 2 groups, and propofol can reduce the incidence of postanesthesia ED, which leads to no significant prevention effects of DEX on POED. Nevertheless, sevoflurane, being as a major maintenance anesthetic in other related studies,

**Table 5**

**Hemodynamic data of pediatric patients included in the study.**

| | | Baseline | 5 min | 10 min | 15 min | 20 min | 25 min | 30 min |
|---|---|---|---|---|---|---|---|---|
| DBP (mm Hg) | Group control | 66.5±11.3 | 56.8±15.0 | 55.6±20.3 | 60.3±17.3 | 56.7±12.1 | 58.4±12.3 | 59.4±13.2 |
| | Group DEX | 71.4±13.2 | 60.5±11.7 | 63.1±12.3 | 63.7±10.6 | 62.2±10.4 | 61.4±10.4 | 59.4±10.2 |
| SBP (mm Hg) | Group control | 111.8±13.9 | 105.1±17.6 | 103.5±19.7 | 98.7±30.4 | 101.2±16.7 | 102.1±15.7 | 104.2±16.9 |
| | Group DEX | 119.0±15.5 | 109.7±11.0 | 109.7±13.8 | 106.7±11.0 | 105.8±11.3 | 106.4±12.1 | 105.1±11.7 |
| HR (bpm) | Group control | 117.7±14.8 | 105.6±21.4 | 95.8±16.0 | 95.1±16.7 | 86.2±23.4 | 92.8±11.5 | 92.6±11.6 |
| | Group DEX | 115.2±20.4 | 83.5±16.9* | 79.4±12.4* | 80.5±11.0* | 79.4±10.7 | 77.8±9.8* | 78.9±12.0* |

Data are represented as a mean±SD.
DBP=diastolic blood pressure, DEX=dexmedetomidine, HR=heart rate, SBP=systolic blood pressure.
* $P<0.05$ versus group control.

**Table 6**

**Postanesthesia care unit data of pediatric patients included in the study.**

| | | 0 min | 5 min | 15 min | 30 min | 45 min | 60 min |
|---|---|---|---|---|---|---|---|
| CPSC | Group control | 3 (1–5) | 3 (1–4) | 3 (1–4) | 2 (1–4) | 2 (1–3) | 2 (1–3) |
| | Group DEX | 2 (1–5) | 2 (1–5) | 2 (1–4)* | 1 (1–3)* | 2 (1–3)* | 2 (1–3) |
| OPS | Group control | 4 (0–9) | 3 (0–7) | 2.5 (0–6) | 2 (0–6) | 2 (0–6) | 2 (0–6) |
| | Group DEX | 0 (0–9) | 0 (0–9) | 0 (0–9)* | 0 (0–5)* | 0 (0–7)* | 0 (0–3) |
| PAED | Group control | 1 (0–18) | 1 (0–9) | 0.5 (0–6) | 0 (0–6) | 0 (0–6) | 0 (0–6) |
| | Group DEX | 0 (0–18) | 0 (0–18) | 0 (0–18) | 0 (0–5) | 0 (0–8) | 0 (0–3) |

Data are represented as a median (range) value of the maximum score.
CPS=Cole 5-point scale, DEX=dexmedetomidine, OPS=objective pain score, PAED=pediatric anesthesia emergence delirium.
* $P<0.05$ versus group control.

has an incidence of POED as high as about 50% to 80%,[35] especially in children and adolescents. It is reported that propofol-combined fentanyl indeed can be used for the prevention of POED after sevoflurane anaesthesia. In consideration of limitation of a relatively smaller sample size, which might lead to no any significant difference in POED score between the 2 groups, further research with a larger sample still will be carried out to clarify the exact causes of POED in the future studies.

Taken together, in the present study, we found that intravenous general anesthesia combined with intraoperative continuous infusion of dexmedetomidine could satisfy the anesthesia requirement for pediatric patients undergoing tonsillectomy with or without adenoidectomy, and had on significant side effects on hemodynamic changes, though a significantly lower incidence of POED has not been observed.

## References


[1] Miyasaka K. Postanaesthetic excitation and agitation. Paediatr Anaesth 2003;13:641–2.

[2] Yamashita M. Postanaesthetic excitation and agitation. Paediatr Anaesth 2003;13:641.

[3] Ibacache ME, Munoz HR, Brandes V, et al. Single-dose dexmedetomidine reduces agitation after sevoflurane anesthesia in children. Anesth Analg 2004;98:60–3.

[4] Voepel-Lewis T, Malviya S, Tait AR. A prospective cohort study of emergence agitation in the pediatric postanesthesia care unit. Anesth Analg 2003;96:1625–30.

[5] Na HS, Song IA, Hwang JW, et al. Emergence agitation in children undergoing adenotonsillectomy: a comparison of sevoflurane vs. sevoflurane-remifentanil administration. Acta Anaesthesiol Scand 2013;57:100–5.

[6] Cohen IT, Hannallah RS, Hummer KA. The incidence of emergence agitation associated with desflurane anesthesia in children is reduced by fentanyl. Anesth Analg 2001;93:88–91.

[7] Cohen IT, Drewsen S, Hannallah RS. Propofol or midazolam do not reduce the incidence of emergence agitation associated with desflurane anaesthesia in children undergoing adenotonsillectomy. Paediatr Anaesth 2002;12:604–9.

[8] Malviya S, Voepel-Lewis T, Ramamurthi RJ, et al. Clonidine for the prevention of emergence agitation in young children: efficacy and recovery profile. Pediatr Anesth 2006;16:554–9.

[9] Aouad MT, Yazbeck-Karam VG, Nasr VG, et al. A single dose of propofol at the end of surgery for the prevention of emergence agitation in children undergoing strabismus surgery during sevoflurane anesthesia. Anesthesiology 2007;107:733–8.

[10] Zhang H, Zhou F, Li C, et al. Molecular mechanisms underlying the analgesic property of intrathecal dexmedetomidine and its neurotoxicity evaluation: an in vivo and in vitro experimental study. PLoS One 2013;8: e55556.

[11] Ge DJ, Qi B, Tang G, et al. Intraoperative dexmedetomidine promotes postoperative analgesia and recovery in patients after abdominal colectomy: a consort-prospective, randomized controlled clinical trial. Medicine (Baltimore) 2015;94:e1727.

[12] Ge DJ, Qi B, Tang G, et al. Intraoperative dexmedetomidine promotes postoperative analgesia in patients after abdominal colectomy: a consort-prospective, randomized, controlled clinical trial. Medicine (Baltimore) 2015;94:e1514.

[13] Ge DJ, Qi B, Tang G, et al. Intraoperative dexmedetomidine promotes postoperative analgesia and recovery in patients after abdominal hysterectomy: a double-blind, randomized clinical trial. Sci Rep 2016; 6:21514.

[14] Li YY, Ge DJ, Li JY, et al. Sex differences in the morphine-sparing effects of intraoperative dexmedetomidine in patient-controlled analgesia following general anesthesia: a consort-prospective, randomized, controlled clinical trial. Medicine (Baltimore) 2016;95:e3619.

[15] Zhao JN, Kong M, Qi B, et al. Comparison of the morphine-sparing effect of intraoperative dexmedetomidine with and without loading dose following general anesthesia in multiple-fracture patients a prospective, randomized, controlled clinical trial. Medicine (Baltimore) 2016;95: e4576.

[16] Zhu M, Wang H, Zhu A, et al. Meta-analysis of dexmedetomidine on emergence agitation and recovery profiles in children after sevoflurane anesthesia: different administration and different dosage. PLoS One 2015;10:e0123728.

[17] Zhang H, Li M, Zhang SY, et al. Intravenous dexmedetomidine promotes spinal bupivacaine anesthesia and postoperative analgesia in lower limb surgery: a double-blind, randomized clinical CONSORT study. Medicine (Baltimore) 2016;95:e2880.

[18] Ren C, Chi M, Zhang Y, et al. Dexmedetomidine in postoperative analgesia in patients undergoing hysterectomy: a consort-prospective, randomized, controlled trial. Medicine (Baltimore) 2015;94:e1348.

[19] Tuffaha HW, Reynolds H, Gordon LG, et al. Value of information analysis optimizing future trial design from a pilot study on catheter securement devices. Clin Trials 2014;11:648–56.

[20] Charan J, Biswas T. How to calculate sample size for different study designs in medical research? Indian J Psychol Med 2013;35:121–6.

[21] Hwang W, Lee J, Park J, et al. Dexmedetomidine versus remifentanil in postoperative pain control after spinal surgery: a randomized controlled study. BMC Anesthesiol 2015;15:21.

[22] Tandon M, Singh A, Saluja V, et al. Validation of a new "objective pain score" vs. "numeric rating scale" for the evaluation of acute pain: a comparative study. Anesth Pain Med 2016;6:e32101.

[23] Hesselgard K, Larsson S, Romner B, et al. Validity and reliability of the Behavioural Observational Pain Scale for postoperative pain measurement in children 1-7 years of age. Pediatr Crit Care Med 2007;8:102–8.

[24] Locatelli BG, Ingelmo PM, Emre S, et al. Emergence delirium in children: a comparison of sevoflurane and desflurane anesthesia using the Paediatric Anesthesia Emergence Delirium scale. Paediatr Anaesth 2013;23:301–8.

[25] Sikich N, Lerman J. Development and psychometric evaluation of the pediatric anesthesia emergence delirium scale. Anesthesiology 2004;100: 1138–45.

[26] Bong CL, Lim E, Allen JC, et al. A comparison of single-dose dexmedetomidine or propofol on the incidence of emergence delirium in children undergoing general anaesthesia for magnetic resonance imaging. Anaesthesia 2015;70:393–9.

[27] Yao Y, Qian B, Lin Y, et al. Intranasal dexmedetomidine premedication reduces minimum alveolar concentration of sevoflurane for laryngeal mask airway insertion and emergence delirium in children: a prospective, randomized, double-blind, placebo-controlled trial. Paediatr Anaesth 2015;25:492–8.

[28] Patel A, Davidson M, Tran MC, et al. Dexmedetomidine infusion for analgesia and prevention of emergence agitation in children with obstructive sleep apnea syndrome undergoing tonsillectomy and adenoidectomy. Anesth Analg 2010;111:1004–10.

[29] Cole JW, Murray DJ, McAllister JD, et al. Emergence behaviour in children: defining the incidence of excitement and agitation following anaesthesia. Paediatr Anaesth 2002;12:442–7.

[30] Peng W, Zhang T. Dexmedetomidine decreases the emergence agitation in infant patients undergoing cleft palate repair surgery after general anesthesia. BMC Anesthesiol 2015;15:145.

[31] Deutsch E, Tobias JD. Hemodynamic and respiratory changes following dexmedetomidine administration during general anesthesia: sevoflurane vs desflurane. Paediatr Anaesth 2007;17:438–44.

[32] Guler G, Akin A, Tosun Z, et al. Single-dose dexmedetomidine reduces agitation and provides smooth extubation after pediatric adenotonsillectomy. Paediatr Anaesth 2005;15:762–6.

[33] Shukry M, Clyde MC, Kalarickal PL, et al. Does dexmedetomidine prevent emergence delirium in children after sevoflurane-based general anesthesia? Paediatr Anaesth 2005;15:1098–104.

[34] Vlajkovic GP, Sindjelic RP. Emergence delirium in children: many questions, few answers. Anesth Analg 2007;104:84–91.

[35] Bakhamees HS, Mercan A, El-Halafawy YM. Combination effect of low dose fentanyl and propofol on emergence agitation in children following sevoflurane anesthesia. Saudi Med J 2009;30:500–3.