

## Original Article

# Effect of intraoperative application of dexmedetomidine on early postoperative cognitive function and serum brain-derived neurotrophic factor (BDNF) in children undergoing tonsillectomy

Yiping Bai\*, Hong Yu\*, Maohua Wang, Yunqiang Wan, Xueru Liu, Ni Tang, Liquan Mo, Jicheng Wei

Department of Anesthesiology, The Affiliated Hospital of Southwest Medical University, Luzhou 646000, Sichuan Province, China. \*Equal contributors.

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**Abstract:** Objective: The purpose of the study was to explore the effect of intraoperative application of dexmedetomidine on early postoperative cognitive function (POCD) and serum brain-derived neurotrophic factor (BDNF) in children undergoing tonsillectomy. Methods: One hundred twenty four children undergoing tonsillectomy were enrolled in the study and divided into two groups at random, a dexmedetomidine group (Dex group) and a total intravenous anesthesia group (T group). After stable anesthesia, children in Dex group were given dexmedetomidine (0.5 µg/kg), at concentration of 0.5 µg/ml. The injection time was 10 min. Children in T group were given the same amount of normal saline (0.9%) at an injection time of 10 min. Intraoperative propofol and remifentanyl dosage, postoperative adverse reaction, etc., were recorded. All children underwent neuropsychological testing on the first day before and the seventh day after surgery, respectively. The Z-value method was used to comprehensively evaluate whether the children developed POCD after surgery. Blood was drawn for serum BDNF levels analysis on the first day before ( $T_0$ ), and the first day ( $T_1$ ) and seventh day ( $T_2$ ) after surgery. Results: Intraoperative consumption of propofol and remifentanyl was reduced in the Dex group, compared with the T group ( $P=0.015$ ,  $P=0.012$ ). The occurrence of postoperative agitation was also reduced in Dex group ( $P=0.026$ ). The children in Dex group had higher verbal IQs, verbal comprehension, and Trail Making Test scores, in neuropsychological testing, compared with those in T group on the seventh day after surgery ( $P=0.044$ ,  $P=0.031$ ,  $P=0.015$ ). In T group, twelve children developed POCD on the seventh day after surgery (16.1%). In contrast, four children developed POCD in Dex group (6.4%). The occurrence of POCD in Dex group was lower than that in T group ( $P=0.032$ ). There were no differences in preoperative serum BDNF levels between Dex group and T group before surgery ( $P=0.206$ ). Compared with the postoperative BDNF levels of T group, postoperative BDNF levels in Dex group were increased significantly on the first day and the seventh day after surgery, respectively ( $P=0.003$ ,  $P=0.035$ ). The logistic regression analysis showed postoperative agitation, and serum BDNF levels were related to the occurrence of POCD in those children undergoing tonsillectomy. Conclusions: Intraoperative dexmedetomidine can reduce the occurrence of POCD after surgery in children undergoing tonsillectomy, which might be related to the increase of BDNF levels induced by dexmedetomidine.

**Keywords:** Dexmedetomidine, children, tonsillectomy, postoperative cognitive dysfunction, brain-derived neurotrophic factor

## Introduction

Postoperative cognitive dysfunction (POCD), a kind of postoperative complication of the central nervous system, is characterized by consciousness, cognition, orientation, thinking, memory, and sleep disorders after surgery and anesthesia. POCD can delay recovery time and prolong hospitalization, and patients may even

develop permanent cognitive impairment that decreases quality of life [1, 2].

One study showed surgical type, operation time, and anesthesia contributed to occurrence of POCD [3], and another study reported that the occurrence rate of POCD was 25.8% one week after surgery and 9.9% three months after surgery in the elderly, respectively [4]. To date,

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some studies have shown that cognitive function of children was impaired by a range of anesthetic agents in the recovery period after day-case anesthesia [5-8]. However, specific occurrence of POCD is still unclear after surgery in children.

Currently, more and more children receive surgical treatment and anesthesia. This means that more children will risk POCD. Some studies showed when infant or juvenile rats accepted anesthetic drugs, they suffered some dysfunctions, such as neuron apoptosis, excessive expression of inflammatory factors, abnormal protein deposition, widespread structural damage, and cognitive dysfunction in the long run [9, 10]. Those results indicate that POCD may have more serious influences on children's personal and social lives. Therefore, it is necessary to find effective drugs to reduce the occurrence of POCD in children. Dexmedetomidine is an anesthetic and sedative drug. This study showed that dexmedetomidine could increase plasma BDNF caused by anesthetics, and this effect lasted for 24 hours after surgery [11]. Meanwhile, another study showed that serum BDNF was reduced in POCD patients after colorectal surgery [12].

However, it is not clear whether dexmedetomidine has a BDNF-related effect on POCD in children. Our study aims to explore whether dexmedetomidine has an effect on POCD in children undergoing tonsillectomy and analyze changes of serum BDNF levels.

### Materials and methods

#### *Enrolled children*

This study was approved by the Health and Human Research Ethics Committee of the Affiliated Hospital of Luzhou Medical College. One hundred twenty four children undergoing tonsillectomy were enrolled in the study (14 years > age > 5 years, [ASA] grade I-II, between January 2014 and September 2015). Exclusion criteria were: (1) history of neurologic or psychiatric disease, (2) current use of mental medication, (3) severe visual, auditory, or motor handicap, (4) acute infection, or (5) other severe system disease. Enrolled children were randomly divided into two groups, a dexmedetomidine group (Dex group) and a total intravenous anesthesia group (T group). Children from another

control group were enrolled to reduce the influence of any practical effect in the neuropsychological test. Control subjects were recruited from a pool of volunteers (14 years > age > 5 years) who were being treated at the study's hospital and did not undergo any surgery. Written informed consents were obtained from the participants and their parents prior to enrollment.

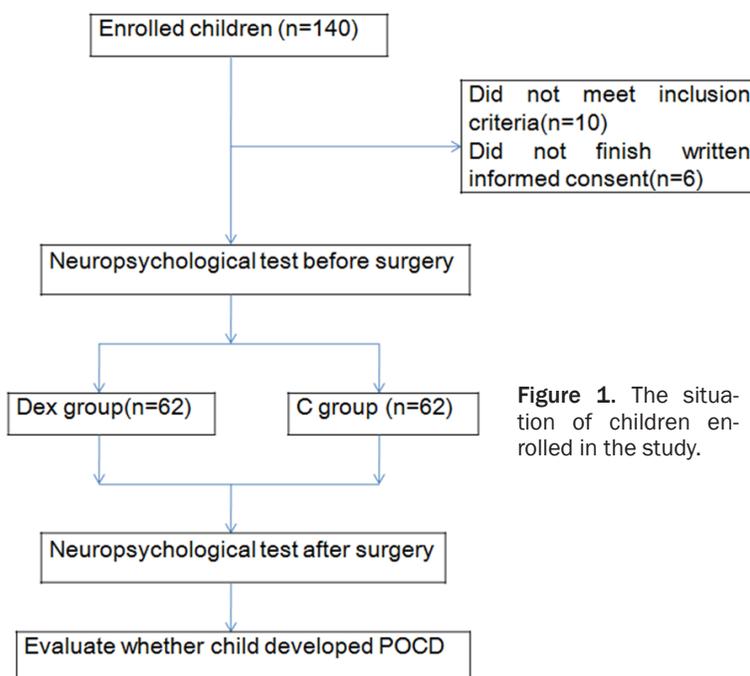
#### *Surgery and anesthesia*

Tonsillectomies were performed by the same surgery team. No preoperative medication was administered. The protocols of anesthesia were standardized: induction with midazolam (0.02-0.04 mg/kg, i.v.), fentanyl (0.001-0.003 mg/kg, i.v.), vecuronium (0.10-0.2 mg/kg, i.v.), and propofol (1.0-2.0 mg/kg, i.v.). After tracheal intubation, anesthesia was maintained with propofol (5-8 mg/kg/h, continuous i.v. infusion), remifentanyl (5-10 µg/kg/h, continuous i.v. infusion), and the sevoflurane concentration was variably adjusted 0.1-1% in order to assure a range of 30 to 60 and the need of operation. After stable anesthesia, children in Dex group, were given dexmedetomidine (0.5 µg/kg, intravenous) at a concentration of 0.5 µg/ml, and the injection time was 10 min. Children in T group were given the same amount of normal saline (0.9%, intravenous), also with an injection time of 10 min. Bispectral indices (BIS) were monitored during the operation, and a target range of 30-60 was maintained during anesthesia. Anesthetic drugs were stopped at 10 minutes before end of the surgery. After surgery and tracheal extubation, children were moved into post-anesthesia care unit (PACU).

#### *Basic information*

The basic information of enrolled children was measured by two senior nurses, including age, gender, education level and family structure, dosage of anesthetic drugs, postoperative agitation, nausea, vomiting, cough, bradycardia, hypotension, etc. (postoperative agitation was scored as follows: 1= awake, calm, cooperative; 2= crying, required consoling; 3= irritable/restless, screaming, inconsolable; 4= combative, disoriented, thrashing. If the score was 3 or 4, this child was classified as agitated. Bradycardia: heart rate < 60/min. Hypotension: 5-10 years, systolic blood pressure (SBP) < (70 + 2 × year) mmHg; > 10 years, SBP < 90

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**Figure 1.** The situation of children enrolled in the study.

mmHg). The Chinese version of the neuropsychological test battery was used to evaluate neuropsychological dysfunction on the first day before and the seventh day after surgery, respectively (interval time: the same number of days as in control group). The battery of tests included the Trail Making Test Part A, the Stroop Color and Word Test, the Digit Span Forward, the Digit Span Backward, the Wechsler Intelligence Scale for Children-III including Full Scale IQ, verbal IQ, and performance IQ, verbal comprehension, perceptual organization, freedom from distractibility, and processing speed. Earlier studies showed that these tests could be performed in children [13-17]. The Chinese version of the visual analog scale (VAS) was used to assess pain after the surgery [18].

### POCD

The Z-value method was used to evaluate whether the children developed POCD after surgery. The Z-value was calculated:  $Z = (X - X_{\text{reference}}) / \text{standard deviation (SD)}$ , where X was the difference between baseline and post-operative cognitive test scores, X-reference was the difference between the baseline and the relevant time in the control group, and SD is the change in score for the control group. If more than two tests (including two tests) had a  $Z > 1.96$ , the child was considered to have developed POCD.

### Serum BDNF measurement

Blood samples were collected on the first day before ( $T_0$ ), the first day ( $T_1$ ) and the seventh day ( $T_2$ ) after surgery, respectively, which were kept at room temperature for 20 min, centrifuged at  $2000 \times g$  for 20 min, and the supernatant was isolated. Serum BDNF levels were measured using an enzyme-linked immunosorbent assay (ELISA) method. BDNF antibody was provided by Rainbow (US). The serum BDNF levels were measured according to the kit instructions.

### Statistical analysis

All data were analyzed using SPSS 19.0 and GraphPad Prism 5.0. The data was presented as the mean  $\pm$  SD or n (%). Statistical comparisons were performed by unpaired or paired t-test for the continuous data, and the Chi-square test for the categorical data. Statistical comparisons of BDNF levels at the different time points were performed by one-way analysis of variance (ANOVA). Logistic regression analysis was used for regression analysis. A P value  $< 0.05$  was considered to represent a statistically significant difference.

## Results

### Related process of the study

The study analyzed data from 140 children undergoing tonsillectomy. Ten children did not meet the inclusive criteria, and six children were excluded because they and their parents disagreed with written informed consent. Therefore, 124 children were enrolled in the study and divided into Dex group and T group at random. The related process of the study is shown in **Figure 1**.

### Characteristics between Dex group and T group

There were no significant differences between Dex group and T group in the basic information of enrolled children, including age, gender, education, body weight, method of birth, history of

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**Table 1.** Demographic, clinical, and surgical characteristics of children undergoing tonsillectomy between Dex group and T group

Characteristic	Dex group	T group	P value
Age (years) <sup>a</sup>	9.8±2.9	9.7±3.3	0.950
Gender (F/M) <sup>b</sup>	28/34	30/32	0.720
Education (years) <sup>a</sup>	3.9±2.0	4.0±1.9	0.910
Body weight (kg) <sup>a</sup>	33.6±11.0	33.5±9.8	0.970
Whole family structure <sup>b</sup>	10/52	8/54	0.610
Way of birth (E/CS) <sup>b</sup>	20/42	22/40	0.710
Surgery and anesthesia <sup>b</sup>	15/47	13/49	0.660
Anesthesia time (min) <sup>a</sup>	41.5±5.0	42.4±4.4	0.640
Surgical time (min) <sup>a</sup>	34.5±5.1	33.7±4.1	0.730
Awake time (min) <sup>a</sup>	8.7±1.5	8.9±2.2	0.830
Propofol (mg) <sup>a</sup>	162.8±41.6	200.3±31.1	0.015
Remifentanyl (ug) <sup>a</sup>	155.4±30.4	185.8±24.7	0.012

Data presented as mean ± SD or -/-, Dex group: dexmedetomidine group, T group: total intravenous anesthesia group, E: eutocia, CS: cesarean section, a: unpaired t-test, b: Chi-square test, statistically significant between-group difference ( $P < 0.05$ ).

**Table 2.** Postoperative adverse reaction characteristics of children undergoing tonsillectomy between Dex group and T group

Variable	Dex group	T group	P value
Nausea <sup>b</sup>	8	5	0.560
Vomiting <sup>b</sup>	5	3	0.710
Cough <sup>b</sup>	20	25	0.450
Bradycardia <sup>b</sup>	2	1	1.000
Hypotension <sup>b</sup>	0	0	1.000
Postoperative infection <sup>b</sup>	3	1	0.620
Postoperative pain (VAS) <sup>a</sup>	0.81±0.06	0.82±0.05	0.690
Postoperative agitation <sup>b</sup>	5	15	0.026

Data presented as mean ± SD or -, Dex group: dexmedetomidine group, T group: total intravenous anesthesia group, a: unpaired t-test, b: Chi-square test, statistically significant between-group difference ( $P < 0.05$ ).

surgery and anesthesia, anesthesia time, surgical time, or awake time ( $P > 0.05$  in all data). However, children in Dex group had lower consumption of propofol and remifentanyl, compared with those in T group ((162.8±41.6 mg vs 200.3±31.1 mg,  $P=0.015$ ), (155.4±30.4 µg vs 185.8±24.7,  $P + 0.012$ )). Data are shown in **Table 1**.

### Postoperative adverse reactions between Dex group and T group

There were also no significant differences between Dex group and T group in some postoperative adverse reactions, including nau-

sea, vomiting, cough, bradycardia, hypotension, postoperative infection, and postoperative pain. However, children in Dex group had lower occurrence rate of postoperative agitation, compared with those in T group (5/62 vs 15/62,  $P=0.026$ ). Data are shown in **Table 2**.

### Neuropsychological test between Dex group and T group

There were no significant differences between Dex group and T group in neuropsychological test on the first day before surgery ( $P > 0.05$  in all data), data was shown in **Supplementary Table 1**. However, children in Dex group had higher verbal IQ, verbal comprehension, and Trail Making Test scores, compared with those in T group on the seventh day after surgery ( $P=0.044$ ,  $P=0.031$ ,  $P=0.015$ ). Data is shown in **Table 3**.

### POCD between Dex group and T group

According to POCD assessment, the result showed that among 62 children in the T group, 12 children developed POCD on the seventh day after surgery (16.1%). In contrast, four children developed POCD in Dex group (6.4%). The occurrence of POCD in Dex group was lower than that in T group ( $P=0.032$ ). Data are shown in **Table 4**.

### Serum BDNF levels between Dex group and T group

There were no differences in preoperative serum BDNF levels between Dex group and T group ( $P=0.206$ ). Compared with the postoperative BDNF levels of T group, postoperative BDNF levels in Dex group increased significantly on the first day and the seventh day after surgery, respectively ( $P=0.003$ , 0.035). Compared with the postoperative BDNF levels of Dex group, postoperative BDNF levels in Dex group also increased significantly on the first day and the seventh day after surgery, respectively ( $P=0.043$ ). Data is shown in **Table 5**.

### The logistic regression analysis between postoperative agitation, serum BDNF levels, and POCD

According to POCD assessment, among 124 children, 16 children had developed POCD after

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**Table 3.** Postoperative characteristics in neuropsychological test of children undergoing tonsillectomy between Dex group and T group

Cognitive test	Dex group	T group	P value
Wechsler Intelligence Scale			
Full Scale IQ <sup>a</sup>	100.0±12.2	95.0±19.5	0.540
Verbal IQ <sup>a</sup>	97.8±13.9	84.0±13.1	0.044
Performance IQ <sup>a</sup>	101.9±12.4	93.8±13.7	0.170
Verbal comprehension <sup>a</sup>	103.5±10.9	93.5±9.0	0.031
Perceptual organization <sup>a</sup>	102.7±8.7	99.5±10.6	0.490
Freedom from distractibility <sup>a</sup>	105.7±7.7	102.5±8.8	0.320
Processing speed <sup>a</sup>	99.2±11.8	102.7±10.7	0.440
Trail-Making Test <sup>a</sup>	83.4±8.2	76.1±5.8	0.015
Stroop Color and Word Test <sup>a</sup>	19.7±3.7	20.7±4.2	0.620
Digit Span Forward <sup>a</sup>	5.6±1.1	5.7±0.7	0.850
Digit Span Backward <sup>a</sup>	2.8±0.7	3.0±0.7	0.330

Data presented as mean ± SD, Dex group: dexmedetomidine group, T group: total intravenous anesthesia group, a: unpaired t-test, statistically significant between-group difference ( $P < 0.05$ ).

**Table 4.** Occurrence of POCD in children undergoing tonsillectomy between Dex group and T group

Variable	Dex group	T group	P value
Two term	2	2	-
Three term	1	3	-
Four term	1	3	-
More than four term	1	5	-
Occurrence of POCD <sup>b</sup>	4	12	0.032

Data presented as -, Dex group: dexmedetomidine group, T group: total intravenous anesthesia group, b: Chi-square test, statistically significant between-group difference ( $P < 0.05$ ). POCD: postoperative cognitive function.

**Table 5.** Comparison of perioperative BDNF contents between the two groups of children (ng/ml)

Variable	Preoperative day one	Postoperative day one	Postoperative day seven	P value <sup>b</sup>
T group	25.1±0.9	25.2±1.1	25.5±1.2	0.564
Dex group	25.6±1.0	26.6±1.2	26.4±1.1	0.043
P value <sup>a</sup>	0.206	0.003	0.035	

Data presented as mean ± SD, Dex group: dexmedetomidine group, T group: total intravenous anesthesia group, a: unpaired t-test, b: one-way analysis of variance (ANOVA), statistically significant between-group difference ( $P < 0.05$ ).

surgery. There were statistically significant differences in some aspects, including history of surgery and anesthesia, postoperative agitation, and serum BDNF levels between POCD children and non-POCD children ( $P < 0.05$ , data was showed in [Supplementary Table 2](#)). The multivariate logistic regression analysis showed

that postoperative agitation and serum BDNF levels were related to the occurrence of POCD in those children undergoing tonsillectomy. Data are shown in [Table 6](#).

### Discussion

First, in this study, enrolled children undergoing tonsillectomy were measured by a neuropsychological test battery, including the Trail Making Test Part A, the Stroop Color and Word Test, the Digit Span Forward, the Digit Span Backward test, and the Wechsler Intelligence Scale. Then, the Z-value method was used to comprehensively evaluate whether the children developed POCD after surgery. This strategy is the most widely uses diagnostic method of POCD because it can eliminate neuropsychological test's learning effect in the POCD diagnosis. This method not only sensitively determines overall cognitive dysfunction in children, but can also discover subtest anomaly in test [19]. Thus, this strategy can be used to evaluate whether a child has developed POCD after surgery.

In this study, the result showed that the children undergoing tonsillectomy in Dex group had lower occurrences of POCD (6.4%), compared with those in the T group (16.1%). The study reported that the occurrence rate of POCD was 9.2% and 21.31% in dexmedetomidine and control group in the elderly, respectively [20]. This result is consistent with our study, although the patients belong to different age groups. In this study, the result also showed that the children with tonsillectomy in Dex group had lower consumption of propofol and remifentanyl and postoperative agitation compared with those in T group. Meanwhile, those children had higher verbal IQ, verbal comprehension, and Trail Making Test scores in neuropsychological tests. Those results are consistent with some other studies. For example, it was reported that dexmedetomidine reduced intra-

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**Table 6.** Analysis of risk factors to POCD

Variable	OR	OR (95% CI)	P value
Surgery/anesthesia	0.331	0.008-13.437	0.559
Postoperative agitation	0.057	0.002-1.645	0.044
Serum BDNF	0.193	0.044-0.857	0.030

Risk factors analysis was based on day seven data.

operative anesthetic dosage, reduced the occurrence of postoperative agitation, and slowed cognitive speed (reaction time, Trail Making Test) [21-23].

Dexmedetomidine is a highly selective alpha-2 adrenergic receptor agonist, which can inhibit the release of norepinephrine and reduce plasma catecholamine concentration [24]. It is widely used in sedation and the treatment of anxiety. Several possible mechanisms may explain why intraoperative dexmedetomidine can reduce the occurrence of POCD in children undergoing tonsillectomy. Firstly, ischemia and hypoxia are common factors of POCD [25]. Dexmedetomidine can provide stable hemodynamics during surgery and has a protective effect on the brain and other organs in children. Secondly, anesthetic drugs are an independent risk factor of POCD [26]. Dexmedetomidine can reduce intraoperative anesthetic dosage in surgery for children. Thirdly, the occurrence of POCD is associated with the release of inflammatory factor [27]. Dexmedetomidine has an anti-inflammatory activity [28]. Additionally, dexmedetomidine has a protective effect on POCD via BDNF for the following reasons: 1) The study showed that BDNF had a protective role in counteracting the inflammatory effect of high sensitivity C-reactive protein [29], and dexmedetomidine could increase the expression of BDNF [11]. Therefore, dexmedetomidine acts as an anti-inflammatory agent by increasing BDNF levels to reduce POCD in children. 2) The study showed that beta-amyloid protein (A $\beta$ ) was related to POCD, and A $\beta$  was increased in POCD patients [30], BDNF could activate tropomyosin receptor kinase B (TrkB) to protect against A $\beta$  toxicity [31]. Dexmedetomidine reduced occurrence of POCD in children by increasing BDNF level, which activated TrkB and protected against A $\beta$  toxicity. Our results also showed serum BDNF levels were related to the occurrence of POCD, and dexmedetomidine increased serum BDNF levels of Dex group,

which were higher than that of T group. Therefore, dexmedetomidine has a role in neuroprotection by controlling various channels to reduce occurrence of POCD in children.

The study also has some limitations. First, the sample size was small. Second, postoperative cognition was only assessed at seven days after surgery. Third, all of the children in this study only underwent tonsillectomy.

In conclusion, intraoperative dexmedetomidine can reduce intraoperative anesthetic dosage, postoperative agitation, and the occurrence of POCD, and increase serum BDNF levels in children undergoing tonsillectomy, providing a novel approach to reducing the occurrence of POCD in children by using dexmedetomidine. Further studies of pharmacological mechanism are needed in future.

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### Disclosure of conflict of interest

None.

### Authors' contribution

Yiping Bai: study design, data collection, data analysis, and composition of the manuscript; Hong Yu: study design, data collection, data analysis, and composition of the manuscript; Maohua Wang: study design, data collection, Statistics analysis and paper lanague revising; Yunqiang Wan: study design and data analysis; Xueru Liu: study design, data collection, data analysis, and composition of the manuscript; Ni Tang: study design, data collection, data analysis, and composition of the manuscript; Liqun Mo: study design, data collection, and data analysis; Jicheng Wei: study design, data collection, and data analysis; Final approval of the version to be submitted: Yiping Bai, Hong Yu, Maohua Wang Yunqiang Wan, Xueru Liu, Ni Tang, Liqun Mo, Jicheng Wei.

**Address correspondence to:** Yiping Bai, Department of Anesthesiology, The Affiliated Hospital of South-

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west Medical University, 25 Taiping Street, Luzhou 646000, Sichuan Province, China. Tel: 0086-18982797213; Fax: 008608303161393; E-mail: 18982797213@163.com

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**Supplementary Table 1.** Preoperative characteristics in neuropsychological test of children undergoing tonsillectomy between Dex group and T group

Cognitive test	Dex group	T group	P value
Wechsler Intelligence Scale			
Full Scale IQ <sup>a</sup>	99.6±12.7	102.2±16.7	0.789
Verbal IQ <sup>a</sup>	98.0±11.3	100.6±14.8	0.763
Performance IQ <sup>a</sup>	98.8.9±11.5	99.8±13.9	0.891
Verbal comprehension <sup>a</sup>	106.0±15.1	101.9±11.2	0.572
Perceptual organization <sup>a</sup>	101.9±13.6	100±10.8	0.865
Freedom from distractibility <sup>a</sup>	108.8±14.3	105.5±12.1	0.584
Processing speed <sup>a</sup>	105.3±10.3	104.0±10.5	0.783
Trail-Making Test <sup>a</sup>	87.7±7.5	88.3±8.6	0.871
Stroop Color and Word Test <sup>a</sup>	20.3±3.1	19.2±3.3	0.453
Digit Span Forward <sup>a</sup>	5.8±0.9	5.5±1.0	0.512
Digit Span Backward <sup>a</sup>	2.6±1.5	2.9±0.8	0.578

Data presented as mean ± SD, Dex group: dexmedetomidine group, T group: total intravenous anesthesia group, a: unpaired t-test, statistically significant between-group difference (P < 0.05).

**Supplementary Table 2.** Comparison between POCD children and non-POCD children

Variable	POCD	non-POCD	P value
Surgery and anesthesia <sup>b</sup>	8/16	20/108	0.005
Postoperative agitation <sup>b</sup>	10/16	10/108	< 0.001
Serum BDNF <sup>a</sup>	24.7±0.7	26.1±0.7	0.001

Data presented as mean ± SD or -, a: unpaired t-test, b: Chi-square test, statistically significant between-group difference (P < 0.05).