Beneficial effects of dexmedetomidine on early postoperative cognitive dysfunction in pediatric patients with tonsillectomy

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Abstract. According to clinical investigations, early postoperative cognitive dysfunction is the most common adverse event in pediatric patients after tonsillectomy. A previous study has indicated that dexmedetomidine (DEX) is an efficient drug for the treatment of postoperative cognitive dysfunction. However, the efficacy of DEX in alleviating early postoperative cognitive dysfunction in pediatric patients following tonsillectomy has remained elusive, which was therefore assessed in the present study. A total of 186 children presenting with cognitive dysfunction subsequent to tonsillectomy were recruited to analyze the efficacy of DEX. Patients were randomly divided into two groups and received intravenous treatment with DEX (n=112) or placebo (n=74). Duration of treatment, dose-limiting toxicities (DLT) and maximum tolerated dose (MTD) of DEX were evaluated in a preliminary experiment. The improvement of postoperative cognitive function in children with tonsillectomy was analyzed with a Mini-Mental State Examination (MMSE) following treatment with DEX. A 40-item quality of life (MONEX-40) questionnaire was used to assess the efficacy of DEX. The plasma levels of interleukin (IL)-6, IL-1, tumor necrosis factor (TNF)-α, superoxide dismutase (SOD), neuron-specific enolase (NSE), C-reactive protein (CRP), cortisol and melatonin were also analyzed. The preliminary experiment determined that the DLT was 10 mg/kg and the MTD was 15 mg/kg. In the major clinical trial, it was revealed that MMSE scores in the DEX treatment group were markedly improved, indicating that DEX had a beneficial effect in pediatric patients with early postoperative cognitive dysfunction after tonsillectomy. In addition, IL-1and TNF-α were downregulated, while IL-6 and SOD were upregulated in patients with cognitive dysfunction after treatment with DEX compared with those in the placebo group. Furthermore, DEX treatment markedly decreased the serum levels of CRP, NSE cortisol and melatonin, which are associated with the occurrence of postoperative cognitive dysfunction in pediatric patients following tonsillectomy. In conclusion, intravenous administration of DEX at a dose of 10 mg/kg improves postoperative cognitive function in pediatric patients with tonsillectomy by decreasing the serum levels of inflammatory factors and stress-associated signaling molecules. Trial registration no. QLSDHOS0200810102C (Qilu Hospital of Shandong University, Jinan, China).

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Introduction

Children undergoing tonsillectomy are at risk of experiencing complications, including postoperative haemorrhage, nausea and vomiting, and cognitive dysfunction (1). A previous study has identified the clinical features of children undergoing tonsillectomy and presented the adverse outcomes and therapeutic schedule (2). Postoperative vomiting and pain due to tonsillectomy are two of the most frequent complications in pediatric patients (3,4). In addition, Eisert *et al* (5) indicated that bleeding remains the most important complication of tonsillectomy in pediatric patients and coagulation tests are widely applied to assess bleeding events. Furthermore, the immunological sequela of tonsillectomy in pediatric patients has also been indicated by physicians (6). Of note, cognitive dysfunction following tonsillectomy is a post-operative complication that occurs most frequently in pediatric patients (7,8). Therefore, prevention and treatment of postoperative cognitive dysfunction following tonsillectomy is essential for pediatric patients (9).

Cognitive impairment following tonsillectomy is a serious clinical problem as it reduces intelligence and emotional stability (10,11). Acute coagulatory dysfunction during adenoidectomy and tonsillectomy has been investigated in a previous case report on a pediatric patient (12). In addition, postoperative cognitive dysfunction, characterized by impaired consciousness and disordered thinking patterns, represents a major complication in pediatric patients after anesthesia and tonsillectomy (13). Although tonsillectomy provides numerous advantages, including less bleeding and fewer infections compared with conventional open procedures, cognitive dysfunction occurs due to adverse effects on cerebral function (14,15). Previous evidence indicates that cerebral oxygenation is decreased following tonsillectomy, as suggested by lightheadedness, nightmares,

nausea, vomiting and constipation, which may be correlated with neurocognitive changes in pediatric patients (16). These results suggest that the cognitive competence of the patients, which is regulated by the nerve center within the brainstem, may be affected by tonsillectomy in pediatric patients.

Dexmedetomidine (DEX) is a highly selective α2-adrenergic receptor agonist and acts as a multifunctional drug in the treatment of various human diseases (17). A previous study has suggested that DEX is efficient in the treatment of nerve diseases through the beneficial effects of acting as an anxiolytic, sedative, analgesic and blocking the sympathetic nervous system (18). In addition, a clinical study has indicated that DEX has analgesic, anxiolytic and anti-delirium effects, while causing little respiratory depression (19). DEX treatment may improve behavioral disturbances, including aggression, agitation and cognitive impairment (20). These neurological function impairments may occur in pediatric patients with postoperative cognitive dysfunction. Therefore, it was hypothesized that DEX may be beneficial for restoring cognitive function in pediatric patients following tonsillectomy.

In the present study, the effects of DEX administration were assessed in pediatric patients with cognitive impairment after tonsillectomy. Although a previous study has suggested that DEX is recommended for decreasing the risk of postoperative vomiting, as well as to alleviate pain, inflammation and nausea for patients in intensive care (21), the therapeutic efficacy of DEX on the restoration of cognitive function has remained elusive. In addition to the influence of DEX on the recovery of cognitive impairment, its effects on the levels of interleukin (IL)-6 and -1, tumor necrosis factor (TNF)-α, C-reactive protein (CRP), neuron-specific enolase (NSE), superoxide dismutase (SOD), cortisol and melatonin in pediatric patients following tonsillectomy were also assessed. The results indicate that DEX improves cognitive impairment in pediatric patients following tonsillectomy, at least in part, through the regulation of IL-6, CRP, cortisol and melatonin levels.

Materials and methods

Patients. Pediatric patients aged 6-12 years who had undergone tonsillectomy at Qilu Hospital of Shandong University (Jinan, China) between May 2014 and July 2015 were subjected to a Mini Mental State Examination (MMSE) and requested to complete a 40-item quality of life (MONEX-40) questionnaire. The MMSE was used to screen for cognitive dysfunction. Only patients post tonsillectomy with post-operative cognitive dysfunction were included in the study. The patients were randomly divided into two groups, and double-blinded trails were performed. Further details, including a description of the inclusion/exclusion criteria and the allocation method, are specified in a previously published study (22). In a preliminary experiment, the patients with cognitive dysfunction received DEX (1.0, 5.0, 10.0, 15.0 and 20.0 mg/kg/day) or placebo (PBS) through intravenous injection for 4 weeks. The dose-limiting toxicities (DLT) and maximum tolerated dose (MTD) of DEX were 10 and 15 mg/kg, respectively, determined by the common treatment-emergent adverse events of DEX as described previously (23).

Study design. The double-blinded study was performed in 3 phases: Baseline stage, double-blinded treatment phase (4-week dose-titration treatment, preliminary experiment) and 4-week post-treatment (maintenance treatment) of those patients who volunteered to continue to complete the ongoing extension study. The patients were randomized into two groups which were treated once a day with DEX or placebo in a double-blinded manner. In the final investigation, treatment was continued with the 10 mg/kg dose of DEX or placebo to achieve the ideal effect throughout the maintenance period.

Outcome measures. The MMSE (24) and The 40-item Monell Extended Sniffin' Sticks Identification Test (MONEX-40) (40 items for assessing functional limitation) (25) were used for assessing the pediatric patients with cognitive dysfunction at prior to treatment and post-treatment. Clinical cognitive function scores were evaluated as described in a previous study (26).

Efficacy and safety assessments. Efficacy assessments, including the median percent reduction scores and response rate, were analyzed with the baseline values as a reference during the 4-week double-blinded treatment period with DEX (10 mg/kg) or placebo. In addition, overall safety and pharmacokinetic analyses were performed according to the protocols of previous clinical studies (27,28). The safety assessments regarding the most frequent treatment-emergent adverse events were performed in all randomized patients. The dosage of DEX was determined by DLT as described above. Dose-response analysis was performed when the last dose of the drug was injected as described previously (29).

ELISA. In the present study, the serum levels of IL-6 (cat. no. D6050), IL-1 (cat. no. DLB50), TNF-α (cat. no. DTA00C), SOD (cat. no. DYC3419-2), NSE (cat. no. DY5169-05), CRP (cat. no. DCRP00), cortisol (cat. no. KGE008B) (all Bio-Rad Laboratories, Inc., Hercules, CA, USA) and melatonin (cat. no. KA1166; Abnova, Taipei, Taiwan) were assessed using commercialized ELISA kits. The ELISAs were performed according to the manufacturer's protocols. The results were determined by measuring the absorbance at 450 nm with an ELISA reader and finally converted to the concentrations of IL-6, IL-1, TNF-α, SOD, NSE, CRP, cortisol and melatonin.

Statistical analysis. All values are expressed as the mean ± standard error of the mean. All data were analyzed using SPSS software version 19.0 (IBM Corp., Armonk, NY, USA). Statistical significance of differences between mean values were assessed by Student's t-test for paired data. Comparisons of data between multiple groups were performed by one-way analysis of variance followed by Tukey's post hoc test. Responder rates and treatment-emergent adverse events were analyzed with the χ^2 test. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Patient characteristics. A total of 186 pediatric patients with early postoperative cognitive dysfunction following tonsillectomy were recruited for the present study. The characteristics of the patients are summarized in Table I. The gender distribution within the cohort was equal. The cognitive dysfunction

Table I. Characteristics of the study population post tonsillectomy.

Characteristic	Value
Total patients with post-operative cognitive dysfunction	186 (100)
Gender	
Male	90 (48)
Female	96 (52)
Median age, years (range)	8.5 (6-12)
MMSE	16.5±3.2
MONEX-40	134.4±12.5
Pain scores	7.2±2.4
Drug therapy	186 (100)
DEX	112 (60)
Placebo	74 (40)

Values are expressed as n (%) or as the mean ± standard error of the mean unless otherwise specified. MMSE, Mini Mental State Examination; MONEX-40, 40-item quality of life questionnaire; DEX, dexmedetomidine.

of the patients was determined by the MMSE at prior to treatment and post treatment. No other medications or painkillers were taken during the treatment period.

Duration of treatment, DLT and MTD of DEX. The median overall duration of DEX treatment was 4 weeks followed by maintenance treatment. The dosing cohorts of DEX were 1.0, 5.0, 10.0, 15.0 and 20 mg/kg to evaluate the optimal dosage. According to the results in Table II, the MTD of DEX was 20 mg/kg once a day. The DLT was determined as 15 mg/kg of DEX once a day. The group treated with the lowest dose of DEX presented with the fewest side effects. Analysis indicated that the common treatment-emergent adverse events of DEX were hypertension, fatigue, proteinuria, hypertriglyceridemia, constipation and peripheral edema. Of note, most of the patients treated with the MTD of DEX required a dose reduction due to cumulative toxicity. Therefore, most of the patients that were subsequently enrolled received a dose of 10.0 mg/kg DEX to achieve ideal tolerability and therapeutic efficacy in the pediatric patients with early postoperative cognitive dysfunction.

Treatment-emergent adverse events associated with DEX. Pediatric patients with early postoperative cognitive dysfunction after tonsillectomy received DEX therapy with post-baseline safety evaluation were included in the safety population. After the administration of the last dose of DEX, it was determined that the most common treatment-emergent adverse events of DEX (10 mg/kg) were hypertension and proteinuria (≥10% each) (Table III). The administration of DEX at ≥15 mg/kg is not advisable due to more side effects and therefore, few patients were treated with such doses. Of the total patient population, 96 completed the overall maintenance period of the phase III study.

Analysis of the efficacy of DEX in alleviating cognitive impairment in pediatric patients after tonsillectomy. In order to investigate the efficacy of DEX in improving of cognitive function in children affected after tonsillectomy, the cognitive competence was assessed in 186 patients using the MMSE and MONEX-40. As presented in Fig. 1, it was demonstrated that DEX treatment significantly improved the cognitive competence of children with cognitive dysfunction determined by the MMSE scores. In addition, assessment with the MONEX-40 questionnaire indicated that DEX treatment reduced postoperative complications (daytime sedation, lightheadedness, nightmares, nausea, vomiting and constipation) compared with the placebo group (Fig. 2). It was also observed that the plasma concentration of NSE was increased in patients after DEX treatment compared with that in the placebo group (Fig. 3). Of note, the plasma concentration of CRP was decreased in the DEX group (Fig. 4). Furthermore, the serum levels of melatonin were increased in patients after DEX treatment compared with those in the placebo group (Fig. 5). Importantly, the plasma concentration of cortisol was upregulated by DEX compared with that in the placebo group (Fig. 6). For all these factors no significant changes were observed in the placebo group between the prior to treatment and post treatment time points. These results suggest that DEX improves cognitive competence through the regulation of nerve growth factors in pediatric patients with cognitive dysfunction after tonsillectomy.

Analysis of inflammatory factors in pediatric patients with tonsillectomy after treatment with DEX. The inflammatory factors in pediatric patients with post-tonsillectomy cognitive dysfunction after treatment with DEX were analyzed. It was indicated that the plasma levels of IL-1 were increased after DEX treatment (Fig. 7). In addition, DEX treatment downregulated the plasma levels of TNF-α to inhibit the inflammatory response (Fig. 8). Furthermore, the plasma concentration of IL-6 was increased after DEX treatment (Fig. 9). Treatment with DEX also improved SOD levels in the plasma, which may contribute to the recovery of cognitive dysfunction after tonsillectomy (Fig. 10). These observations indicate that inflammatory factors in pediatric patients with tonsillectomy were improved after treatment with DEX. For the above factors no significant changes were observed in the placebo group between the prior to treatment and post treatment time points.

Discussion

Previous studies have indicated that early postoperative cognitive dysfunction is one of the most common adverse effects in pediatric patients after tonsillectomy (30,31). DEX has been approved by the Chinese Food and Drug Administration for the treatment of inflammation (32). In addition, it has been suggested that DEX is an efficient drug for the treatment of postoperative cognitive dysfunction (33,34). In the present study, the clinical therapeutic effects of DEX on recovery of cognitive dysfunction in pediatric patients that had undergone tonsillectomy were investigated. In a preliminary study, the DLT and MTD of DEX were evaluated in pediatric patients with cognitive dysfunction after tonsillectomy. The

Table II. Overall incidence of treatment-emergent adverse events of DEX.

Adverse event	Total (n=32)	DEX (mg/kg)		
		1-10 (n=10)	15 (n=14)	20 (n=8)
Hypertension	5	1	2	2
Fatigue	3	1	1	1
Proteinuria	4	0	1	3
Hypertriglyceridemia	2	0	1	1
Constipation	3	0	1	2
Edema peripheral	3	1	1	1

DEX, dexmedetomidine.

Table III. Severity of treatment-emergent hypertension and proteinuria as adverse events of DEX.

Adverse event/grade	Total (n=32)	DEX (mg/kg)		
		1-10 (n=10)	15 (n=14)	20 (n=8)
Hypertension	5	1	2	2
1	1	0	0	1
2	2	0	1	1
3	2	1	1	0
Proteinuria	4	0	1	3
1	1	0	0	1
2	2	0	1	1
3	1	0	0	1

DEX, dexmedetomidine. Grading scale of hypertension and proteinuria was determined by WHO hypertension and proteinuria grade.

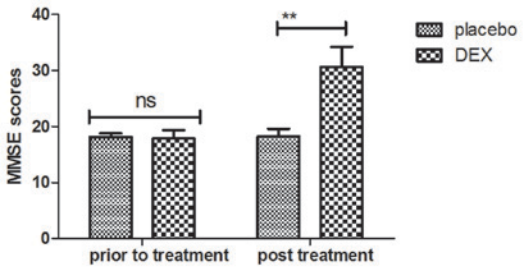

Figure 1. Evaluation the effects of DEX on cognitive dysfunction using MMSE scores. **P<0.01 vs. control. MMSE, Mini Mental State Examination; DEX, dexmedetomidine; ns, not significant.

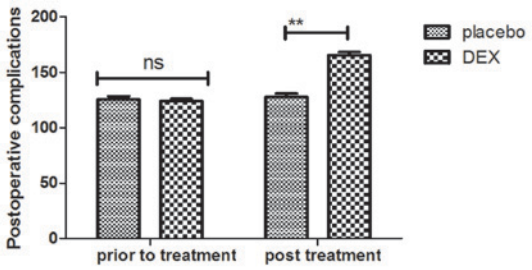

Figure 2. Analysis of efficacy of DEX on improvement of postoperative complications in children with tonsillectomy. **P<0.01 vs. control. DEX, dexmedetomidine; ns, not significant.

treatment-emergent adverse events of DEX were analyzed to evaluate the clinical efficacy and pharmacodynamics. Furthermore, the serum levels of inflammatory and nerve growth factors were analyzed to determine the mechanism of DEX-induced recovery of cognitive function. The results indicate that DEX improves cognitive dysfunction in children after tonsillectomy through inhibition of the expression of inflammatory factors and enhancement of neuroprotective protein expression. These results suggest that DEX may be an efficient cognitive function-enhancing drug for the treatment of tonsillectomy-associated cognitive impairment in pediatric patients.

Postoperative cognitive dysfunction is a multifactorial adverse event and most frequently occurs in pediatric and elderly patients after surgery (35). Surgical therapy is the most common clinical treatment of frequent tonsil inflammation. Tonsillectomy is also one of the most common surgical procedure performed in preschool children (36). Although tonsillectomy provides numerous benefits, various adverse reactions, including throat pain, haemorrhage, tonsillar fossa

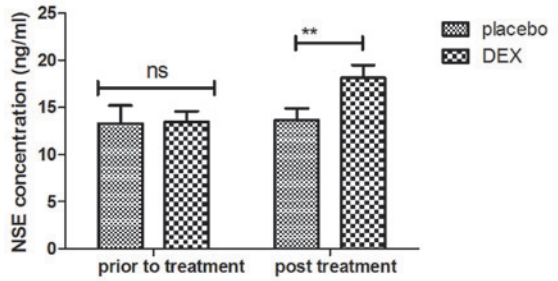

Figure 3. Analysis of efficacy of DEX on NSE plasma concentration after an 8-week treatment period. **P<0.01 vs. control. DEX, dexmedetomidine; NSE, neuron-specific enolase; ns, not significant.

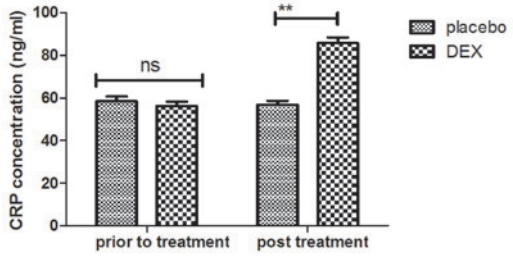

Figure 4. Detection of CRP plasma concentration levels between DEX and placebo groups. **P<0.01 vs. control. DEX, dexmedetomidine; CRP, C-reactive protein; ns, not significant.

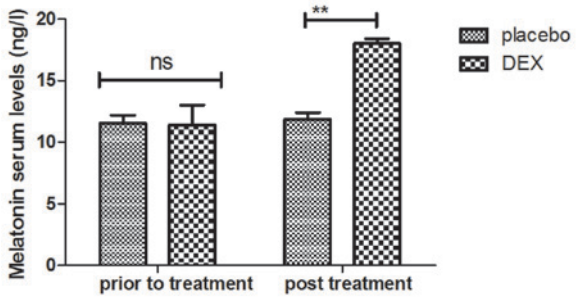

Figure 5. Changes of melatonin serum levels in pediatric patients with post-operative cognitive dysfunction after DEX treatment. **P<0.01 vs. control. DEX, dexmedetomidine; ns, not significant.

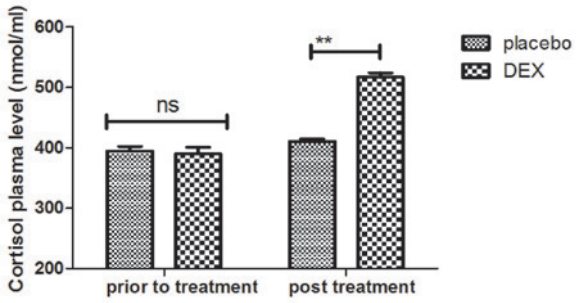

Figure 6. Analysis of efficacy of DEX in regulating the cortisol plasma concentration. **P<0.01 vs. control. DEX, dexmedetomidine; ns, not significant.

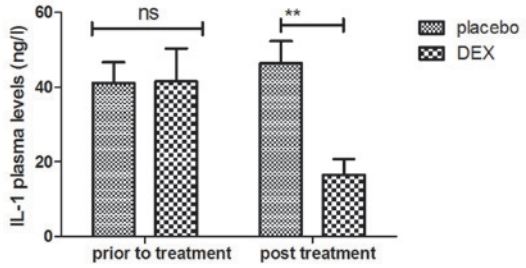

Figure 7. Clinical analysis of IL-6 plasma levels after DEX treatment. **P<0.01 vs. control. DEX, dexmedetomidine; IL, interleukin; ns, not significant.

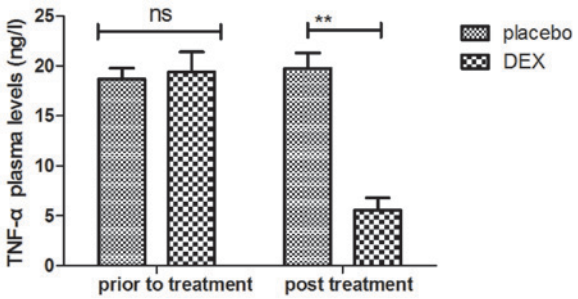

Figure 8. Clinical analysis of IL-1 plasma levels after DEX treatment. **P<0.01 vs. control. DEX, dexmedetomidine; IL, interleukin; ns, not significant.

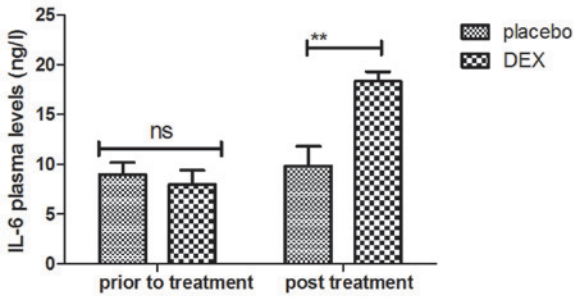

Figure 9. Analysis of the effect of DEX on the plasma concentration of TNF-α. **P<0.01 vs. control. DEX, dexmedetomidine; TNF, tumor necrosis factor; ns, not significant.

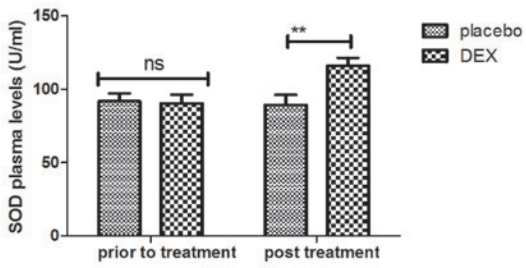

Figure 10. Analysis of the effect of DEX on the plasma concentration of SOD. **P<0.01 vs. control. DEX, dexmedetomidine; SOD, superoxide dismutase; ns, not significant.

epithelisation and even cognitive dysfunction, may occur in patients after tonsillectomy (37). A previous study has reported that cognitive dysfunction may affect children for up to 6 months after the operation (13). Therefore, the treatment of postoperative cognitive dysfunction is essential for pediatric patients in the clinic.

DEX has been increasingly applied during clinical surgery as a regional anesthetic (38). It is a multifunctional drug and a highly efficient and specific α2 agonist, which may reduce

the release of norepinephrine, the activity of norepinephrine receptors exert anxiolytic and calming effects, and ameliorate sleep cycle disorders (22,39). Numerous clinical trials and studies have demonstrated that DEX protects cells in the hippocampus against injury and reduces ischemia-reperfusion injury of human organs (40,41). The present study further explored the neuroprotective effects of DEX in pediatric patients with cognitive dysfunction after tonsillectomy. DEX has sedative, analgesic and hypnotic effects, and antagonizes sympathetic activity, which results in improvement of cognitive competence. A previous study has indicated that recovery from cognitive dysfunction required >6 weeks for pediatric patients with tonsillectomy (42). The present study only implemented a 4-week observation period and in the placebo group, no improvement was seen; however, it should be clarified that the post-operative cognitive dysfunction following tonsillectomy is a non-permanent condition, and that recovery may take >4 weeks. However, further study is required to assess the average time of recovery from cognitive dysfunction in pediatric patients following tonsillectomy procedures, and the specific effects of DEX and the underlying molecular mechanisms of its cerebral protection require to be elucidated.

An integrative review has examined the use of DEX as an anesthetic for monitored anesthesia care and regional anesthesia, and has evaluated the effect of DEX on the incidence of postoperative cognitive dysfunction after non-cardiac and non-neurologic surgery (43). DEX acts as an antagonist of transmembrane G protein-coupled receptor that significantly contributes to distribution of hippocampal focal adhesion kinase tyrosine phosphorylation in the peripheral nervous system, autonomic ganglia and central nervous system (44). The major function of DEX is to selectivity activate α2 adrenergic receptors to regulate the locus coeruleus of the central nervous system. A phase III double-blinded, randomized controlled trial has suggested that the effects of a single low dose of dexamethasone prior to non-cardiac and non-neurologic surgery and general anesthesia provides beneficial effects on postoperative cognitive dysfunction (45). Another clinical trial reported on the preventive effects of low-dose DEX on postoperative cognitive dysfunction and the quality of recovery in oral cancer patients through modulating the kinetics of cortisol, expression of inflammatory cytokines and plasma concentration of melatonin (46). The present study indicates that DEX has a beneficial effect on the recovery from cognitive dysfunction in pediatric patients after tonsillectomy through inhibition of the expression of inflammatory factors and enhancement of neuroprotective protein expression. However, as it was not determined whether the patients had any cognitive dysfunction prior to surgery, it may not have been surgery-associated in all cases.

In conclusion, the present study observed that DEX increased the plasma concentration of cortisol in pediatric patients with early postoperative cognitive dysfunction after tonsillectomy, and cortisol is negatively associated with the risk of cognitive dysfunction. Of note, DEX reduced the serum levels of IL-1 and TNF-α to decrease nerve injury. Furthermore, DEX treatment improved the cognitive ability and relieved cognitive dysfunction caused by tonsillectomy. Taken together, DEX improves cognitive impairment in children after tonsillectomy through regulation of the expression of inflammatory factors and neuroprotective proteins, which may widely apply for impairments of brain function caused by tonsillectomy.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

WL designed the study. CH and RF performed the experiments and analyzed the data.

Ethical approval and consent to participate

This phase-III study (no. QLSDHOS0200810102C) was performed in strict accordance with the recommendations in the Guidelines of Qilu Hospital of Shandong University (Jinan, China) between October 2008 and May 2014. All patients and their guardians were required to review trial protocols and their amendments, and provide informed consent.

Consent for publication

All patients provide written informed consent for the publication of their data.

Competing interests

The authors declare that they have no competing interests.

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