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Original Article

Administration of surgical anesthetic dexmedetomidine improves cognitive and neurological function in infants with congenital heart disease

Xing Wei, Chen Zhou, Yangjie Ou, Qicai Qu

Department of Anesthesiology, The Second Affiliated Hospital of Kunming Medical University, Kunming 650101, Yunnan, China

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Abstract: Objective: The aim of the current study was to investigate the effects of dexmedetomidine on cognitive and neurological function, after anesthesia, in infants with congenital heart disease (CHD). Methods: This study selected and retrospectively analyzed 106 cases of infants diagnosed with CHD. A total of 56 infants received fentanyl combined with midazolam through intravenous injections (control group) before surgery, supplemented with isoflurane during surgery. The other 50 patients received preoperative fentanyl combined with dexmedetomidine via intravenous injections and isoflurane supplementation (observation group). General data, perioperative circulatory data, cognitive function assessment date, and serum NSE, NGF, and BDNF levels were observed. Results: Fluctuations in these indicators in the observation group were significantly lower than those observed in the control group, from the time of incision to the immediate end of surgery (P<0.05). Falling ranges of language and behavioral scores in the observation group were significantly lower than those in the control group (P<0.05). At 3 months after surgery, serum levels of neuron-specific enolase (NSE) in the observation group were lower than those in the control group (P<0.05), but levels of nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) in the observation group were significantly higher than those in the control group (P<0.05). Neuron-specific enolase levels, 3 months after surgery, in both groups were significantly lower than levels measured before and 3 days after surgery. However, NGF and BDNF levels were significantly higher than levels measured before and 3 days after surgery (P<0.05). Conclusion: Dexmedetomidine is a worthy anesthetic alternative for reduction of anesthesia-induced neurological and cognitive impairments. Therefore, it should be recommended in clinical practice.

Keywords: Dexmedetomidine, intravenous anesthesia, congenital heart disease, neurological function, cognitive function

Introduction

Congenital heart disease (CHD) is a malformation of the heart, present at birth. This occurs when either the heart or blood vessels develop abnormally in the early stages of pregnancy or the heart channel closes after birth. Main manifestations include cardiac insufficiency and cyanosis [1, 2]. Infants with CHD account for approximately one percent of living infants, indicating that the number of newly diagnosed infants with CHD could reach up to hundreds of thousands each year. Therefore, diagnosis and treatment of CHD are of great clinical importance [3, 4]. The vast majority of infants with CHD require surgery [5].

The main anesthetic used in congenital heart surgeries is a high-dose of opioids [6]. By the age of 3, the nervous system has rapidly developed. This is the most sensitive stage in which the brain is highly susceptible to developmental disorders, induced by various factors [7, 8]. In recent years, the influence of preoperative anesthesia on cognitive and neurological function in infants has been a major research subject in the field of anesthesiology. Since infants have a lower tolerance for pain, anesthetics for surgical treatment must not only maintain an effective depth of anesthesia, but also minimize the impact on postoperative recovery [9, 10]. Dexmedetomidine is a highly selective α2-adrenergic receptor agonist. Besides its sedative and analgesic effects, dexmedetomidine also exhibits anti-sympathetic and anxiolytic effects [11]. In recent years, studies have reported that dexmedetomidine combined with anesthesia showed few effects on the recovery of cognitive function after various surgical procedures [12, 13]. However, reports concerning the application of anesthetics used in infants with CHD, along with their neurological effects, are limited. Neuron-specific enolase (NSE), nerve growth factor (NGF), and brain-derived neurotrophic factor (BDNF) are molecular markers with clinical application value. Studies have reported a close relationship between these markers and neurological function [14, 15]. The current study retrospectively analyzed the clinical records of 106 infants with CHD. They underwent surgery to determine the effects of dexmedetomidine on cognitive and neurological function in infants.

Materials and methods

Research subjects

From January to October 2018, a total of 106 cases of infants, diagnosed with CHD and requiring surgical treatment, in Daqing Longnan Hospital, were selected. They were retrospectively analyzed for the current study. Inclusion criteria: Adult patients diagnosed with CHD, requiring surgical treatment and administration of dexmedetomidine. Exclusion criteria: Adult patients lacking data for one or more of the following end points: Duration of MV, ICU, LOS, hospital LOS, incidence of junctional ectopic tachycardia (JET), and mortality. The control group consisted of 56 infants that received fentanyl combined with midazolam, intravenously, before surgery. The observation group (n=50) received preoperative fentanyl combined with dexmedetomidine, intravenously. All infants met the diagnostic criteria for congenital heart disease [5]. The physical status of the infants was graded based on the American Society of Anesthesiologists Physical Status Classification System from ASA I to III. The infants showed no allergic reactions to dexmedetomidine. No familial cardiomyopathy was found during the study period. Infants with liver and kidney dysfunction and those complicated with CHD with ventricular septal defects, hemolytic disease, and congenital mental retardation, such as trisomy 21 syndrome, were excluded. This study was approved by the Medical Ethics Committee of Daqing Longnan Hospital and informed consent was obtained from the family members of all subjects.

Administration of anesthesia

All infants were banned from eating 4-5 hours before surgery and from preoperative medication. They were intramuscularly injected with 0.02 mg/kg atropine (Guangdong Nanguo Pharmaceutical Co., Ltd., GYZZ H44024022) 30 minutes before the operation. This was to establish and monitor invasive arterial pressure, central venous pressure, electrocardiogram, blood pressure, heart rate, pulse, and oxygen protection. After calculating pediatric age and body weight, anesthesia was induced under target-controlled infusion with midazolam at 0.2 mg/kg (Jiangsu Enhua Pharmaceutical Co., Ltd., GYZZ H10980025), fentanyl at 10 μg/kg (Yichang Renfu Pharmaceutical Co., Ltd., GYZZ H20030197), and vecuronium bromide at 0.2 mg/kg (Zhejiang Xianju Pharmaceutical Co., Ltd., GYZZ H19991172). After induction, endotracheal intubation was performed for mechanical ventilation using an anesthesia machine (Yi-An Anesthesia Machine Aeon 7200, Shanghai Hanfei Medical Devices Co., Ltd.). The control group was infused with midazolam at 0.2 mg/kg/h and fentanyl at 10 μg/kg/h. Levels were maintained at 0.5 μg/kg/h and 5 μg/kg/h after 60 minutes, respectively. The observation group was infused with fentanyl at 10 μg/kg/h and dexmedetomidine at 1 μg/kg/h (Sichuan Guorui Pharmaceutical Co., Ltd., GYZZ H20143195). Levels were maintained at 5 μg/kg/h and 0.5 μg/kg/h after 60 minutes, respectively.

Observational indicators

Circulatory signs were recorded before induction of anesthesia (T1), 1 hour after anesthesia (T2), immediately before incision (T3), immediately after incision (T4), end of the surgery (T5), and blood flow dynamics at 10 minutes after the end of surgery (T6). Cognitive assessment was performed using the Bayley Scales of Infant and Toddler Development (BSID-III). Serum levels of NSE, NGF, and BDNF at 3 days before surgery, 3 days after surgery, and 3 months after surgery (3 m) were analyzed.

Table 1. Comparison of general data between the two groups of infants

	Control (n=56)	Observe (n=50)	Statistics	*P*-value
Sex				0.86
Male	30	26		
Female	26	24		
Age (month)	12.3±5.8	12.9±6.4	0.506	0.614
Operation time (min)	173.6±60.4	176.9±68.4	0.264	0.793
Connecting time (min)	84.3±42.6	88.6±44.5	0.508	0.613
Aortic cross clamp (min)	45.6±22.3	44.2±23.4	0.315	0.753
Awakening time (min)	12.4±2.8	11.7±2.4	1.374	0.173
Ejection fraction (%)	67.3±6.8	68.2±6.4	0.699	0.486
ASA grade [(n%)]			0.001	0.978
I-II	38	35		
III	18	15		
Classify			0.132	0.834
No tap class	3	5		
Left to right shunt classes	36	30		
Right to left shunt class	17	15		

Statistical analysis

Statistical analysis was performed with SPSS version 19.0 (Asia Analytics, China, formerly SPSS). Enumeration data are expressed by [n (%)]. For comparison rates, Chi-squared (x^2) tests were conducted. Measurement data are expressed as $\overline{x}$ ± sd. The two groups were compared using the Wilcoxon rank sum test. Repeated variance measurement experiments were carried out at different times within the groups. *P*-values less than 0.05 indicate statistical significance.

Results

No differences in general data between two groups of infants

A total of 106 infants were included in this study. There were 56 in the control group, including 30 males and 26 females. The mean age was 12.3±5.8 months. Fifty infants were in the observation group, including 26 males and 24 female patients. The mean age was 12.9±6.4 months. No significant differences were found in gender and age between the two groups (P>0.05). No significant differences were found in operation times, extracorporeal circulation transit times, aortic blocking times, recovery times, ejection fraction, ASA classification ratios, and CHD classification between the two groups (all P>0.05, **Table 1**).

Significant differences in circulatory after surgery

No differences were found in heart rates, systolic blood pressure, diastolic blood pressure, and oxygen saturation between the two groups before induction of anesthesia (T1), 1 hour after anesthesia (T2), before incision (T3), and 10 minutes after the end of surgery (T6, P>0.05). Significant differences were found immediately after skin incision (T4) and immediately after the end of surgery (T5, P<0.05) (**Figure 1A**). Heart rates, systolic blood pressure, diastolic blood pressure, and oxygen saturation in the two groups were significantly lower at T2 than at T1 (P<0.05) (**Figure 1B**). Heart rates, systolic blood pressure, diastolic blood pressure, and oxygen saturation of the two groups were similar at T2 (**Figure 1C**). A significant increase was found at T4, compared with T3 (P<0.05). At T5, heart rates, systolic blood pressure, diastolic blood pressure, and oxygen saturation were not significantly different, compared to those at T4 (P>0.05). At T6, no significant differences were observed in heart rates, systolic blood pressure, diastolic blood pressure, and oxygen saturation, compared with those at T5 (P>0.05, **Figure 1D**).

Statistically significant differences in language scores and behavioral scores between the two groups

No significant differences were observed in preoperative cognitive, language, motor, emotion, and behavioral scores of the two groups (all P>0.05). Statistically significant differences were found between language scores, behavioral scores 3 days after surgery, and emotional scores 3 months after surgery between the two groups (P<0.05). No significant differences were observed in cognitive function scores between the two groups at the other time points (P>0.05). Cognition, language, movement,

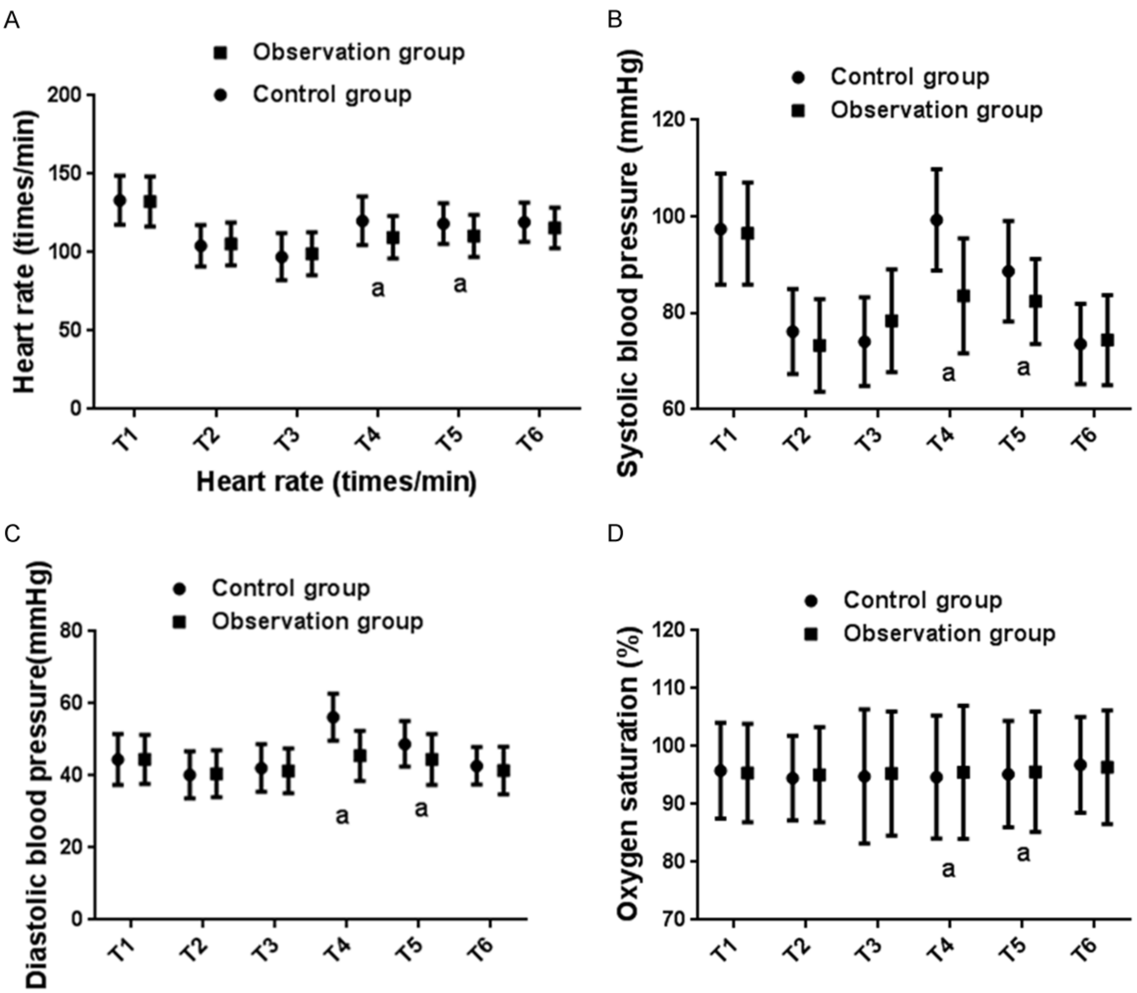

Figure 1. Perioperative Circulatory Data. A: Heart rate; B: Systolic blood pressure; C: Diastolic blood pressure; D: Oxygen saturation. a: P<0.05.

emotion, and behavior scores in the two groups were lower than those observed 3 days before surgery (P<0.05). At 3 months after surgery, cognition, language, and behavior of the two groups were observed. Emotional scores in the observation group returned to levels observed before surgery. They were not significantly different from preoperative scores (P>0.05). Emotional scores were higher than those seen at 3 days after surgery (P<0.05), but still lower than those observed before surgery (**Table 2**).

NGF and BDNF levels significantly lower after dexmedetomidine

No significant differences were found in levels of NSE, NGF, and BDNF of the two groups before surgery and 3 days after surgery (P>0.05). After 3 months, NSE levels in the observation group were significantly lower than those seen in the control group (P<0.05) (**Figure 2A**). NGF and BDNF levels in the observation group were significantly higher than those in the control group (P<0.05). No differences in NSE and BDNF levels were observed in the groups. There were no differences in NGF levels in the control group, 3 days after surgery, compared to preoperative levels (P>0.05). NGF levels in the observation group, 3 days after surgery, were significantly higher than levels observed before surgery (P<0.05; **Figure 2B**). NSE levels at 3 months after surgery were significantly lower than those seen before surgery and 3 days after surgery in the two groups (P<0.05). NGF and BDNF levels were significantly higher than those before surgery and 3 days after surgery (P<0.05, **Figure 2C**).

Table 2. Assessment of cognitive function between the two groups of infants

		Control (n=56)	Observe (n=50)	Statistics	*P*-value
Cognitive	Preoperative	103.4±5.7	104.1±6.2	0.606	0.546
	3 d	96.7±4.4[a]	97.5±5.7[a]	0.814	0.418
	3 m	102.6±5.5[b]	103.8±4.7[b]	1.200	0.233
Language	Preoperative	104.2±4.2	104.9±4.3	0.847	0.399
	3 d	96.3±4.1[a]	98.2±4.6[a]	2.249	0.027
	3 m	103.6±4.4[b]	105.2±5.1[b]	1.734	0.086
Action	Preoperative	102.1±6.9	102.6±5.8	0.401	0.689
	3 d	94.7±4.1[a]	96.7±4.6[a]	2.367	0.020
	3 m	102.3±5.6[b]	102.6±4.8[b]	0.294	0.769
Emotional	Preoperative	102.1±7.4	101.9±7.1	0.142	0.888
	3 d	90.8±6.7[a]	91.2±7.3[a]	0.294	0.769
	3 m	98.4±7.1[b]	101.5±6.2[b]	2.381	0.019
Behavior	Preoperative	100.1±8.4	100.6±7.2	0.327	0.744
	3 d	91.2±7.9[a]	92.4±7.3[a]	0.809	0.420
	3 m	100.1±7.7[b]	101.5±8.1[b]	0.912	0.364

Note: a is more than preoperative P<0.05, and b is more than 3 d P<0.05.

Discussion

CHD accounts for about 28% of all kinds of congenital malformations, most of which are caused by environmental factors. Only 8% of CHD cases are caused by genetic factors [16]. Most infants with CHD require surgical treatment. However, the effects of anesthesia on the nervous system have become a major public health concern [17]. Studies have reported that incidence of neurological complications after cardiac surgery is as high as 50% in infants, greatly impacting their physical and mental development [18]. Therefore, development of new anesthetic methods or drugs has become an important research area. This study aimed to analyze surgical data from 106 infants with CHD, exploring the effects of dexmedetomidine on cognitive and neurological function in infants.

In this study, 50 infants underwent anesthesia using dexmedetomidine and fentanyl combined with isoflurane. A total of 56 infants in the control group received midazolam and fentanyl combined with isoflurane. Data analysis between the two groups showed no significant differences in terms of operation times, extracorporeal circulation transit times, aortic occlusion times, and recovery times of infants undergoing different anesthetic methods. Therefore, the influence of these basic conditions could be excluded.

This study analyzed and compared hemodynamic parameters between the two groups. Establishing and maintaining hemodynamic stability, during and after surgery, is imperative for patient recovery. According to results of this study, heart rates, systolic blood pressure, diastolic blood pressure, and blood oxygen saturation fluctuated during the operation. After skin incision, heart rate, systolic blood pressure, diastolic blood pressure, and oxygen saturation of blood of both groups decreased to varying degrees. However, indicators within the observation group fluctuated significantly lower than those in the control group from the time of incision to the end of surgery. This indicates that dexmedetomidine is superior to midazolam in the maintenance of hemodynamic stability during surgery. Compared with midazolam, dexmedetomidine is a α2 receptor agonist and its influence on hemodynamics is more complex. Dexmedetomidine inhibits the action of norepinephrine by exciting α2 receptors, exerting sedative, analgesic, and anti-sympathetic effects to maintain hemodynamic stability [19, 20]. Cheng et al. found that fluctuations in heart rates and blood pressure during surgery with dexmedetomidine anesthesia were smaller than those with propofol [21]. It is thought that dexmedetomidine infusion in infants with CHD undergoing extracorporeal circulation may be superior to propofol anesthesia. Pan also reported that the use of dexmedetomidine anesthesia in infants with CHD undergoing surgery maintained hemodynamics, in accord with current findings [22].

The current study evaluated the cognitive function of infants using the most widely used multiscale battery test, BSID-III, assessing development in five areas: cognition, language, motor, emotion, and behavior. Its greatest feature is the ability to sensitively detect clinically significant changes in outcomes [23, 24]. Cognitive function analysis between the two groups showed fluctuations at varying degrees 3 days

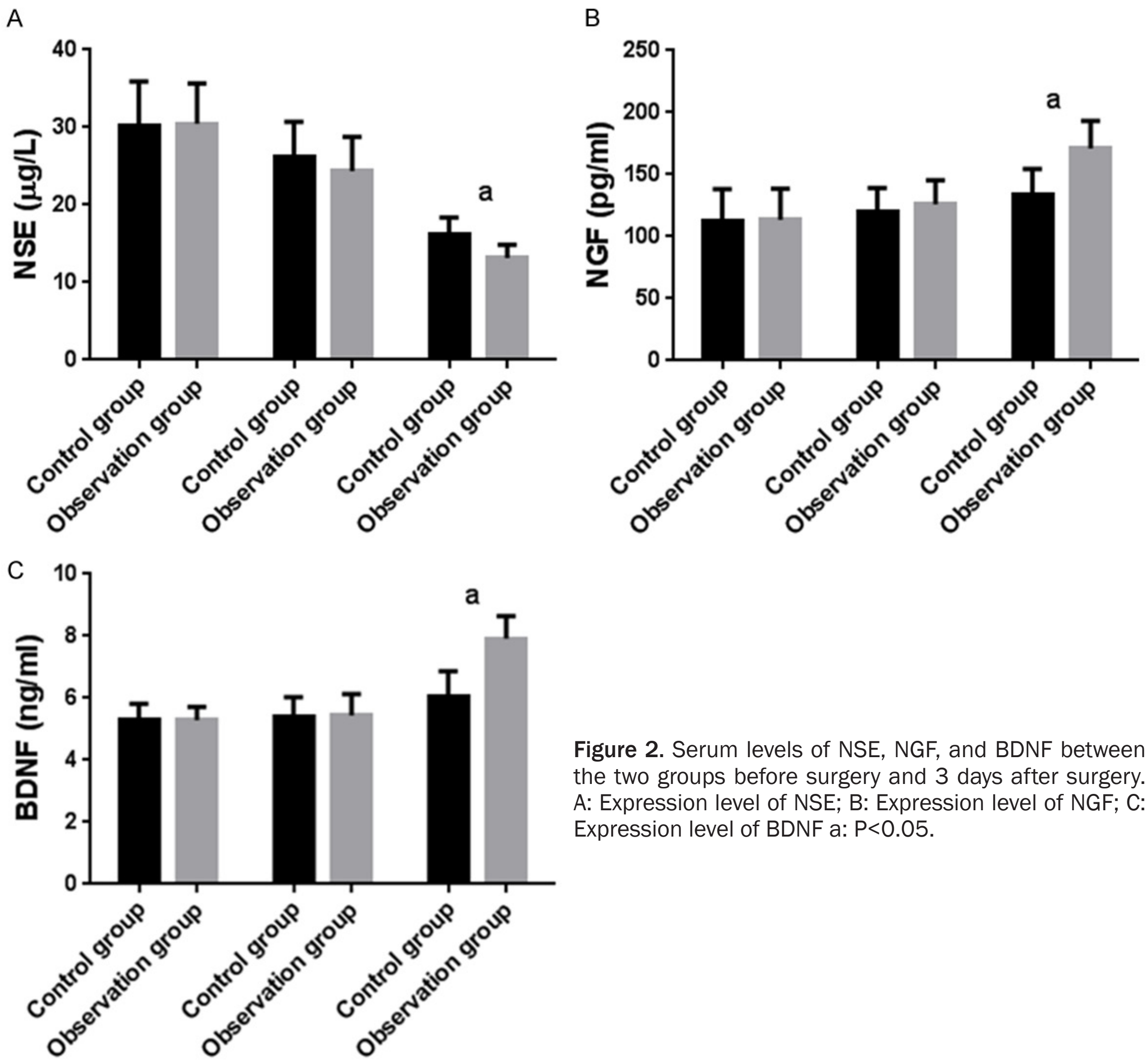

Figure 2. Serum levels of NSE, NGF, and BDNF between the two groups before surgery and 3 days after surgery. A: Expression level of NSE; B: Expression level of NGF; C: Expression level of BDNF a: $P<0.05$.

after surgery. However, the falling range of language and behavior scores in the observation group was lower than that in the control group. Three months after surgery, cognitive function in both groups recovered to levels before surgery. However, emotional scores in the control group were still lower than those before surgery. No differences were found in emotional scores from the observation group, compared to preoperative scores. Midazolam, which can cause transient anterograde memory loss in patients, can neither effectively prevent and counteract sympathetic hyperactivity nor improve hemodynamic instability effects on the cognitive function of patients during surgery [25]. However, dexmedetomidine resists sympathetic hyperactivity and better stabilizes hemodynamics during surgery. This may be one of the reasons why the degree of cognitive impairment within the observation group was lower than that in the control group. Many studies have also reported that dexmedetomidine can improve cognitive function levels, postoperatively. However, there are few reports on the effects of dexmedetomidine on cognitive function in infants undergoing cardiac surgery [26, 27].

Studies have reported that dexmedetomidine has neuroprotective effects [28, 29]. Therefore, this study detected three molecular markers, NSE, NGF, and BDNF, which have been found to be closely related to neurological function. Neuron-specific enolase mainly exists in neurons in the brain and neuroendocrine cells. When neurological impairment occurs, NSE serum levels elevate accordingly. The severity of neurological impairment positively correlates to higher NSE levels. Nerve growth factor was the first neurotrophic factor to be discovered. Upon neuronal damaged, NGF expression significantly increases to protect and repair damaged neurons. Brain-derived neurotrophic factor is a class I peptide hormone and one of the nutritional factors necessary for nerve cells to survive and perform normal functions [14, 15]. Results of this study showed that NSE levels, 3 months after surgery, were significantly lower than those seen before surgery and 3 days after surgery. Three days after surgery, NGF levels began to increase. Brain-derived neurotrophic factor levels were significantly higher, 3 months after surgery, compared to those before surgery and 3 days after surgery. Neurological function within the two groups of infants was restored, but NSE levels in the observation group were lower than those seen in the control group 3 months after surgery. However, NGF and BDNF levels were higher than those in the control group, indicating that the nerve repairing ability of the observation group was higher than that of the control group. This may also be the reason why the degree of cognitive impairment in the observation group was lower than that in the control group. Bai reported that intraoperative dexmedetomidine could reduce incidence of cognitive impairment after tonsillectomies in infants. This may be related to an increase in BDNF levels induced by dexmedetomidine [30]. Jia also reported that dexmedetomidine in infants undergoing adenoidectomies with general anesthesia can improve postoperative cognitive impairment [31]. They speculated that this improvement may be related to NSE expression.

Zhang found that dexmedetomidine can improve postoperative NGF levels and cognitive function in patients with ischemic cerebrovascular disease [32]. However, they did not analyze NGF levels and cognitive function. This study also failed to validate a definite relationship between dexmedetomidine, cognitive function, and neurological function (NSE, NGF, and BDNF levels), due to limited conditions. In light of their research, it was speculated that dexmedetomidine can improve postoperative cognitive function in infants with CHD. This may be related to hemodynamic stability maintenance and improved NSE, NGF, and BDNF serum levels.

There were some limitations and flaws to this retrospective study, however. The sample size was small. Results and conclusions should be confirmed by a larger sample size. Due to time limitations, this study included fewer indicators which reflect hemodynamics and neurological function. Analysis of dexmedetomidine also included only one dosing range. Future studies should address these issues. The hope that the current study will promote more in-depth research on the application of dexmedetomidine in pediatric anesthesia.

In summary, fentanyl and isoflurane combined with dexmedetomidine can reduce degrees of neurological and cognitive impairment in infants resulting from surgical anesthetics.

Disclosure of conflict of interest

None.

Address correspondence to: Chen Zhou, Dianmian Avenue No.374, Department of Anesthesiology, The Second Affiliated Hospital of Kunming Medical University, Kunming 650101, Yunnan, China. Tel: +86-15808866927; E-mail: zhouchenwr@163.com

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