

Influence of dexmedetomidine to cognitive function during recovery period for children with general anesthesia

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Abstract. – **OBJECTIVE:** We studied the influence of Dexmedetomidine on cognitive function in children during the recovery period of general anesthesia.

PATIENTS AND METHODS: Ninety-three children who underwent general anesthesia were selected and randomly divided into (1) the control group, (2) the dexmedetomidine group, and (3) the dezocine group. Fentanyl, propofol, and rocuronium were used in all patients to induce anesthesia, while sevoflurane inhalation and propofol were used to maintain anesthesia. In the control group, 20 ml NS were infused intravenously 10 min before anesthetic induction. In the dexmedetomidine group, 1.0 µg/kg dexmedetomidine in 20 ml was infused for 10 min. In the dezocine group, 0.1 mg/kg dezocine in 20 ml was infused for 10 min. Mean arterial blood pressure, average heart rate, and average oxygen saturation (SaO₂) were compared at the following time points: end of surgery (T0), before extubation (T1), during extubation (T2), and 30 min after extubation (T3). The VAS scale, Ramsay sedation score, delirium grading scale and occurrence of adverse reactions at 30 min after extubation were recorded. The occurrence of postoperative cognitive dysfunction (POCD) and the expression of serum neuron-specific enolase (NSE) and IL-6 at postoperative days 1 and 7 were recorded.

RESULTS: Comparing mean arterial blood pressure, average heart rate, and average oxygen saturation (SaO₂) at the different time points in the dexmedetomidine group, there were no statistically significant differences ($p > 0.05$). The difference in the occurrence of adverse reactions in the different groups was statistically significant ($p < 0.05$). The occurrence of postoperative cognitive dysfunction (POCD) at postoperative day 1 was significantly higher in the control group than the other two groups ($p < 0.05$), and on the postoperative day 7th, the differences were not statistically significant ($p > 0.05$). Regarding the expression of neuron-specific enolase (NSE) and IL-6, the levels were the highest in the control group, followed by the dezocine group ($p < 0.05$).

CONCLUSIONS: The dexmedetomidine is safer than dezocine in aspects of hemodynamics, sedation, analgesia, degree of delirium, occurrence of adverse reactions, and postoperative cognitive dysfunction (POCD). The improvement in the occurrence of postoperative cognitive dysfunction (POCD) is related to the levels of serum neuron-specific enolase (NSE) and IL-6.

Key Words:

Dexmedetomidine, Dezocine, Cognitive dysfunction, Ramsay sedation score, Restlessness rating, Delirium grading scale, Serum neuron-specific enolase (NSE), IL-6.

Introduction

With the imperfect development of the nervous system, techniques such as general anesthesia, the dose of anesthetics, the duration and complications of anesthesia, extubation during the recovery period, and other factors may cause various acute and chronic stress injuries to the nervous system of children¹. It is vital to search safe and effective anesthetics that can assist sedation, analgesia, and anti-sympathetic activity during general anesthesia, and improve the quality of anesthesia and decrease complications. Dexmedetomidine (Dex) is a newly discovered adrenoceptor agonist, which has a high α -2 specificity, and is an adjuvant anesthetic with broad clinical applications owing to its characteristics of causing few disturbances in hemodynamics, low respiratory depression effect, ease of waking up after its use, stable pharmacokinetics, high pharmacokinetics, and its anti-anxiety, anti-convulsion, and anti-epileptic functions^{2,3}. Currently, many studies focus on the function of Dex combined with normal saline (NS) in aspects of hemodynamics, analgesia, and

restlessness in children under general anesthesia. However, there is a lack of studies on its effect on postoperative cognitive function^{4,5}. As a mixed agonist-antagonist of opioid receptors, dezocine can partially decrease the hyperalgesia induced by fentanyl, and relieve pain at the level of the spinal cord, which is often adopted in clinics⁶. Through comparing the influence of Dex, dezocine, and NS on postoperative cognitive dysfunction (POCD) during the recovery period of general anesthesia in children, this research provides a basis for the proper selection of anesthetics.

Patients and Methods

Patients

We selected 93 children admitted to our hospital with a surgical indication for adenoidectomy or adenotonsillectomy from June 2013 to January 2016. Airway abnormalities, stenosis, dysplasia, neck trauma, history of surgery, asthma, inflammation and other conditions, which were unsuitable for surgery, were excluded. The study was approved by the Ethics Committee of our hospital and patients or their families signed the informed consent. According to the order of admission, the cases were divided into the control group, dexmedetomidine group, and dezocine group, each one with 31 cases. There were 19 males and 12 females in control group, with mean age of 12.4 ± 5.3 years (range: 8-16 years); 18 males and 13 females in the dexmedetomidine group, with mean age of 13.3 ± 5.5 years (range: 7-18 years); 17 males and 14 females in the dezocine group, with mean age of 13.6 ± 5.9 years (range: 7.5-17.5 years). The comparison of sex and age between the three groups revealed no significant differences.

Anesthesia

All of the children underwent anesthesia induction with $4 \mu\text{g}/\text{kg}$ fentanyl (Yichang Renfu Pharmaceutical Co., Ltd, Xilin, Yichang, Hubei, China), $2 \text{ mg}/\text{kg}$ propofol (AstraZeneca Pharmaceutical Co., Ltd, North Wilmington, DE, USA), $0.6 \text{ mg}/\text{kg}$ rocuronium (GlaxoSmithKline, Philadelphia, PA, USA), 2.5% inhalational sevoflurane (Abbott Pharmaceutical Co., Ltd, Abbott Park, IL, USA) and propofol to sustain anesthesia. The venous access was opened and lactated ringer's solution was infused before anesthetic induction. In the control group, 20 ml NS was infused in 10 min. A total of 20 ml of $1.0 \mu\text{g}/\text{kg}$ dexmedetomi-

dine (Ai Beining, produced by Jiangsu Hengrui Medicine Co., Ltd, Lianyungang, Jiangsu, China) was infused in 10 min in the dexmedetomidine group. A total of 20 ml of $0.1\text{-mg}/\text{kg}$ dezocine (Yichang Renfu Pharmaceutical Co., Ltd, Xiling Qu, Yichang Shi, Hubei Sheng, Cina) was infused in 10 min for the dezocine group.

Observational Indexes

The mean arterial blood pressure, average heart rate, and average oxygen saturation (SaO_2) at the different time points: end of surgery (T0), before extubation (T1), during extubation (T2) and 30 min after the extubation (T3) were compared. Furthermore, the VAS scale, Ramsay sedation score, delirium grading scale, and occurrence of adverse reactions 30 min after extubation were determined. The occurrence of postoperative cognitive dysfunction (POCD) and the expression of serum neuron-specific enolase (NSE) and IL-6 on postoperative days 1 and 7 days were also determined. The statistical analysis of mean arterial blood pressure, average heart rate, and average oxygen saturation (SaO_2) were also determined with the anesthesia machine (Datex-Ohmeda Aestiva/5) GE Corporation (Fairfield, CT, USA).

The VAS scale was scored from 0-10. A higher score was associated with more apparent pain. The Ramsay sedation score was divided into the following grades: 1 point represented dysphoria, 2 points represented calm and cooperative, 3 points represented sleepiness with active reaction to instruction and slurred speech, 4 points represented the condition of sleep and could be awoken, 5 points represented slow response to calling, 6 points represented the condition of deep sleeping or anesthesia and no response to calling.

The restlessness rating was divided into different grades as follows: 1 point represented calm, 2 points represented agitated but easy to be appeased, 3 points represented difficult to be appeased, and moderate anxiety or agitation, 4 points represented aggressive, excited, and disoriented. A total of 13 parameters were included in the delirium grading scale: sleep-wake cycle disorders, disturbance of perception, delusion, emotional volatility, speaking and thinking process, psychomotor retardation, disorientation, attention, short-term memory, long-term memory, and visual-spatial ability. The score was set between 0-3 for each parameter. A higher score was associated with more severe delirium. The adverse reactions included vomiting, convul-

sion, bronchial spasm, and apnea. The judgment of postoperative cognitive dysfunction (POCD) was conducted by the following tests: MMSE, DSPT, DSYT, TMT, WRD, and VBF. ELISA was adopted to measure neuron-specific enolase (NSE) and IL-6, and the kit was from Beijing Zhongshan Golden Bridge Biotechnology (Co., Ltd, Beijing, China) and was used according to the manufacturer's instructions.

Statistical Analysis

SPSS19.0 (IBM Corporation, Armonk, NY, USA) was used for data analysis. Quantitative data are presented as mean \pm standard deviation, and one-way ANOVA was used for comparisons between groups. The LSD method was used for pairwise comparisons. Repeated measures ANOVA or paired *t*-test were adopted in-group comparisons. Qualitative data are presented as cases or percentages (%), and χ^2 -test was used for comparisons. $p < 0.05$ was considered statistically significant.

Results

Comparison of Mean Arterial Blood Pressure, Average heart rate, and Average Oxygen Saturation (SaO₂) at Different Time Points

The differences in mean arterial blood pressure, average heart rate, and average oxygen saturation (SaO₂) in the dexmedetomidine group at the different time points were not statistically significant ($p > 0.05$). There was an increasing trend in mean arterial blood pressure and average heart rate in the dezocine group and control group. The differences were statistically significant ($p < 0.05$). The mean arterial blood pressure in the dexmedetomidine group at T0 was higher than in the other two groups, and was lower at the other time points. Furthermore, the average heart rate at all time points was significantly lower than the other two groups ($p < 0.05$). The mean arterial blood pressure in the dezocine group at T0 was higher than in the control group, and lower at the other time points. The average heart rate at all time points was significantly lower than in the control group ($p < 0.05$). The comparison of average oxygen saturation (SaO₂) between the dexmedetomidine group and dezocine group at all time points was also statistically significant ($p > 0.05$). The average oxygen saturation (SaO₂) in the control group was significantly decreased from T0 to T1, and significantly

increased from T3 ($p < 0.05$). The comparison of average oxygen saturation (SaO₂) at T0 between the three groups was not statistically significant ($p > 0.05$). From T1 to T3, the dexmedetomidine group had the highest average oxygen saturation (SaO₂), followed by the dezocine group second, and the difference was statistically significant ($p < 0.05$) as shown in Table I.

Comparison of VAS scale, Ramsay Sedation Score, Restlessness Rating, and Delirium Grading scale

Comparisons of VAS scale, Ramsay sedation score, restlessness rating, and delirium grading scale between the groups were statistically significant ($p < 0.05$) as shown in Table II.

Comparison of the Occurrence of Adverse Reaction

There were two cases of vomiting, one case of convulsion, and one case of bronchial spasm in control group; one case of vomiting and one case of convulsion in the dezocine group; one case of vomiting and one case of bronchial spasm in the dexmedetomidine group, and the vital signs were normal after symptomatic treatment. The occurrence of adverse reactions was not statistically significant ($\chi^2 = 1.037$, $p = 0.595$).

Comparison of the Occurrence of Postoperative Cognitive Dysfunction (POCD)

There were nine cases of postoperative cognitive dysfunction (POCD) (29.0%) in the control group, two cases in the dexmedetomidine group (6.5%), and three cases in the dezocine group (9.7%) on postoperative day 1, and the occurrence rate was significantly increased in the control group ($\chi^2 = 6.902$, $p = 0.032$). There were five cases of postoperative cognitive dysfunction (POCD) (16.1%) in the control group and one case in the dexmedetomidine group and dezocine group (3.2%), respectively, on postoperative day 7. The comparison was not statistically significant ($\chi^2 = 4.610$, $p = 0.100$).

Comparison of the Levels of Serum Neuron-Specific Enolase (NSE) and IL-6

The levels of serum neuron-specific enolase (NSE) and IL-6 in the three groups decreased significantly ($p < 0.05$). The levels of serum neuron-specific enolase (NSE) and IL-6 were significantly higher in the control group, followed by the dezocine group ($p < 0.05$) as shown in Table III.

Table I. Comparison of mean arterial blood pressure, average heart rate, and average oxygen saturation (SaO₂) at different time points.

Group		Control group	Dexmedetomidine group	Dezocine group	F	p
Mean arterial blood pressure (mmHg)	T0	60.8±3.0	62.0±2.3	61.3±2.4	4.321	0.041
	T1	65.7±3.3	62.4±2.5	63.6±2.8	4.865	0.035
	T2	69.2±3.5	63.5±2.6	65.7±3.0	5.203	0.030
	T3	73.3±3.6	63.0±2.7	67.2±3.3	5.624	0.024
	F	7.230	0.957	6.548		
	p	0.013	0.234	0.025		
Average heart-rate (time/min)	T0	76.6±5.2	72.6±4.3	74.5±5.0	4.865	0.038
	T1	82.1±5.5	73.5±4.5	77.8±5.3	5.120	0.035
	T2	85.4±5.6	74.0±4.7	79.2±5.5	5.623	0.032
	T3	89.2±5.4	75.3±4.3	83.0±5.7	5.948	0.027
	F	7.653	0.654	6.855		
	p	0.010	0.528	0.021		
SaO ₂ (%)	T0	98.3±2.6	98.6±1.3	98.5±2.0	0.321	0.638
	T1	97.6±2.8	98.7±1.2	98.2±2.3	4.235	0.043
	T2	96.8±3.0	98.5±1.5	98.3±2.4	4.637	0.040
	T3	98.2±3.2	98.6±1.3	98.4±2.3	4.852	0.038
	F	5.321	0.789	0.458		
	p	0.036	0.632	0.603		

Note: T0, at the end of operation; T1, before extubation; T2, during extubation; T3, 30 mins after the extubation.

Table II. Comparison among VAS scale, Ramsay sedation score, restlessness rating and delirium grading scale.

Group	VAS scale	Ramsay sedation score	Restlessness rating	Delirium grading scale
Control	4.3±0.8	1.2±0.3	3.5±0.8	22.3±4.5
Dexmedetomidine	2.4±0.6	2.3±0.5	2.1±0.6	10.2±4.0
Dezocine	3.0±0.5	3.4±0.7	2.6±0.5	14.5±4.3
F	5.627	5.123	5.102	5.867
p	0.026	0.031	0.032	0.023

Table III. Comparison between the level of serum NSE and IL-6.

Group	NSE (ng/mL)				IL-6 (pg/mL)			
	Postoperative 1day	7d	t	p	Postoperative 1day	7d	t	p
Control	13.5±3.4	12.4±3.0	3.659	0.045	25.3±6.2	18.2±6.0	6.003	0.035
Dexmedetomidine	7.9±2.2	5.7±2.0	5.328	0.032	12.6±3.5	6.9±3.0	6.421	0.027
Dezocine	10.6±3.0	8.5±2.6	5.120	0.036	18.5±4.7	11.7±4.5	6.326	0.030
F	6.230	6.548			5.897	6.213		
p	0.032	0.029			0.036	0.033		

Discussion

Dexmedetomidine has various modes of administration such as oral administration, nasal

administration, subcutaneous injection, intravenous injection, and intravenous infusion⁷. The pharmacological function of dexmedetomidine on respiration is mainly manifested as a light

decrease in minute-ventilation at the time of resting and decrease in the respiratory tract response. The degree of respiratory depression is less than with midazolam, propofol and opioid drugs, and can decrease the usage of midazolam and fentanyl. Furthermore, it has no synergistic action with opioid analgesic drugs, which may cause respiratory depression⁸. The speed- and dose-dependent effects on blood pressure, heart rate, and cardiac output of cardiovascular system should be monitored carefully⁹. Through activating α_2 adrenergic receptors, inhibiting the reaction of the central nervous system, decreasing the releasing of epinephrine and norepinephrine, and decreasing the body's stress response, dexmedetomidine achieves the functions of sedation, analgesia, and anti-anxiety. The sedative function can simulate normal sleeping, from which patients can be awoken¹⁰. During the recovery period of general anesthesia, children are difficult to appease, flail about, suffer from incoherence and dysphoria, and fail to recognize people or things that are familiar to them. The disease condition is unstable and is associated with certain dangers¹¹. Dexmedetomidine manifested good effects according to the VAS scale, Ramsay sedation score, restlessness rating, delirium grading scale, and postoperative adverse reactions. It can be administered preoperatively and postoperatively¹². Dexmedetomidine acts on the *Nucleus Ceruleus* in the central nervous system to achieve of sedation and hypnosis, and antagonizes the sympathetic activity through the joint action of central and peripheral neurotransmitters¹³. Hoffman et al¹⁴ found that dexmedetomidine is cerebroprotective for general anesthesia, and significantly decreases the levels of NO, TNF- α , and SOD. Dexmedetomidine can prevent injury of the hippocampus, thalamus, and cortex induced by isoflurane inhalation in a dose-dependent manner. Also, it has a long-term effect on neural cognitive function¹⁵. It has a protective function after traumatic brain injury and is related to decreasing inflammation¹⁶. As a neurochemical marker that reflects brain injury, neuron-specific enolase (NSE) can be used to monitor cerebral ischemic injury, and is regarded as an early diagnostic marker of subclinical brain injury^{17,18}. Neuron-specific enolase (NSE) is stable in body fluid and does not cross react with the non-neuronal enolase. Cooper¹⁹ proved that neuron-specific enolase (NSE), as a biochemical marker of neuronal injury, is an effective

index to test for the death of neurons. For patients with brain injury, the positive correlation between the serum levels of neuron-specific enolase (NSE) and IL-6 indicates that higher serum levels of IL-6 indicate more severe cerebral inflammation. More severe neuronal injury, in turn, leads to the higher occurrence of postoperative cognitive dysfunction (POCD)²⁰. By decreasing the levels of serum neuron-specific enolase (NSE) and IL-6, dexmedetomidine decreased the occurrence of postoperative cognitive dysfunction (POCD) on postoperative day 1, and there was no statistically significance difference compared with the occurrence of postoperative cognitive dysfunction (POCD) on postoperative day 7. This was considered to be related to the small sample-size and metabolism of general anesthetics.

Conclusions

Dexmedetomidine is safer than dezocine in aspects of hemodynamics, sedation, analgesia, delirium, and the occurrence of adverse reaction and postoperative cognitive dysfunction (POCD). The improvement of the occurrence of postoperative cognitive dysfunction (POCD) is related to the serum levels of neuron-specific enolase (NSE) and IL-6. Dexmedetomidine is an important auxiliary narcotic drug with high safety, and is suitable for a wide range of diseases and populations in the clinic.

Conflict of interest

The authors declare no conflicts of interest.

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