

The postoperative effect of sevoflurane inhalational anesthesia on cognitive function and inflammatory response of pediatric patients

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Abstract. – OBJECTIVE: To investigate the effect of sevoflurane on cognitive function and inflammatory response of children after general anesthesia at different times.

PATIENTS AND METHODS: Ninety-three pediatric patients who underwent general anesthesia surgery were enrolled and divided into groups based on time under general anesthesia: group A (<1 h, n=27), group B (1-3 h, n=36), and group C (\geq 3 h, n=30). Changes in cognitive function and serum inflammatory index were compared.

RESULTS: The occurrence of postoperative cognitive dysfunction (POCD) in group A and B was lower than in group C and the difference was statistically significant ($p<0.05$). The levels of caspase-3, TNF- α , and IL-6 in the POCD group at the different time points were significantly higher than in the non-POCD group and the differences were statistically significant ($p<0.05$). Caspase-3, TNF- α , and IL-6 levels in the POCD group at the different time points significantly changed and were highest during the recovery period, while there were no significant changes in the non-POCD group at the different time points.

CONCLUSIONS: The prolonged sevoflurane inhalational anesthesia time (\geq 3 h) enhanced the occurrence of POCD and was related to the expression levels of serum caspase-3, TNF- α , and IL-6.

Key Words:

Sevoflurane inhalation anesthesia, Cognitive function, Caspase-3, TNF- α , IL-6.

esthesia induction takes effect quickly with a low blood-gas partition coefficient of 0.63. It has an aromatic odor and does not greatly irritate the respiratory tract of children. Endotracheal intubation can be completed without muscle relaxant, hemodynamics are stable and recovery from anesthesia is quick with few complications, which greatly reduces the stay in the monitoring room and improves the quality of analgesia^{2,3}. Postoperative cognitive dysfunction (POCD) occurs frequently among older patients at about 10-35%, and severely reduces the anesthetic effect and long-term quality of life⁴. Various degrees of brain injury can be easily caused because of imperfect physiological function, poor stress response ability, and abnormal sensitivity of the nervous system to external stimulation⁵. POCD is closely related to injury of the brain, in which the hippocampus is an important region involved in learning and memory. As shown from animal models⁶, the abnormal expression of hippocampal caspase-3, TNF- α , IL-6, and other inflammatory factors, mediates apoptosis and are involved in the occurrence of POCD. Whether sevoflurane results in POCD and its degree of severity may be related to anesthesia time⁷. The present study provides a reference for the correct application of anesthesia in children and prevention of POCD, by evaluating the effect of sevoflurane inhalational anesthesia on cognitive function and the inflammatory response of children at different time points after surgery.

Introduction

Intravenous inhalational anesthesia is widely used clinically¹. With long recovery time after anesthesia, it has several complications including reflux aspiration, dysphoria, coughing, and hoarseness of voice. Sevoflurane inhalational ane-

Patients and Methods

We selected 93 pediatric patients who were admitted and underwent surgery in our hospital from January 2014 to January 2016.

The exclusion criteria included patients with congenital dysplasia, prior brain surgery, mental retardation, surgical failure or with severe complications. The study was approved by the Ethics Committee of our hospital. The informed consent from the patients' families was obtained. Patients were divided into group A (< 1 h, n=27) group B (1-3 h, n=36), and group C (\geq 3 h, n=30) based on anesthesia time. In group A, 16 cases were male and 11 were female, aged 1-13 years old with average age of 5.6 ± 3.3 years. The anesthesia time was 30-55 min with an average time of 42.6 ± 10.5 min. Types of surgery: oral and facial surgery in seven cases, thoracic and abdominal surgery in 12 cases, and limb surgery in three cases. In group B, 19 cases were male and 17 were female, aged 1.5-15 years old with average age of 6.0 ± 3.8 years. The anesthesia time was 75-165 min with an average time of 112.5 ± 28.4 min. Types of surgery: oral and facial surgery in 10 cases, thoracic and abdominal surgery in 13 cases, and limb surgery in 13 cases. In group C, 17 cases were male and 13 were female, aged 1-12.5 years old with average age of 5.3 ± 3.4 years. The anesthesia time was 190-325 min with an average time of 265.8 ± 45.6 min. Types of surgery: oral and facial surgery in six cases, thoracic and abdominal surgery in 14 cases, and limb surgery in 10 cases. Comparing the gender, age and types of surgery among the three groups, the differences were not statistically significant ($p > 0.05$).

Anesthesia

All patients were given sevoflurane inhalational anesthesia, and intramuscular injection of 0.1 mg/kg Atropine. A DE Dansh4000 monitor and Drager 2000 anesthesia machine were used. The respiratory tidal volume was 10 ml/kg with respiratory frequency of 15-28 times/min. Vaporizer concentration of 8% was used for induction, and pre-charged for 1 min if gas flow was > 6 L/min to make the inhalation concentration 5-6%. When brain concentration was up to 0.33MAC, hand controlled breathing was carried out for 2 min, and tracheal intubation was conducted when end-tidal concentration reached 1.3MAC and inhalation concentration was regulated to 3-4% with gas flow of 2 L/min. End-tidal concentration at 0.8-1.3MAC was maintained, and the vaporizer was closed within 5 min before the end of surgery. When gas flow was 4 L/min, lung lavage was carried out.

Observational Indexes

The changes in cognitive function and serum inflammatory index of patients after surgery were compared. POCD diagnosis included: dysfunction related to cognition such as confusion and anxiety, psychomotor disturbances, concentration problems, reduced memory, language disability, abnormal sensation, mental and behavioral disorders, including mood disorder, aggressive behavior, fatigue and sleepiness. Measurement scales such as the Wechsler Intelligence Scale for Children, Cambridge neuropsychological test automation and Bender Gestalt testing were evaluated in line with clinical performance and corresponding cognition. Serum inflammatory index includes measurement of caspase-3, TNF- α , and IL-6 levels. 5 ml peripheral venous blood was drawn at anesthesia, during the recovery period and 7 days after surgery. Blood was centrifuged for 20 min at a speed of $2500 \times g$ and stored at -20°C until use. ELISA was used to measure levels of inflammatory mediators. Kits were purchased from Sigma-Aldrich (St. Louis, MO, USA), microplate reader was from Beijing Zhongshan Golden Bridge Biotechnology Co., Ltd and used according to the manufacturer's instructions.

Statistical Analysis

SPSS 20.0 software (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0, Armonk, NY, USA) was used to carry out statistical analyses. Measurement data are expressed as mean \pm standard deviation, comparison among groups was made by *t*-test. Repeated measure variance analysis was used for inter-group comparisons at different time points. Count data are expressed as the number of cases or as percentage (%) and comparisons among groups were made by χ^2 -test. $p < 0.05$ was taken as statistically significant.

Results

Comparison of Occurrence of POCD

The occurrence of POCD in group A and B was lower than in group C, and the difference was statistically significant ($p < 0.05$) (Table I).

Comparison of Serum Inflammatory Index

Caspase-3, TNF- α , and IL-6 levels of the group with POCD at different time points were significantly higher than in the non-POCD group,

Table I. Comparison of occurrence of POCD.

Group	Case	Dysfunction related to cognition	Mental and behavioral disorders	Fatigue and sleepiness	Total occurrence of POCD
Group A	27	0	0	2 (7.4)	2 (7.4)
Group B	36	0	0	3 (8.3)	3 (8.3)
Group C	30	1 (3.3)	1 (3.3)	7 (23.3)	9 (30.0)
χ^2					7.234
<i>p</i>					0.027

Note: group A, <1 h; group B, 1-3 h; group C, \geq 3h.

and the differences were statistically significant ($p < 0.05$). Caspase-3, TNF- α , and IL-6 levels in the POCD group had significant changes, and reached the highest levels at the recovery period, while these parameters had no evident changes in the non-POCD group (Table II).

Discussion

POCD is the result of central nervous system (CNS) injury. Inflammatory responses generally occur in the periphery, where they can spread to the CNS through a series of cascade reactions. Research in healthy volunteers showed that peripheral intravenous injection of endotoxin resulted in increased levels of peripheral IL-6, TNF- α , and other inflammatory factors as well as transient anxiety, depression, and memory decline⁸. Cells can interact with each other by means of autocrine, paracrine and endocrine signals, and

widely affect the immune, nervous and endocrine systems. In an autopsy study, comparison was made between brain tissues from patients with lifelong delirium and control brain tissues (without delirium) of similar age⁹, showing that the levels of IL-6 level in brain tissues (including the thalamus, frontal lobe, and white matter) from patients with delirium were higher. In addition, the proportion of activated microglial cells and astrocytes were higher, which indicated that the occurrence of POCD was closely related to the inflammatory response of the CNS.

Inflammatory responses occurring at peripheral areas are likely to affect the brain through various means: 1. Inflammatory mediators can diffuse to the brain through periventricular organs¹⁰. A previous study showed that, when innate immunity was activated, inflammatory mediators were able to activate brain macrophages and microglial cells through periventricular organs and cause neurological symptoms.

Table II. Comparison of serum inflammatory index

Group		POCD group (n=14)	Non-POCD group (n=79)	<i>t</i>	<i>p</i>
Caspase-3 (ng/ml)	During anesthesia	3.5 \pm 1.0	1.2 \pm 0.5	6.235	0.025
	In recovery period	4.0 \pm 1.3	1.3 \pm 0.6	6.864	0.020
	7 days after surgery	3.6 \pm 1.2	0.9 \pm 0.3	6.328	0.023
	<i>F</i>	5.623	1.234		
	<i>p</i>	0.034	0.127		
TNF- α (ng/ml)	During anesthesia	1.2 \pm 0.4	0.3 \pm 0.2	6.532	0.021
	In recovery period	1.5 \pm 0.6	0.4 \pm 0.2	6.865	0.018
	7 days after surgery	1.0 \pm 0.5	0.3 \pm 0.2	6.239	0.024
	<i>F</i>	5.235	0.658		
	<i>p</i>	0.036	0.323		
IL-6 (pg/ml)	During anesthesia	86.5 \pm 14.6	43.6 \pm 22.4	6.521	0.026
	In recovery period	126.3 \pm 20.5	45.7 \pm 26.3	6.865	0.021
	7 days after surgery	78.6 \pm 21.3	43.2 \pm 25.7	6.429	0.030
	<i>F</i>	6.235	0.639		
	<i>p</i>	0.024	0.452		

2. Through capillary endothelial and perivascular cells¹¹. When systemic inflammatory responses occurs, inflammatory mediators from the periphery are able to activate brain capillary endothelial cells and perivascular cells (mainly including microglial cell and astrocytes) to cause a central inflammatory response. Microglial cells are similar to peripheral macrophages, and can produce different phenotypes in different environments. Microglial cells showed inflammatory phenotypes in infection and injury and were shown to proliferate and release a variety of inflammatory factors, which further aggravated the inflammatory response of the CNS. 3. Through increased permeability of the blood-brain barrier¹². 4. Through the vagus nerve¹³.

We observed the effect of sevoflurane inhalational anesthesia on cognitive function and inflammatory response of children at different time points following surgery. Primary brain injury and traumatic brain surgery were excluded from the analysis. The occurrence of POCD in group A and B was lower than in group C and the difference was statistically significant. The levels of caspase-3, TNF- α , and IL-6 in the POCD group at the different time points were significantly higher than in the non-POCD group and the differences were statistically significant. The inflammatory mediators of the POCD group had evident changes, and reached the highest levels during the recovery period, whereas they were not different in the non-POCD group. POCD was evaluated with various comprehensive cognitive performance scales. Dysfunction related to cognition, mental and behavioral disorders, as well as fatigue and sleepiness were regarded as POCD. Fatigue and sleepiness occurred in a large proportion of children with POCD, which contrasted with the observation in older patients¹⁴.

Caspase-3 is the main end-cleaving protease in the apoptotic process. Activated caspase-3 can induce apoptosis, while neuronal apoptosis can induce cognitive dysfunction¹⁵.

Conclusions

To summarize, the extension of sevoflurane inhalational anesthesia time (≥ 3 h) can increase the occurrence of POCD, which is associated with changes in serum caspase-3, TNF- α , and IL-5. Limitations of the study included small

sample size, and time grouping was related to the types of surgery and experience of the operators. Furthermore, the causes of POCD include inhalational concentration of sevoflurane, respiratory parameters, and medication during and after surgery. A multi-factor regression analysis, and analysis of the relevance of POCD occurrence and caspase-3, TNF- α , and IL-6 were not carried out.

Conflict of Interest

The Authors declare that they have no conflict of interest.

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