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ORIGINAL ARTICLE

Prognostic study of sevoflurane-based general anesthesia on cognitive function in children

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Abstract
Purpose It is unclear whether volatile general anesthetics have sustained adverse effects on the immature brains of children. We performed a self-controlled study to evaluate the effects of strabismus surgery under sevoflurane-based general anesthesia on the cognitive function of pediatric patients.
Methods The study included 100 children of ages 4 to 7 years old scheduled to undergo strabismus correction under sevoflurane-based general anesthesia. Cognitive function was tested 1 day before the operation (T1), 1 month after the operation (T2), and 6 months after the operation by the Wechsler Preschool and Primary Scale of Intelligence (WPPSI) (Third Edition) method, which consists of 150 items. The scores at T1 were compared with scores at T2 and T3.
Results Seventy-two children completed the three tests. At T1, they were 66.1 ± 7.7 months old and had a mean body weight of 21.6 ± 4.0 kg. The mean anesthesia time was 67.3 ± 9.8 min. The mean interval between T1 and T2 was 25.4 ± 6.8 days, and that between T1 and T3 was 182.1 ± 27.7 days. No statistically significant decrease in WPPSI scores was observed between T1 and T2, or between T1 and T3.
Conclusion These findings from our self-controlled study show that sevoflurane-based general anesthesia does not have significantly adverse effects on the cognitive function of 4- to 7-year-old children at 1 month and 6 months after strabismus surgery. Additional studies with a larger sample size are needed.

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Introduction

It is important to determine whether volatile gaseous anesthetics have sustained adverse effects on the developing brains of children. Previous studies have suggested that volatile anesthetics may induce brain cell apoptosis and neurodegeneration in children [1–7].

Few studies have investigated the effects of anesthetic exposure on the long-term cognitive development in children younger than 7 years of age [8, 9]. Several studies have assessed the effects of anesthetics on postoperative cognitive function of children by surveying their parents [10–12]. However, because of the limited language ability of children and the subjective nature of parental perception, the accuracy and completeness of the data collected by this method are questionable. Other studies have examined the effects of anesthetics on cognitive function in children shortly after an operation, but they did not eliminate the effects of the operations or the residual effects of anesthetics [13].

In the current study, we compared the cognitive function of children before and after surgical strabismus correction. Our objective was to determine whether general anesthesia (mainly sevoflurane) adversely affects the medium- to long-term cognitive function of 4- to 7-year-old children.

Materials and methods

One hundred children (aged 3 years, 10 months, and 16 days to 6 years, 7 months, and 15 days) scheduled to undergo surgical strabismus correction under general anesthesia in our hospital were included in this self-controlled study. All children were classified as category I–II according to the American Society of Anesthesiologists physical status classification system. Children with any of the following conditions were not included: a history of emergency treatment at birth, antecedent history of surgical operations, a history of mental disorders or mental disabilities, metabolic diseases, and major life events during this study (e.g., parental divorce or death). Children with Wechsler Preschool and Primary Scale of Intelligence Third Edition (WPPSI-III) scores <70 (as tested 1 day before strabismus correction operation) were also excluded. This study was approved by the Research Ethics Committee of Eye & ENT Hospital of Fudan University. Written informed consents were obtained from the parents or guardians of the children.

For each child, WPPSI-III scores were tested at three time points: 1 day before strabismus correction (T1); 1 month after correction (T2); and 6 months after correction (T3). The modified Chinese version of a WPPSI manual published in the United States was used for the tests [14]. Compared with the original manual, the Chinese version was modified by leading pediatric institutions in China to suit children from 3 years, 10 months, 16 days of age to 6 years, 7 months, and 15 days of age. The modified Chinese version assigns different scores to different age intervals and, therefore, eliminates intelligence score differences resulting from age differences. This Chinese version has been accepted as the standard evaluation method for children in China.

The WPPSI-III tests consisted of verbal tests and performance tests. The verbal tests included five types of subtests as follows. (1) Information: the child was asked to answer the names or functions of human organs, the names of animals, number of months in a year or the number of days in a month (or week), as well as other questions regarding history, geography, and people. (2) Vocabulary: the child was asked to explain the meanings of 22 words. (3) Arithmetic: the child was asked to complete 20 counting or arithmetic questions. (4) Similarities: the child was asked to identify and explain the similarity between two words (total of 16 pairs) given by the examiner. This test was designed to test the abstract reasoning ability of the child. (5) Comprehension: the child answered 15 questions regarding daily matters, social rules, and ethics. The child was also asked to explain the reasoning (or actions) of their answers.

The performance tests included five types of subtests. (1) Animal house: the child was provided with a template with pictures of different animals and 28 small wood rods of different colors. The child was told that each animal had a favorite color. The child inserted rods into the holes under the animal pictures to match each animal with its favorite color. (2) Picture completion: the child was asked to view a picture (total, 23) and point out the missing part and its location. (3) Mazes: the child used red pencils to go through mazes ($n = 10$) printed on paper. (4) Geometric design: the child was supplied with papers marked with the symbol E and numbers 1–10, two red pencils, and 10 collated cards with pictures. The child was asked to sequentially redraw the pictures printed on the cards with the same shapes and sizes. (5) Block design: the child was given 14 flat wood blocks (6 blocks having one face red and the opposite face white; 8 blocks: one face was red and the opposite face was half-red/half-white), and three collated cards with pictures. The child was required to reproduce the designs shown in the cards within a specified time limit.

The preliminary score on each test and the time spent on that test were measured. The preliminary score was transformed into the scale score using a table in the WPPSI-III manual (Chinese version). The overall verbal IQ score and performance IQ score were also determined using a WPPSI-III table. All tests were conducted by one staff member. Before the actual tests, trial tests were performed in ten randomly chosen children of appropriate ages under the supervision of two clinicians with experience in WPPSI tests. Potential examiner and examinee biases in trial tests were carefully recorded and prevented in subsequent tests. Data from these trial tests were not used in statistical analysis. All tests used consistent methods and requirements.

The general conditions (Table 1) of the child were examined 1 day before strabismus correction operation. The child then received the first test (T1). When possible, the child was required to finish the test without the presence of parents. Conversely, parents (or relatives) were allowed to be present during the test but were not allowed to provide any hints. Furthermore, the parents were instructed not to give any instructions on the test questions before completion of the third test (T3). The child received T2 and T3 at 1 and 6 months after the operation, respectively. After the completion of T3, the child was allowed to know the correct answers to the questions, and the parents (or relatives) were informed of the test results.

Before the strabismus correction operation, children were fasted and not given preoperative medication. After being transferred to the operation room, children were monitored for vital signs (e.g., electrocardiogram, noninvasive blood pressure, blood oxygen saturation) using a GE-DASH 4000 system (GE Healthcare, Finland). Sevoflurane (Hengrui Pharma, Shanghai, China; lot no. 10082531) was delivered by inhalation (sevoflurane, 8 %; oxygen flow, 8 l/min; oxygen concentration, 100 %) using a Drager Primus anesthesia workstation (Drager, Luebeck, Germany). After the loss of consciousness (0.01 mg/kg atropine; Harvest Pharma, Shanghai, China; lot no. 31021172), fentanyl

Table 1 General patient information and conditions during the perioperative period

	Number of patients or measurement result (mean ± standard deviation)	Percentage of patients (%)
Sex		
Male	39	54.2
Female	33	45.8
Age (months)	66.1 ± 7.7	
Body mass (kg)	21.6 ± 4.0	
Highest parent education level		
Grade 1–6	2	2.8
Grade 7–9	9	12.5
High school or technical school	24	33.3
Associate bachelor degree	18	25
Bachelor degree	13	18.1
Graduate degree or higher	6	8.3
Preoperative status		
Calm and cooperative	46	63.9
Stressed and nervous	26	36.1
Irritated and crying	0	0
Time under anesthesia (min)	67.3 ± 9.8	
Time to awakening (min)	21.6 ± 6.1	
Interval between tests (days)		
T1–T2	25.4 ± 6.8	
T1–T3	182.1 ± 27.7	
T2–T3	156.5 ± 28.3	
Laryngospasm incidence during perioperative period (%)	0	0.0
Hypoxia incidence during perioperative period (%)	0	0.0

Time under anesthesia, the time span from anesthesia induction to operation completion; time to awakening, the time span from operation completion to leaving PACU; T1, first test (1 day before surgical strabismus correction); T2, second test (1 month after strabismus correction); T3, third test (6 months after strabismus correction)

(3–4 μg/kg; Renfu Pharmaceutical, Yichang, Hubei, China; lot no. 100505) and rocuronium (Organon, Oss, Netherlands; 0.4 mg/kg) were injected via the peripheral limb veins. A laryngeal mask was then placed and the sevoflurane concentration was reduced to 3 %. The oxygen flow rate was reduced to 2 l/min and the concentration was reduced to 50 %. The minimum alveolar concentration (MAC) was maintained between 1.1 and 1.3. The anesthesia workstation was operated at the pressure control ventilation [8–12 cmH_2O, 12–20 breaths/min, inspiratory:expiratory ratio = 1:2, no positive end-expiratory pressure (PEEP)]. Ventilation parameters were adjusted to maintain the end-tidal carbon dioxide pressure ($P_{ET}CO_2$) between 35 and 45 mmHg. Sevoflurane delivery was ended immediately after the completion of the operation, and 5 μg/kg ramosetron hydrochloride (Cisen Pharmaceutical, Jining, Shandong, China; lot no. 09100510101) was administered by intravenous injection. The child was then transferred to a post-anesthesia care unit (PACU). When the tidal volume became greater than 6 ml/kg and the respiratory rate greater than 12 breaths/min, the laryngeal mask was removed during sleep. Children were returned to the inpatient room after meeting the criteria for leaving the PACU. Patient conditions during the perioperative period are summarized in Table 1.

The general conditions, final scale scores of WPPSI, and the overall IQ scores were analyzed with SPSS 16.0 (SPSS, Chicago, IL, USA). A general linear model was applied to analyze repeated measurements over different time points, and Mauchly's test of sphericity was used to detect correlation among the measurements before the analysis of variance. If the data fit Mauchly's test of sphericity ($P > 0.05$), analysis of variance (ANOVA) can be done without correction. If any data do not fit $P < 0.05$, correction is needed. This study used the most conservative lower-bound method to correct the data. A P value of less than 0.05 was considered statistically significant. Data are expressed as mean ± standard deviation.

Results

Of the 100 child patients, 10 were used for initial trial tests and their results were not included in the statistical analysis. Eleven children were lost to follow-up, 3 yielded excessively low scores (<70), and 4 failed to complete T1.

Therefore, 72 children completed this study, including 39 boys (54.2 %) and 33 girls (45.8 %). At T1, children were 66.1 ± 7.7 months old and had a mean body weight of 21.6 ± 4.0 kg. The parents of 58.3 % of these children had higher than primary education levels (mainly high school or associate bachelor degrees; based on the highest education level of the parents of a child). Before the operation, most (63.9 %) of these children were calm and cooperative, 36.1 % of the children were nervous, but no child was crying. During the operation, the mean anesthesia period was 67.3 ± 9.8 min. The children awoke from anesthesia 21.6 ± 6.1 min after the operation. The mean interval between T1 and T2 was 25.4 ± 6.8 days, and that between T1 and T3 was 182.1 ± 27.7 days.

This study found, through the Mauchly's test of sphericity, that only 4 indices—information, arithmetic, picture completion, and geometric design—follow the spherical distribution; the rest of the indices (10) show significant correlation (Table 2). Thus, this study used the most conservative lower bound to perform corrected ANOVA or multivariate ANOVA between measured data.

Generally, the scores recorded from T2 (Table 2) were slightly higher than the T1 scores, and the T3 scores were higher than both the T1 and T2 scores. Specifically, the T3 and T2 scores were significantly higher than the T1 scores in five test items: animal house ($P = 0.028$), picture completion ($P = 0.002$), block design ($P < 0.001$), performance IQ ($P < 0.001$), and full IQ ($P < 0.001$). Although the T2 scores were slightly decreased, the T3 scores were significantly higher than the T1 and T2 scores in three test items: information ($P = 0.014$), similarities ($P = 0.004$), and verbal IQ ($P = 0.005$). There were no significant differences among T3, T2, and T1 scores in other items. Therefore, no significant decrease in the WPPSI scale score was detected from T1 to T2, and from T1 to T3.

The outcome of linear fitness of scores shows that the three detection score showed a linear rise ($P < 0.05$) (Table 3) in the rest of the indices except vocabulary, mathematics, understanding, maze, and geometric design. Linear fitting results are consistent with the variance analysis result.

Discussion

The potential adverse effects of inhalational anesthetics on the developing brains of children have been the focus of intensive research. The results from the present study suggest that sevoflurane-based general anesthesia did not produce significantly negative effects on the cognitive function of children at 1 and 6 months after surgical strabismus correction.

Strabismic children were used as subjects in this study because they were typically 4 to 7 years old and required review examinations at 1 and 6 months after surgical correction. These conditions facilitated the successful completion of this study. The cognitive functions of these children were evaluated by the WPPSI-III test, which is a relatively scientific method for IQ assessment. This method covers multiple aspects related to cognitive functions (e.g., learning ability, language comprehension, memory, perceptual organization, and mental concentration) and yields comprehensive, systematic, and accurate information on the cognitive functions of examinees [15]. Moreover, the scaling system of this test adjusts the final scores according to the examinee age and thus eliminates the effects of age differences on the assessment results. The WPPSI-III test was modified by authoritative institutes in China to better suit the characteristics of Chinese children. Lobello et al. [16, 17] reported that WPPSI tests frequently gave clerical and scoring errors during examinations. In our study, potential biases and source of errors were identified by trial tests. In subsequent formal tests, corresponding procedures were consistently enforced to minimize these biases and errors.

The 72 children who completed this study had a mean age of 66.1 months, and many (58.3 %) of their parents

Table 2 Summary of test scores

	Test scores			Mauchly's test of sphericity		Univariate test	
	T1	T2	T3	Chi-square	*P* value	*F*	*P* value
Time spent on test (min)	69.5 ± 9.9	63.8 ± 10.9	60.0 ± 9.3	2.11	0.347	35.45	<0.001
Information	11.5 ± 2.6	11.1 ± 3.3	12.6 ± 2.4	0.31	0.855	6.80	0.014
Vocabulary	10.5 ± 4.2	10.3 ± 4.2	11.3 ± 3.4	17.86	<0.001	2.91	0.099
Arithmetic	11.3 ± 2.8	11.3 ± 2.6	12.0 ± 2.0	5.82	0.055	1.50	0.231
Similarities	8.5 ± 3.9	8.5 ± 4.4	10.8 ± 3.9	6.10	0.047	9.75	0.004
Comprehension	8.5 ± 4.0	8.8 ± 3.9	9.43 ± 3.5	21.90	<0.001	1.49	0.232
Verbal IQ	100.0 ± 18.5	99.9 ± 20.2	108.2 ± 17.1	15.59	<0.001	9.33	0.005
Animal house	11.5 ± 2.3	12.5 ± 1.9	12.3 ± 1.4	7.83	0.020	5.34	0.028
Picture completion	10.5 ± 3.1	11.2 ± 2.8	12.3 ± 2.8	5.78	0.056	12.11	0.002
Mazes	13.6 ± 3.2	14.6 ± 2.6	14.6 ± 2.1	9.60	0.008	3.66	0.066
Geometric design	13.5 ± 3.4	13.9 ± 2.7	13.8 ± 2.2	1.33	0.514	0.66	0.423
Block design	9.6 ± 2.8	11.2 ± 2.3	11.9 ± 1.6	6.36	0.042	25.28	<0.001
Performance IQ	112.5 ± 15.5	119.2 ± 11.5	121.2 ± 10.6	7.56	<0.001		
Full IQ	106.8 ± 15.4	110.23 ± 14.8	116.0 ± 13.6	13.66	<0.001		

Results from 72 children who completed this study, and expressed as mean ± standard deviation

T1, first test (1 day before surgical strabismus correction); T2, second test (1 month after strabismus correction); T3, third test (6 months after strabismus correction)

Table 3 Linear fitness of scores in the three tests (T1, T2, and T3)

Test item	Mean squares	*df*	*F*	*P* value
Information	18.15	1	6.47	0.017
Vocabulary	9.60	1	2.13	0.155
Arithmetic	6.67	1	1.95	0.174
Similarities	81.67	1	10.90	0.003
Comprehension	12.15	1	1.82	0.187
Verbal IQ	1,000.42	1	9.46	0.005
Animal house	9.60	1	5.20	0.030
Picture completion	50.42	1	16.79	0.000
Mazes	15.00	1	3.63	0.067
Geometric design	1.67	1	0.59	0.450
Block design	74.82	1	35.18	<0.001
Performance IQ	1,135.35	1	22.34	<0.001
Full IQ	1,260.42	1	20.44	<0.001

$P < 0.05$ considered statistically significant ($n = 72$)

df degree of freedom

had high school or associate bachelor degrees. Children with T1 scores of less than 70 typically had mental disorders or were uncooperative during the test. Therefore, results from these children were excluded from statistical analysis [18]. After being transferred into the operation room, 63.9 % of children were calm and cooperative. None of the children was irritated and crying. This satisfactory cooperation was probably attributed to excellent communication between the anesthesiologist and the patients 1 day before the operation, which created trust in the patients for the anesthesiologist. Additionally, appropriate measures were performed during the perioperative period to reduce psychological stress on the patients. Such measures may have also prevented psychological and mental disturbances during the perioperative period, thus contributing to patient cooperation [19, 20].

The children were anesthetized primarily by sevoflurane inhalation, in conjunction with intravenous injection of small doses of rocuronium, fentanyl, and ramosetron hydrochloride. Sevoflurane is a new halogenated ether general inhalational anesthetic with stable physicochemical properties, quick and smooth anesthesia induction, and a sweet fragrance without irritation. Based on these advantages, this anesthetic has been widely used in pediatric operations. However, many studies have shown that high concentrations of sevoflurane can induce brain cell apoptosis and neurodegeneration in young rats and nonhuman primates [1–3]. Criswell et al. [21] reported that sevoflurane dose-dependently inhibits NMDA-gated currents in cultured neurons and stimulates overexpression of NMDA receptor subunit MR_2B to produce a high concentration of oxygen free radicals. Wong et al. [22] found that sevoflurane stimulates hydrogen peroxide formation in peripheral lymphocytes, which damages mitochondrial membranes to exert cytotoxic effects.

In our study, the scores recorded from T2 (Table 2) were slightly higher than the T1 scores, and the T3 scores were higher than both the T1 and T2 scores. Specifically, the T3 and T2 scores were significantly higher than the T1 scores in five test items: animal house, picture completion, block design, performance IQ, and full IQ. There were no significant differences among T3, T2, and T1 scores in other items. The outcome of linear fitness of scores shows that the three detection scores showed a linear rise (Table 3) in the rest of the indices except vocabulary, mathematics, understanding, maze, and geometric design. Linear fitting results were consistent with the variance analysis result. Therefore, no significant decrease in the WPPSI scale score was detected from T1 to T2, and from T1 to T3. The major observation from the present study is that the children had no significant decrease in cognitive function at 25 and 182 days after strabismus surgery under general anesthesia. Many earlier studies observed that general anesthesia induces neuronal damage in the developing brains of rats and children [1, 2, 21–23]. However, several studies [24, 25] have suggested that children's brains have strong repair and regeneration capabilities, although these processes require certain time spans. Loepke et al. [26] reported that, after exposure to a high concentration of isoflurane for several hours, neonatal mice developed brain cell degeneration and deterioration in spontaneous locomotion, spatial learning, and memory function. After these mice reached adulthood, the adverse effects resulting from childhood exposure to isoflurane disappeared. Given the similar anesthetic mechanisms between isoflurane and sevoflurane, this post-anesthesia neural recovery may also apply for sevoflurane.

In addition, the negative results might be related to the relatively lower concentrations of sevoflurane used in our study. Gibert et al. [27] demonstrated that major epileptiform signs (MES) occurred in 50 % of the children receiving 1.7 MAC sevoflurane, which could increase the risk of seizures and apoptosis in the immature brain. However, concerning unstable hemodynamics, recovery time, emergence agitation, and postoperative pain, we chose a protocol of combination of fentanyl and relatively lower concentration of sevoflurane (induced with sevoflurane 8 % and maintained with sevoflurane 1.1–1.3 MAC; this delivered concentration had been used as most normal doses by us in our hospital). As reported in the literature, relatively lower concentrations of sevoflurane would also lead to adverse changes in pediatric patients. Keaney et al. [6] mentioned that negative behavioral changes (NBC) might occur in more than two-thirds of pediatric patients following sevoflurane anesthesia (induced with sevoflurane 8 % and maintained with sevoflurane 2–4 %; duration of surgery was 22.32 min). Therefore, we thought that further research should explore the effects of relatively lower concentrations of sevoflurane on cognitive function in pediatric patients. Other reasons might be the learning effects (i.e., repeated tests using similar questions and tasks) as well as an improvement in confidence after strabismus correction.

The children experienced anesthesia for 67.3 min (mean value), and no laryngospasm or hypoxia was observed in any case. The mean interval between T1 and T2 was 25.4 days, and that between T1 and T3 was 182.1 days. The intervals generally complied with the predetermined postoperative examination intervals of 1 and 6 months, thus preventing the potential interference of operative trauma and residual anesthetic effects on test results (if conducted shortly after the operation). Furthermore, tests at 6 months after the operation may more accurately predict the future longer-term effects of general anesthesia on cognitive development.

The current study involved several limitations. First, a control group was absent in this self-controlled study. The subjects in this study consisted of strabismic children from various regions of China visiting our hospital for surgical correction. Consequently, it was difficult to recruit normal children from various regions of the country to serve as controls. Second, the sample size of this study was relatively small. However, our study on this topic is ongoing, and more subjects will be continuously included for study to strengthen the reliability of the results. Third, the study provided no information on effects of prolonged exposure to higher-concentration sevoflurane on cognitive function in children because of research ethics and safety concerns. Finally, the effects of multiple exposures to general anesthesia on cognitive function in children are unknown, and this will be investigated in future studies.

In conclusion, the current study found that sevoflurane-based general anesthesia does not produce significantly adverse effects on the cognitive function of children 4 to 7 years old at 1 and 6 months after surgical strabismus correction, but these findings should be further confirmed with a larger sample size.

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