Original Article

First anesthesia exposure effects on short-term neurocognitive function among 1- to 36-month-old children: a case-control pilot study

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Background: Multiple human studies have shown no significant long-term results of anesthesia exposure during early childhood compared to the general population; however, reports on short-term neurodevelopmental assessment before and after anesthesia exposure are limited. This study aimed to evaluate the short-term characteristics of neurocognitive function post-anesthesia in noncardiac surgery compared with baseline.

Methods: This prospective case-control pilot study recruited healthy participants in the control group and hospitalized children in the anesthesia group. Children aged 1–36 months without previous anesthesia were included. Neurocognitive function was assessed at baseline and seven days after anesthesia administration using a cognitive scale of the Bayley Scales of Infant and Toddler Development, third edition. The control group received only a baseline assessment. The cognitive composite score had a mean of 100 and a standard deviation (SD) of 15, with a difference of score >1/3 SD (5 points) defined as clinically significant.

Results: Twenty and 39 participants in the control and anesthesia groups, respectively, were included in the final analysis. The baseline cognitive scale score of the anesthesia group was statistically and clinically lower than that of the control group. The mean (SD) cognitive composite scores in the control and anesthesia group were 111.50 (11.71) and 97.13 (9.88), P<0.001. The mean difference [95% confidence interval (CI)] was −14.37 (−8.28 to −20.47). In the anesthesia group, the post-anesthesia cognitive composite score was statistically higher than that at baseline, but without clinical significance. The mean (SD) of baseline and post-anesthesia cognitive composite scores were 97.05 (9.85) and 101.28 (10.87), P=0.039, respectively. The mean difference (95% CI) was 4.23 (0.23–8.23). However, 7 (17.9%) participants had decreased cognitive composite scores after anesthesia exposure.

Conclusions: Children in the anesthesia group had lower baseline cognitive composite scores than those

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in the control group. The post-anesthesia cognitive score did not decrease compared with the baseline assessment. Anesthetic exposure resulted in a decline in the cognitive composite score in 17.9% of the participants.

Keywords: General anesthesia; developmental disabilities; child development

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Introduction

There is a growing concern that sedatives and anesthetics may have long-lasting effects on the brain (1). The United States Food and Drug Administration (USFDA) warned about the risk of anesthetic neurotoxicity to pediatric patients under three years old, which is the "vulnerable time window" of synaptogenesis (1,2). The animal model studies revealed that anesthetic-induced neurotoxicity is dose-dependent and age-specific (3-7). Most human studies were observational and evaluated intermediate- to long-term outcomes at different ages compared with the general population. Multiple human studies have shown no consistent significant effect of anesthesia exposure on deficits in academic achievement, general intelligence, memory, and language (2,8-13). However, deficiencies in the neurodevelopmental assessment subscale have been more consistently reported, including behavior, executive function, social communication, motor function, and diagnosis of attention deficit hyperactivity disorder (12-15).

Highlight box

Key findings

- Eighteen percent of participants with anesthesia exposure in noncardiac surgery had declined cognitive function compared with their baseline during a short-term assessment.

What is known and what is new?

- Long-term cognitive outcomes after anesthesia exposure during early childhood were shown to not be different from those in the general population
- This study found that 17.9% of children had short-term cognitive decline compared to their baseline following anesthesia exposure.

What is the implication, and what should change now?

- This study may fill the gap in understanding the trajectory of cognitive function following anesthesia exposure. Patients at risk should be identified for appropriate developmental intervention.

Pre-operative and post-operative neurodevelopmental assessments can compare the effects of anesthetic neurotoxicity in the same patient instead of the general population. Most available pre- and post-studies were conducted in specific infants at risk of impaired neurodevelopmental status such as craniosynostosis (16,17) or complex cardiac surgery (18,19). Infants with craniosynostosis are at risk of developmental delay due to surgical conditions, and neurodevelopmental status can be improved after surgical correction (16,17). In complex cardiac surgery, pre-operative and early post-operative assessments showed declined gross motor scores in 26–64% (18,19). Beyond anesthetic neurotoxicity, factors associated with neurological injury included altered cerebral perfusion, cellular metabolic insufficiency (hypoglycemia, hypoxia, high and unmet metabolic demand), and neurotoxic mediators (20). There is limited evidence regarding pre- and post-operative neurodevelopmental assessments in pediatric patients undergoing noncardiac surgery.

The primary outcome aimed to evaluate short-term post-anesthesia neurocognitive function after noncardiac surgery and compare it with the baseline. Secondary outcomes included the incidences of perioperative adverse events and differences in baseline neurodevelopmental characteristics between children requiring anesthesia and a healthy population. We present this article in accordance with the STROBE reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-22-673/rc).

Methods

Study design and ethical considerations

This prospective observational case-control pilot study was conducted from November 2017 to November 2019 at the Faculty of Medicine, Siriraj Hospital, Mahidol University. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study

was approved by the Siriraj Institutional Review Board (No. Si456/2017) and was registered at thaiclinicaltrials.org (No. TCTR20211209006). Written informed consent was obtained from all participants' parents or legal guardians.

Selection criteria of patients

Normal developing children aged 1–36 months without exposure to general anesthesia were included. Healthy participants were recruited from the Siriraj Daycare Center for the control group using consecutive convenience samples. Children scheduled for elective noncardiac surgery were recruited to the anesthesia group. Premature infants, known developmental delays, children with neurological diseases, and children with a history of neurotoxic agent exposure were excluded.

Sample size calculation

This pilot study estimated that the population of the anesthesia group was 40 participants. The participants in the control group were calculated using a 2:1 ratio; therefore, the sample size of the control group was 20 participants.

Study parameters

Cognitive development was assessed using the Bayley Scales of Infant and Toddler Development, third edition (Bayley-III) by one of the two clinical psychologists. Baseline neurocognitive function was evaluated in both groups. The participants in the anesthesia group were reassessed for neurocognitive function seven days post-anesthesia or as soon as possible if they could not have a post-anesthesia follow-up visit within seven days.

Demographic data, including birth and family histories, were also collected. In the anesthesia group, we recorded the anesthetic technique, duration, and the incidence of perioperative events resulting in impaired neurocognitive function, including hypoxia, laryngospasm, bradycardia, hypotension, and hypocarbia. Hypoxia was defined as an oxygen saturation below 90% for >60 s, while laryngospasm was recorded as an event if positive-pressure ventilation or medication was required to correct the condition. Bradycardia was defined as a heart rate of <60 beats per min which required atropine administration to correct the condition. Hypotension was defined as a systolic blood pressure of <60, 70, or 74 mmHg in infants, one year, or two years, respectively, for longer than 5 min. Hypocarbia was defined as end-tidal carbon dioxide less than 30 mmHg for >15 min or arterial tension of carbon dioxide less than 35 mmHg.

Neurocognitive function assessment

To evaluate the developmental function of infants and toddlers, Bayley-III is widely used to measure the developmental function of infants and toddlers aged 1–42 months. The Bayley-III consists of five distinct scales: cognitive, language, motor, social-emotional, and adaptive behavior (21). Only the cognitive scale was assessed in this study because it is least likely to be disturbed by perioperative events compared to the other subscales. Indeed, acute post-operative pain and surgical wounds may affect the evaluation of the motor domain. In addition, negative behavioral changes have been reported to be multifactorial, not limited to anesthetic neurotoxicity but also including post-operative stress, hospitalization, and other psychosocial factors (22,23). The cognitive scale comprises 91 items that consider memory, problem-solving, and manipulation.

Raw scores from the cognitive scale were converted to scaled scores, with a mean of 10 and a standard deviation (SD) of 3. Normative scaled scores were derived based on the child's age. A scaled score is converted to a composite score equivalent to a mean of 100 and an SD of 15 (21). A Bayley-III cognitive composite score of less than 85 is considered moderate to severe neurodevelopmental delay. We categorized the cognitive composite scores into three subgroups based on 1 SD (15 points): category I—above average cognitive development (116–160 points), category II—normal cognitive development (85–115 points), and category III—cognitive delay (40–84 points). Due to ethical issues, a developmental intervention was applied to participants with baseline cognitive composite scores ≤2 SD below the mean during the study period.

Statistical analysis

Descriptive statistics were used to describe the demographic data. The comparison of baseline Bayley-III scores between the control and anesthesia groups was analyzed using an independent *t*-test. The comparison between the baseline and post-anesthesia assessments in the anesthesia group was analyzed using paired *t*-tests. According to the General Anesthesia compared to Spinal Anesthesia (GAS) trial, a difference of five points (1/3 SD) was defined as clinical

significance (24). If the 95% confidence interval (CI) of the difference in means lies within ± five points, there is no clinical difference between the two groups. Participants in the anesthesia group were also categorized into the declined and non-declined groups. Participants with a post-anesthesia cognitive composite score lower than baseline by more than five points were considered to have declined cognitive function. Intraoperative data between the declined and non-declined groups were compared using an independent *t*-test for continuous data and a chi-squared test for categorical data. Continuous data without normal distribution were presented as median (interquartile range) and analyzed using the Mann-Whitney U test. Statistical significance was defined as a two-tailed P value <0.05. All data were analyzed using PASW Statistics for Windows (version 18.0; SPSS Inc., Chicago, IL, USA). The number of missing data was described in the results.

Results

Twenty healthy participants were assigned in the control group while 47 participants were assigned in the anesthesia group and received baseline assessments; only 39 received post-anesthesia assessments and were included in the final analysis. The recruitment process is illustrated in the flow diagram (*Figure 1*). Participants in the anesthesia group were significantly younger than those in the control group, the median (P25, P75) ages were 8.3 (4.1, 14.2) and 16.5 (10.2, 28.2) months (P=0.005), respectively. Body weight below the 25th percentile was reported to be higher in the anesthesia group than in the control group (40.4% *vs.* 10.0%, P=0.014). The ages of the fathers and mothers in the anesthesia group were lower than those in the control group (P=0.015 and 0.027), respectively. In the anesthesia group, mothers had lower educational attainment (P=0.009). The birth history, co-existing diseases, and family history are described in *Table 1*. Among the anesthesia group, types of surgeries were as follows: 19 (40.4%) superficial, 9 (19.1%) inguinal, 7 (14.9%) urological and urethral, 8 (17.0%) cleft lip/palate, 2 (4.3%) major gastrointestinal, and 2 (4.3%) craniosynostosis surgeries.

The baseline cognitive scale score of the anesthesia group was statistically and clinically lower than that of the control group (P<0.001), as described in *Table 2*. The mean (SD) cognitive composite scores in the control and anesthesia groups were 111.50 (11.71) and 97.13 (9.88), P<0.001. The mean difference (95% CI) was –14.37 (–8.28 to –20.47). Four (8.5%) participants in the anesthesia group were categorized as having cognitive delay (cognitive composite score <1 SD below the mean). One participant in the anesthesia group (2.1%) had a baseline cognitive composite score of ≤2 SD below the mean.

Among the 39 participants in the anesthesia group who received both baseline and post-anesthesia assessments, the post-anesthesia cognitive composite score was statistically higher than that at baseline, but without clinical significance (*Table 3*). Mean (SD) of baseline and post-anesthesia cognitive composite scores were 97.05 (9.85) and 101.28 (10.87), P=0.039, with a mean difference (95% CI) of 4.23 (0.23–8.23). Seven (17.9%) participants had post-anesthesia scores lower than the baseline by more than 5 points and were considered in the declined group. The mean difference (95% CI) of cognitive composite scores in the declined and non-declined groups were –13.57 (–17.97 to –9.17) and 8.13 (4.62 to 11.64), respectively (*Figure 2*). Three (7.7%) participants had a post-anesthesia cognitive composite score lower than the baseline of ≥1 SD. The median (P25, P75) duration of anesthesia was 2 h 30 min (1 h 45 min, 3 h 25 min). The median (P25, P75) duration from baseline assessment to operation was 1 (1, 1) day. The median (P25, P75) duration between the date of operation and the post-anesthesia assessment was 19 (8, 80) days.

All participants received volatile-based balanced anesthetics with opioids. Muscle relaxants were administered to 35 (89.7%) participants. There were no differences in patient and procedure characteristics between the non-declined and declined groups (*Table 4*). The overall incidence of intraoperative adverse events among the 46 anesthetized individuals was 1 (2.2%) hypoxia, 1 (2.2%) hypotension, 2 (4.3%) bradycardia, and 14 (30.4%) hypocarbia. No laryngospasm was observed. One participant whose baseline cognitive composite score was ≤2 SD below the mean underwent developmental intervention (including speech therapy and early intervention for fine motor-adaptive skills) after craniosynostosis surgery. The participant's post-anesthesia cognitive composite score was higher than the baseline score by 1 SD.

Discussion

The baseline cognitive composite score of children in the anesthesia group was significantly lower than that of healthy participants in the control group. Generally, children in the anesthesia group were assumed to be at risk of developmental delay due to several factors. The anesthesia group was younger and have poor growth,

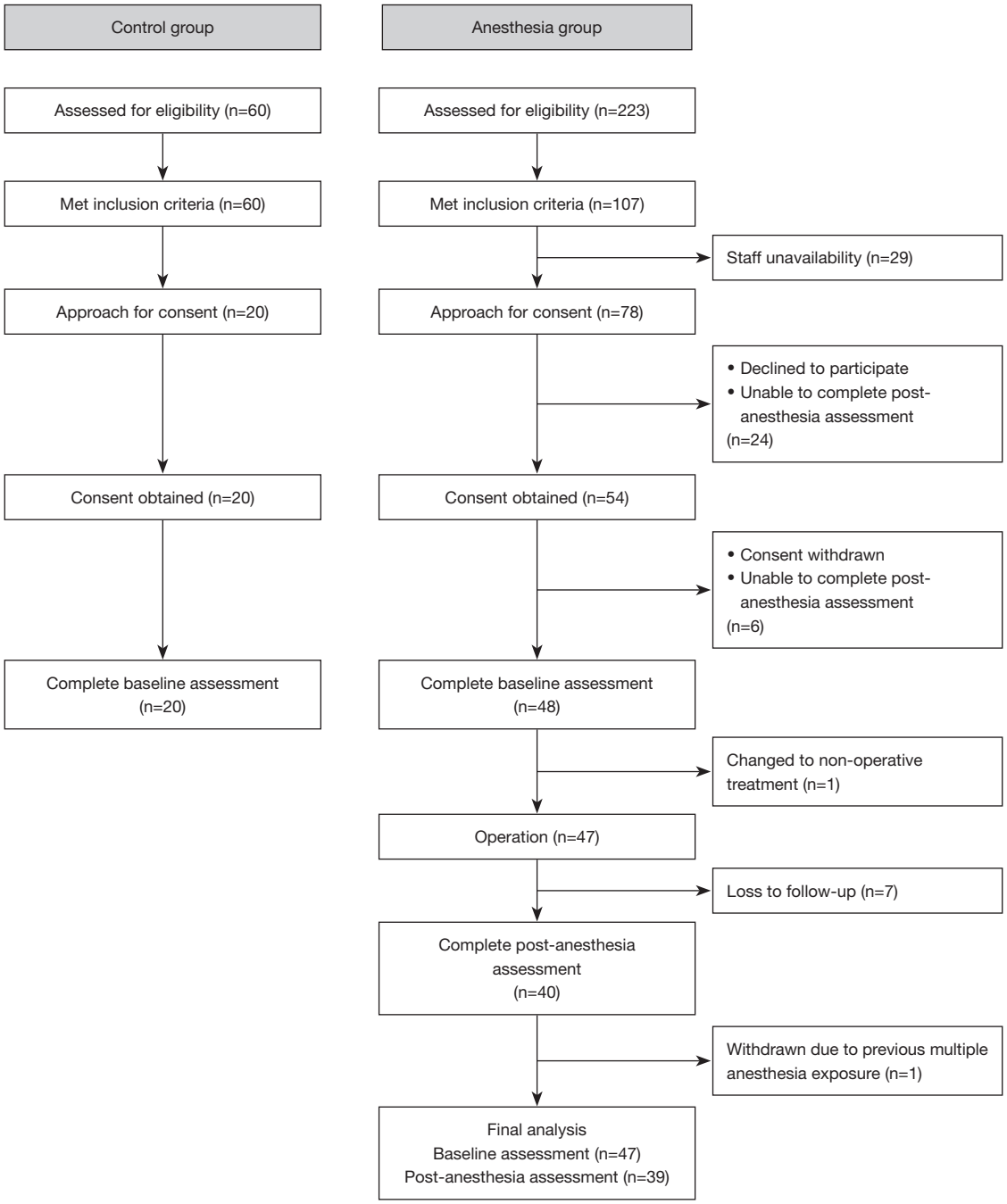

Figure 1 Flow diagram of the recruitment process.

younger parents, and a lower maternal education level. A possible explanation for the different characteristics could be that patients in public hospitals were paid by government insurance and may come from any socioeconomic status, while daycare participants must be from families who can afford necessities. These factors contribute to poorer developmental outcomes in addition to their surgical conditions. Four percent of participants were scheduled for craniosynostosis surgery, which is the risk factor for pre-operative developmental delay (16,17). To compare with the national standard of care, health workers provide the national child developmental screening program

Table 1 Demographic data

Patients' characteristics	N*	Control (N=20)	Anesthesia (N=47)	P
Sex, male	20/47	10 (50.0)	30 (63.8)	0.291
Age (months)	20/47	16.5 (10.2, 28.2)	8.3 (4.1, 14.2)	0.005
Weight below the 25th percentile	20/47	2 (10.0)	19 (40.4)	0.014
Co-existing disease	20/47	2 (10.0)	4 (8.5)	1.000[a]
Birth history				
Birth weight <2,500 gm	20/47	3 (15.0)	6 (12.8)	1.000[a]
Singleton	20/47	20 (100.0)	47 (100.0)	N/A
Mode of delivery: normal labor	19/42	8 (42.1)	13 (31.0)	0.396
Complications after birth (e.g., jaundice, meconium, hypoxia)	19/43	5 (26.3)	12 (27.9)	0.897
Maternal complication	19/41	4 (21.1)	3 (7.3)	0.193[a]
Extended of hospital stay[b]	19/41	13 (68.4)	25 (61.0)	0.578
Family history				
Father's age, years	20/47	38.4 (5.4)	34.5 (6.5)	0.015
Father's level of education	20/47			0.442
Primary		1 (5.0)	4 (8.5)	
High school		2 (10.0)	14 (29.8)	
Vocational degree		3 (15.0)	5 (10.6)	
Bachelor's degree		10 (50.0)	16 (34.0)	
Above bachelor's degree		4 (20.0)	8 (17.0)	
Father's education: bachelor's degree or above	20/47	14 (70.0)	24 (51.1)	0.152
Mother's age, years	20/47	35.3 (4.1)	32.6 (5.0)	0.027
Mother's level of education	20/47			0.111
Primary		0	2 (4.3)	
High school		2 (10.0)	12 (25.5)	
Vocational degree		0	6 (12.8)	
Bachelor's degree		12 (60.0)	16 (34.0)	
Above bachelor's degree		6 (30.0)	11 (23.4)	
Mother's education: bachelor's degree or above	20/47	18 (90.0)	27 (57.4)	0.009

Data were presented as number (%), mean (SD), or median (P25, P75). [a], Fisher's exact test; [b], normal labor >2 days, caesarean section >3 days. *, control group number/anesthesia group number. N/A, not available.

during routine vaccination. The screening tool comprised 8–10 developmental surveillance and promotion manual (DSPM) exercises (25). Neurodevelopmental assessment by psychologists is available upon consultation per medical condition. We found that 8.5% of participants in the anesthesia group had an undiagnosed cognitive delay, while national data reported that 15% of children failed the first screening during their routine vaccination (25).

Our study compared each participant with their baseline and found that 17.9% of participants in the anesthesia group had a post-anesthesia assessment lower than their baseline, with clinical significance. Our study is one of

Table 2 Comparison of baseline cognitive composite scale scores in the control and anesthesia groups

Score	Control group (N=20)	Anesthesia group (N=47)	Mean difference (95% CI)	P
Scaled score	12.30 (2.34)	9.36 (2.10)	−2.94 (−1.70 to −4.17)	<0.001
Composite score	111.50 (11.71)	97.13 (9.88)	−14.37 (−8.28 to −20.47)	<0.001
Percentile rank	72.30 (20.90)	43.68 (21.69)	−28.62 (−17.19 to −40.05)	<0.001
Category by the composite score			N/A	0.002
I Above average cognitive development (116–160)	7 (35.0)	2 (4.3)		
II Normal cognitive development (85–115)	13 (65.0)	41 (87.2)		
III Cognitive delay (40–84)	0	4 (8.5)		

Data were presented as mean (SD) or number (%). N/A, not applicable.

Table 3 Comparison of cognitive scores between baseline and post-anesthesia assessments

	Baseline	Post-anesthesia	Mean difference (95% CI)	P
Overall (N=39, 100%)				
Scaled score	9.33 (2.12)	10.31 (2.12)	0.97 (0.15 to 1.80)	0.023
Composite score	97.05 (9.85)	101.28 (10.87)	4.23 (0.23 to 8.23)	0.039
Percentile rank	43.85 (21.60)	53.41 (25.08)	9.56 (0.61 to 18.52)	0.037
Non-declined (N=32, 82.1%)				
Scaled score	9.13 (2.12)	10.84 (1.87)	1.72 (0.94 to 2.50)	<0.001
Composite score	96.09 (9.73)	104.22 (9.34)	8.13 (4.62 to 11.64)	<0.001
Percentile rank	42.00 (21.38)	60.19 (21.74)	18.19 (10.29 to 26.09)	<0.001
Declined (N=7, 17.9%)				
Scaled score	10.29 (1.98)	7.86 (1.35)	−2.43 (−3.16 to −1.70)	<0.001
Composite score	101.43 (9.88)	87.86 (6.36)	−13.57 (−17.97 to −9.17)	<0.001
Percentile rank	52.29 (22.16)	22.43 (13.40)	−29.86 (−40.91 to −18.81)	0.001

Data were presented as mean (SD).

a few to describe short-term sequelae after noncardiac surgery. Indeed, most studies that assessed developmental outcomes one week after the operation and compared them with pre-operative assessments have been conducted in the field of cardiac surgery. Fan *et al.* (26) reported significantly lower post-operative cognitive scores, and Uzark *et al.* (18) reported lower post-operative motor scores with a 64% gross motor decline after cardiac surgery. In contrast, studies of cardiac surgeries by Limperopoulos *et al.* (27) and Campbell *et al.* (19) found that pre-operative and post-operative assessments of cognitive and motor function remained unchanged. Our study emphasizes the need to identify vulnerable patients for cognitive declined who require early exposure to anesthesia in both cardiac and noncardiac surgeries, pre-operatively. In addition, developmental interventions should be implemented in such high-risk patients to reduce the risk of negative developmental outcomes affected by anesthesia and surgery.

Although 17.9% of participants in the anesthesia group were shown to have a lower cognitive composite score than that at baseline, the average post-anesthesia cognitive scores in the anesthesia group did not decrease compared to the baseline assessment. This finding was consistent with the GAS study, which is the only currently available randomized controlled trial on the topic. The study compared the effects of sevoflurane-based general anesthesia with those

Table 4 Patients' characteristics and anesthetic data between the non-declined and declined groups

Characteristics	Total (N=39)	Non-declined (N=32)	Declined (N=7)	P
Part I: patients' characteristics				
Male	24 (61.5)	18 (56.3)	6 (85.7)	0.216[f]
Age (months)	8.2 (3.5, 14.2)	7.9 (3.5, 13.4)	12.3 (8.2, 27.8)	0.164
Weight (kg)	8.0 (6.0, 9.6)	7.8 (6.0, 9.5)	8.1 (7.4, 12.8)	0.227
Co-existing disease	3 (7.7)	1 (3.1)	2 (28.6)	0.077[f]
Low birth weight <2,500 gm	4 (10.3)	4 (12.5)	0	1.000[f]
Normal labor[a]	13 (34.2)	13 (41.9)	0	0.072[f]
Birth problem[a]	10 (26.3)	8 (25.8)	2 (28.6)	1.000[f]
Father's education (bachelor or higher)	21 (53.8)	18 (56.3)	3 (42.9)	0.682[f]
Mother's education (bachelor or higher)	23 (59.0)	19 (59.4)	4 (57.1)	1.000[f]
Part II: procedure characteristics				
Type of surgery				0.687
Skin and superficial	14 (35.9)	12 (37.5)	2 (28.6)	
Inguinal (hernia, hydrocele, testis)	8 (20.5)	6 (18.8)	2 (28.6)	
Urologic and urethra	5 (12.8)	3 (9.4)	2 (28.6)	
Cheiloplasty and palatoplasty	8 (20.5)	7 (21.9)	1 (14.3)	
Major gastrointestinal	2 (5.1)	2 (6.3)	0	
Craniosynostosis	2 (5.1)	2 (6.3)	0	
General and regional anesthesia	13 (33.3)	11 (34.4)	2 (28.6)	1.000[f]
MAC during maintenance				0.418[f]
0.5–1.0 MAC	18 (46.2)	16 (50.0)	2 (28.6)	
1.0–1.5 MAC	21 (53.8)	16 (50.0)	5 (71.4)	
Intraoperative adverse event	13 (33.3)	10 (31.3)	3 (42.9)	0.666[f]
Hypoxia	2 (5.1)	1 (3.1)	1 (14.3)	0.331[f]
Hypocarbia	13 (33.3)	10 (31.3)	3 (42.9)	0.666[f]
Hypotension	1 (2.6)	1 (3.1)	0	1.000[f]
Bradycardia	1 (2.6)	0	1 (14.3)	0.179[f]
Duration of surgery (h:m)	1:35 (0:45, 2:35)	1:35 (0:45, 2:31)	1:55 (0:50, 2:35)	0.798
Duration of anesthesia (h:m)	2:30 (1:45, 3:25)	2:27 (1:45, 3:22)	2:45 (1:55, 3:40)	0.510
Length of hospital stay (days)	2 (1, 6)	2 (1, 6)	2 (1, 7)	0.801
Post-operative ICU admission	4 (10.3)	3 (9.4)	1 (14.3)	0.563[f]
Timing of assessment after anesthesia (days)	19 (8, 80)	16 (8, 43)	145 (8, 181)	0.084

Data were presented as median (P25, P75) or number (%). [a], 1 missing data in non-declined group; [f], Fisher's exact test. MAC, minimum alveolar concentration; ICU, intensive care unit; h, hour; m, minutes.

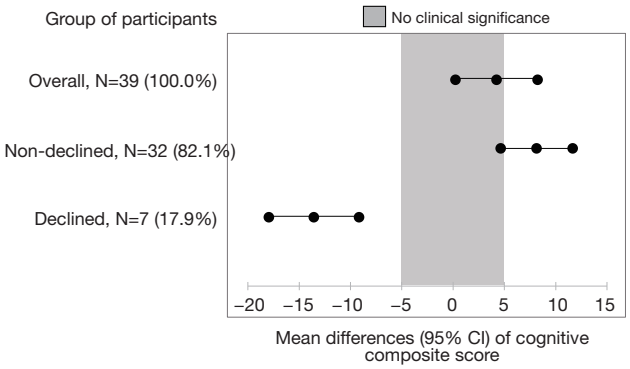

Figure 2 Comparison of mean differences (95% confidence interval) of the cognitive composite score (post-anesthesia-baseline). Remark: A difference of five points (1/3 standard deviation) was defined as clinically significant.

of awake-regional anesthesia in participants prior to 60 weeks postmenstrual age and confirmed that cognitive function was equivalent between the two experimental groups at ages two and five years (9,24). Several long-term studies also reported that anesthetic exposure did not affect general intelligence compared to the general population (10-12). Most short-term to mid-term outcome studies after noncardiac surgery have been primarily conducted in the school-age population. Fan *et al.* (28) reported no significant intellectual changes after strabismus surgery in children aged four to seven years evaluated at one month and six months after the operation. Aun *et al.* (29) also evaluated cognitive function in children aged five to twelve years undergoing elective noncardiac surgery and reported four cognitive function tests at baseline, one day, and six weeks after the operation; post-operative cognitive dysfunction was 5.1% on day one and 3.4% at six weeks.

We reported the incidence of hypoxia during general anesthesia in children aged 1–36 months as 2.2%, which was lower than 6% from a more extensive study that was conducted in children aged 0–16 years old (30). Brain dysmaturation and neurodevelopmental abnormalities have been reported in children with chronic hypoxia from single ventricle physiology (31). Developing white matter is particularly vulnerable to hypoxia-ischemia, contributing to both white matter dysmaturation and injury. Limperopoulos *et al.* reported that low arterial oxygen saturation (<85%) during open heart surgery was associated with abnormal findings on neurodevelopmental examination (27). Even though the participants who experienced hypoxia in this study had a declined cognitive composite score post-anesthesia, the number was too small to conclude the effect of the brief duration of hypoxia on neurodevelopmental outcomes.

In our study, the neurodevelopmental function was only assessed once post-anesthesia. Serial post-anesthesia assessment after cardiac and noncardiac surgery showed improvement over time (26,28,32). Dwyer *et al.* (32) reported a longitudinal evaluation of infants who underwent major surgery within 90 days of life at ages one and three years compared with healthy controls. Children who underwent surgery were developmentally normal, but mean scores were lower than controls in the cognition, receptive language, and fine motor domains. The incidence of cognitive delay at one year and three years were 8% and 4%, respectively. The developing brain can demonstrate "developmental recovery," thus parental education regarding strategies to promote neurodevelopment should be addressed during the perioperative period in addition to other routine surgical care, especially for children with cognitive decline after anesthesia.

Our comparison of baseline and post-anesthesia assessments can be generalized to typical pediatric anesthesia practices. However, this study has several limitations. First, Bayley-III should be re-administered at an interval of three months for children under twelve months of age and six months for children older than twelve months. This study attempted to minimize patients' hospital visits by including this neurocognitive assessment within the same visit to the post-operative follow-up. The median (P25, P75) duration of post-anesthesia assessment was 19 [8, 80] days. The higher post-anesthesia score compared with the baseline can be attributed to relatively short intervals and learning processes. Second, we evaluated only the cognitive subscale out of the five subscales in Bayley-III. Neurodevelopmental changes in other subscales, such as the motor domain or negative behavioral changes, could exist but were not evaluated. Third, the participants were assessed by one of the two trained psychologists, and the inter-rater reliability was not reported. Finally, participants in the control group had different baseline characteristics, were unmatched, and did not undergo repeated assessment. The baseline comparisons between the two groups cannot be generalized to the general population.

Future research may investigate short-term neurodevelopmental outcomes with a longitudinal assessment to illustrate recovery over time. Parental questionnaires should be included to identify potential psychosocial factors. This study was too small to demonstrate an association

between rare perioperative adverse events and neurocognitive outcomes. A large prospective study is required to identify the effects of non-anesthetic factors on neurotoxicities, such as hypoxia, hypotension, and hypocarbia. The role of developmental interventions in reducing post-anesthesia cognitive decline can be addressed, particularly in patients who require multiple anesthetics.

Conclusions

Children in the anesthesia group had lower baseline cognitive composite scores than those in the healthy control group. Overall, the cognitive composite score did not decline after anesthetic exposure, but anesthetic exposure resulted in a decline in the cognitive composite score in 17.9% of the participants. Patients at risk should be identified for appropriate developmental intervention.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-22-673/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Siriraj Institutional Review Board (No. Si456/2017). Written informed consent was obtained from all participants' parents or legal guardians.

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