

# Short-Term Changes in Postoperative Cognitive Function in Children Aged 5 to 12 Years Undergoing General Anesthesia

## A Cohort Study

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**Abstract:** Due to the neurotoxicity effects of general anesthesia (GA) and sedatives found in animal studies, there is a general recommendation to avoid nonurgent surgical procedures requiring anesthesia in children younger than 3 years of age. The aim of this study was to determine the incidence of anesthesia-related postoperative cognitive dysfunction (POCD) on the first day (Day 1) and at 6 weeks after elective noncardiac surgery in school-age children.

This was a prospective cohort study of 118 children undergoing GA and 126 age-matched controls of school children aged 5 to 12 years. All children were given a panel of 4 neuropsychological assessments (Hong Kong List Learning for verbal memory, Visual Matching for processing speed, Visual Memory, and General Comprehension Skill from the Hong Kong Wechsler Intelligence Scale for Children). The primary outcome was the incidence of POCD on Day 1 and at 6 weeks after surgery. POCD was defined as when at least 2 of the 4 cognitive function

tests showed individual Z-scores  $\leq -1.96$  or a combined Z-score  $\leq -1.96$ .

Using the combined Z-score definition, the incidence of POCD in the GA group on Day 1 and at 6 weeks were 5.1% (95% confidence interval [CI]: 2.1–10.3) and 3.4% (95% CI: 1.1–8.0), respectively. No POCD was found using the other definition. The incidences of decline and improvement in neuropsychological tests were similar between groups over time except for a higher risk in visual matching impairment in the anesthesia group (11.9%) versus control group (1.6%) on Day 1 ( $P < 0.01$ ). The adjusted relative risk ratio of postoperative cognitive decline to improvement between groups on Day 1 and at 6 weeks were 0.85 (95% CI: 0.10–7.05) and 0.45 (95% CI: 0.04–4.84), respectively. The observed risk of POCD is assumed to apply to current drugs and techniques used in GA.

In conclusion, the incidence of POCD was low. GA was associated with a transient effect on visual matching. When using the widely accepted Z-score definitions and relative risk ratio methodology, we found no anesthesia-related POCD per se in school-age children.

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**Abbreviations:** 95% CI = 95% confidence interval, CrI = credible interval, GA = general anesthesia, HKLL = Hong Kong List Learning, HK-WISC = Hong Kong Wechsler Intelligence Scale for Children, IQ = intelligence quotient, IQR = interquartile range, OR = odds ratio, POCD = postoperative cognitive dysfunction, POCI = postoperative cognitive improvement, RRR = relative risk ratio, SD = standard deviation, VAS = visual analog scale.

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## INTRODUCTION

Many children require anesthesia for surgical procedures and investigations each year, with approximately 450,000 children undergoing in-patient surgery each year in the United States.<sup>1</sup> A common parental concern is whether general anesthesia (GA) has potentially deleterious effects on children's cognitive and academic development. A consensus statement by the US Food and Drug Administration, SmartTots, and the American Academy of Pediatrics<sup>2</sup> recommends avoiding nonurgent surgical procedures requiring anesthesia in children younger than 3 years of age because of the neurotoxicity and neuroplasticity effects of GA and sedatives shown in animal studies.<sup>3</sup>

Postoperative cognitive dysfunction (POCD) has been defined as a subtle impairment of memory, concentration, and speed of information processing after surgery.<sup>4</sup> While the epidemiology of POCD in adults after cardiac<sup>5</sup> and noncardiac surgery<sup>6,7</sup> has been well established, most existing pediatric studies have focused on the long-term neurodevelopmental outcomes after GA exposure before the age of 4 years.<sup>8,9</sup> Current

evidence suggests that early exposure to anesthesia is associated with an increased risk of neurodevelopmental deficits (odds ratio 1.9, 95% credible interval 1.2–3.0).<sup>8</sup> However, the risk of language and abstract reasoning deficits at age 10 after an initial exposure to anesthesia in children over 3 years old was similar to other children with no exposure to anesthesia.<sup>10</sup>

There is a paucity of studies on the short-term effects of anesthesia on cognitive function performance in school-age children. A randomized controlled trial of propofol versus isoflurane in 58 children aged between 5 and 14 years showed that both groups had visual memory deficits at 24 h after dental surgery.<sup>11</sup> Compared with sevoflurane, children given propofol had visual memory deficits at 1 week, but recovered at 3 months, after elective hernia surgery.<sup>12</sup> In contrast, there was no effect of halothane-nitrous oxide GA on reasoning, motor or memory functions at 24 h after myringotomy in children aged between 5 and 8 years when compared with a control group (no anesthesia).<sup>13</sup> These findings highlight the heterogeneity in study designs, type of neuropsychological tests, POCD definition, and timing of POCD used.

Therefore, the effects of GA on early postoperative cognitive function in school-age children undergoing noncardiac surgery are not well understood. We hypothesized that GA has no effect on short-term postoperative cognitive function. To control for the practice learning effects of serial neuropsychological tests, we included a control group of students of similar ages from a local school in this prospective cohort study to determine the incidence of anesthesia-related POCD on the first day (Day 1) and at 6 weeks after elective noncardiac surgery.

## METHODS

### Study Design, Setting, and Participants

Ethical approval for this study (CRE-2000.063) was provided by the Chinese University of Hong Kong Faculty of Medicine Clinical Research Ethics Committee, Hong Kong, on March 28, 2001. After parents gave written informed consent, we recruited children with American Society of Anesthesiologists physical status class I or II, aged 5 to 12 years old undergoing elective general, urologic or orthopedic surgery of at least 60 min duration from April 2001 to January 2005. Patients were assessed a day before surgery (baseline), a day after surgery (Day 1), and 6 weeks afterwards. While it is ideal to perform the first follow-up at 1 week, for logistical reasons, we chose 1 day after surgery. The control group included students of similar ages from a local school. We recruited them from July 2001 to November 2002 after we obtained the school approval and written informed parental consents. Children in the control group were followed up at their school at the same time intervals described in the anesthesia group.

All participants undertook an intelligence screening test which consisted of the Vocabulary and Digit Span subtests from the Hong Kong Wechsler Intelligence Scale for Children (HK-WISC).<sup>14</sup> Exclusion criteria included subjects with intelligence screening test below 70, inability to perform cognitive function tests during the perioperative period due to uncooperativeness, inability to understand instructions, presence of a visual or auditory impairment, or expected need for postoperative intensive care.

### Anesthesia Management

EMLA cream (lidocaine 2.5% and prilocaine 2.5%) and oral midazolam 0.5 mg/kg up to a maximum of 15 mg were

given as premedication. Anesthesia was induced with intravenous agents, thiopentone or propofol. In cases with difficult venous access, sevoflurane inhalation was used. All patients were intubated using a nondepolarizing neuromuscular blocking agent. Anesthesia was maintained with isoflurane or sevoflurane, nitrous oxide and oxygen, and mechanical ventilation. At the end of surgery, the residual paralysis was reversed with atropine and neostigmine. The choice of intraoperative and postoperative analgesics was at the discretion of the attending anesthesiologist. Pulse oximetry, noninvasive blood pressure, electrocardiography, core temperature, end tidal carbon dioxide, and anesthetic concentrations were monitored. Normothermia and normocapnia were maintained. The anesthetic depth was adjusted clinically by the attending anesthesiologist. The Bispectral Index (BIS), not revealed to the anesthesiologists, was continuously monitored and recorded using the A-2000 BIS monitoring system (Aspect Medical Systems, Inc., Newton, MA) and a standard adult (Ziprep) electrode. All the parameters monitored were downloaded using software developed in our department. Any episode of desaturation ( $SpO_2 \leq 90\%$  for 30 s or more) or hypotension (systolic blood pressure  $<80$  mm Hg for 3 min) after excluding the effect of artifacts, were recorded for data analysis. Pain scores on the first day after surgery and at 6 weeks were recorded using the visual analog scores (VAS). The pain levels were categorized as mild (VAS 5–44 mm), moderate (VAS 45–74 mm), and severe (VAS  $\geq 75$  mm).<sup>15</sup>

### Cognitive Function Assessments

The research staff was trained in the administration of neuropsychological tests and interview techniques for this study. To familiarize the children with the cognitive function assessments, we gave an explanation of the tests and ran a brief trial with all participants. In the anesthesia group, the baseline tests were administered, after the preoperative visit by the anesthesiologists a day before surgery, in an isolation room in the ward or a corner in the ward with least traffic. Postoperative cognitive function assessments were conducted in the ward or at the patient's home. All children in the control group undertook all tests in a quiet room at their school. If the child was unable to do the assessment at the scheduled time, a nearest possible time was arranged.

The panel of 4 cognitive function tests included:

1. Hong Kong List Learning (HKLL) test,<sup>16</sup> a verbal memory test consisting of a list of 16 items (words) that was read to the child in Cantonese. The child was then asked to recall these words in any order immediately. This was repeated a second time. Finally, the child was asked to recall from the list as many items as possible after a 10-min period of distraction. For data analysis, we used the scores obtained for the correct items in the final recall. The test has been validated and local normative data are available.<sup>17</sup>
2. Visual Matching test from the Woodcock–Johnson tests of cognitive ability.<sup>18</sup> This test measured the speed of processing and consisted of rows of figures that were presented to each child. Each row comprised of 6 numbers. The child was asked to circle the 2 numbers that were the same in each row over 3 min. We used the age standardized scores for analysis. The test yielded a test–retest reliability in American participants aged 6 and 9 years of 0.73 and 0.78, respectively.<sup>18</sup>
3. Visual Memory test from the Gardner Test of Visual-Perceptual Skills Revised (1996).<sup>19</sup> This test consisted of 16

two-dimensional line pictures to memorize. Each of these pictures was presented to the child for 5 s. The page was then turned to a next page containing 5 similar pictures with minor variations. The child was to identify the 1 that was presented earlier. Testing was discontinued if incorrect identification was made for 4 consecutive pictures. We used the age standardized scores for correct pictures for analysis. The split-half reliability of this task for American children was 0.80.<sup>19</sup>

- General Comprehension subtest from the HK-WISC<sup>14</sup> measured the social comprehension and practical judgment and consisted of 30 orally administered questions that was given to each child. Each answer was allotted a rating from 0 to 2 points, based on the quality of the answer given. This test was terminated once the child scored 0 on 5 consecutive questions. Age standardized scores were used for data analysis.

**Statistical Analysis**

The mean and standard deviation (SD) or median and interquartile range (IQR) were reported as appropriate for continuous data after checking data for normality using the Shapiro–Wilk test. Independent sample *t* test, Mann–Whitney *U* test, or  $\chi^2$  tests were used to compare perioperative differences between groups. Pearson correlation analysis was used to assess the test–retest reliability of the cognitive function tests between baseline and follow-up sessions.<sup>20</sup> We modeled individual serial changes in cognitive function tests using mixed-effects linear regressions by assuming different random intercepts for each participant and adjusted for baseline intelligence quotient (IQ), age, gender, and any previous exposure to anesthesia. List-wise deletion was used to deal with missing completely at random follow-up data; it has been recommended that tests with missing data should not be used for evaluation of cognitive function.<sup>21</sup>

The primary outcome was incidence of POCD. This was estimated from the Z-scores methodology that requires data from the control group outlined by Rasmussen et al.<sup>21</sup> We used 2 criteria to define the direction of change (either decline or improvement) in the postoperative cognitive function in each child. POCD was defined as either at least 2 of the 4 cognitive functions tests with an individual Z-score  $\leq -1.96$  or a combined Z-score of  $\leq -1.96$ . Similarly, postoperative cognitive improvement (POCI) was defined as either at least 2 of the 4 cognitive functions tests with an individual Z-score  $\geq 1.96$  or a combined Z-score of  $\geq 1.96$ . To identify whether the postoperative cognitive decline in performance in these children

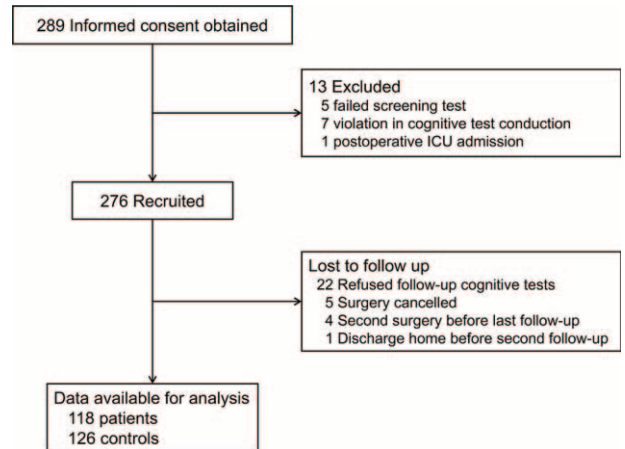


FIGURE 1. Flow of participants in the cohort study.

represented a true deterioration or random variation, we used multinomial logistic regression to estimate the relative risk ratio of POCD to POCI between groups (POCD/POCI-RRR)<sup>20</sup> after adjusting for IQ, age, and gender. All analyses were performed using STATA 14.0 (StataCorp, College Station, TX). The level of significance was set at  $P < 0.05$ .

Based on pilot data of 7 subjects (3 controls and 4 patients), a repeated measures analysis of variance design of 2 groups (control and anesthesia) measured at 3 times, we calculated that 110 subjects in each group (total  $n = 220$ ) would be required to detect a difference of a small effect size of 0.20 at 90% power with correlation between repeated measures of 0.70 at 5% significance level (nQuery Advisor 4.0, Janet D Elashoff 2000).

**RESULTS**

Of the 289 participants screened, 276 were recruited but 32 were lost to follow-up (11.6%), leaving 244 for analysis (Figure 1). The refusal rate of follow-up cognitive tests was similar between anesthesia (9.9%) and control (6.7%) groups ( $P = 0.34$ ). The demographic characteristics were comparable between groups, except for gender (Table 1). The median time to the second follow-up was similar between anesthesia (42.5 days, IQR 40.0–46.0) and control (42.0 days, IQR 42.0–43.0) groups ( $P = 0.59$ ).

Among the 118 patients, 114 (96.6%) received midazolam premedication. Intravenous anesthetics for induction were given in 106 (89.8%); 99 (83.8%) had thiopentone (median

TABLE 1. Comparison of Baseline Characteristics of Children by Group

	Anesthesia (n = 118)	Controls (n = 126)	P Value
Median (IQR) age, y	8.0 (6.7–9.9)	8.4 (6.8–10.9)	0.290
Males, %	86 (72.9)	66 (52.4)	0.001
Median (IQR) body weight, kg	26.5 (21.0–36.1)	28.1 (24.0–35.0)	0.188
Median (IQR) IQ	115 (95–140)	120 (100–135)	0.430
Median (IQR) vocabulary test score*	13 (10–17)	12 (10–14)	0.120
Median (IQR) digit span test score*	11 (9–13)	11 (9–13)	0.406
Previous anesthesia exposure, %	10 (8.5)	7 (5.6)	0.371

IQ = intelligence quotient, IQR = interquartile range.  
\* Scaled score.

**TABLE 2.** Incidence (%; 95% CI) of Cognitive Decline and Improvement by Group Over Time

Cognitive Function Tests	Day 1		6 wk	
	Anesthesia (n = 118)	Control (n = 126)	Anesthesia (n = 118)	Control (n = 126)
Hong Kong List Learning				
Decline	2 (1.7, 0.3–5.5)	5 (4.0, 1.5–8.6)	2 (1.7, 0.3–5.5)	2 (1.6, 0.3–5.1)
Improvement	1 (0.8, 0.0–4.1)	2 (1.6, 0.3–5.1)	5 (4.2, 1.6–9.1)	5 (4.0, 1.5–8.6)
Visual Matching				
Decline	14 (11.9, 6.9–18.7)	2 (1.6, 0.3–5.1)	2 (1.7, 0.3–5.5)	3 (2.4, 0.6–6.3)
Improve	2 (1.7, 0.3–5.5)	3 (2.4, 0.6–6.3)	3 (2.5, 0.7–6.8)	4 (3.2, 1.0–7.5)
Visual Memory				
Decline	5 (4.2, 1.6–9.1)	2 (1.6, 0.3–5.1)	6 (5.1, 2.1–10.3)	2 (1.6, 0.3–5.1)
Improvement	4 (3.4, 1.1–8.0)	3 (2.4, 0.6–6.3)	6 (5.1, 2.1–10.3)	4 (3.2, 1.0–7.5)
General Comprehension				
Decline	4 (3.4, 1.1–8.0)	3 (2.4, 0.6–6.3)	2 (1.7, 0.3–5.5)	1 (0.8, 0.0–3.9)
Improvement	3 (2.5, 0.7–6.8)	5 (4.0, 1.5–8.6)	4 (3.4, 1.1–8.0)	4 (3.2, 1.0–7.5)
At least 2 tests				
Decline	0 (0.0, 0.0–2.5)	0 (0.0, 0.0–2.3)	0 (0.0, 0.0–2.5)	0 (0.0, 0.0–2.3)
Improvement	0 (0.0, 0.0–2.5)	0 (0.0, 0.0–2.3)	1 (0.8, 0.0–4.1)	0 (0.0, 0.0–2.3)
Combined Z-score				
Decline	6 (5.1, 2.1–10.3)	5 (4.0, 1.5–8.6)	4 (3.4, 1.1–8.0)	5 (4.0, 1.5–8.6)
Improvement	2 (1.7, 0.3–5.5)	2 (1.6, 0.3–5.1)	3 (2.5, 0.7–6.8)	2 (1.6, 0.3–5.1)

95% CI = 95% confidence interval.

dose 4.4 mg/kg, IQR 3.9–4.9) and 7 (5.9%) had propofol (median dose 2.6 mg/kg, IQR 2.2–3.3). Eighteen (15.3%) patients were given sevoflurane. The majority of patients (n = 116, 98.3%) had isoflurane for maintenance. Nitrous oxide was used in 91 (77.1%) patients while the rest had an air and oxygen mixture. All patients had atropine and neostigmine for reversal of residual paralysis. The median duration of anesthesia was 122 min (IQR 76–193). The median time to obeying commands was 15 min (IQR 7–33). In the 107 children with recorded BIS values, the mean (SD) was 54.1 (7.4).

Most patients (98.3%) had intraoperative opioids (fentanyl and/or morphine). In the postoperative period, 31 (26.3%) had opioids, 71 (60.2%) had paracetamol, 7 (5.9%) nonsteroidal anti-inflammatory drugs, and 70 (59.3%) had regional anesthesia for analgesia. Of the 110 patients with recorded pain scores on Day 1, 43 (39.1%), 37 (33.6%), and 10 (9.1%) children experienced mild, moderate, and severe pain, respectively. At 6 weeks, 20 (17.7%) of 113 patients with pain assessments reported experiencing some pain.

The test–retest reliability was high ( $r > 0.7$ ) for HKLL, visual matching, and general comprehension and was acceptable ( $0.4 < r < 0.6$ ) for visual memory over the 3 time points. The serial changes in the cognitive function test scores are shown in Figure 2. Despite adjustment for confounders, the baselines' scores were significantly lower in the anesthesia group than the control group for HKLL (mean difference  $-1.0$ , 95% confidence interval [CI]:  $-0.3$  to  $-1.7$ ) and visual matching (mean difference  $-9.3$ , 95% CI:  $-5.1$  to  $-13.5$ ). There was a significant group–time interaction for visual matching ( $P < 0.01$ ) and visual memory ( $P = 0.03$ ). Compared with the control group, children undergoing anesthesia had significantly lower overall group means for HKLL ( $P = 0.001$ ), visual matching ( $P < 0.001$ ), visual memory ( $P < 0.01$ ), and general comprehension ( $P = 0.01$ ).

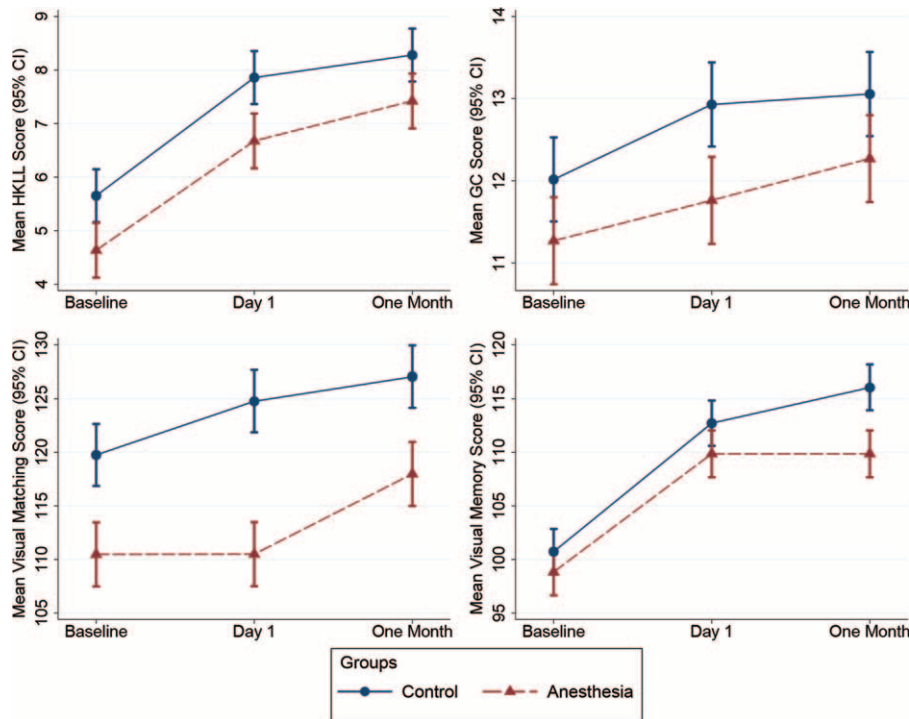
The incidences of cognitive function decline and improvement between groups at the 2 follow-up times are shown in

Table 2. Compared with the control group, the risk of a decline in visual matching was higher in the anesthesia group on Day 1 ( $P = 0.001$ ; risk difference 10.3%, 95% CI: 3.2–17.3). In a post hoc analysis of visual matching data on Day 1, the crude and adjusted POCD/POCI-RRR was 10.50 (95% CI: 1.02–107.66,  $P = 0.048$ ) and 6.82 (95% CI: 0.76–60.82,  $P = 0.09$ ), respectively. Using the combined Z-scores, the crude and adjusted POCD/POCI-RRR on Day 1 were 1.20 (95% CI: 0.12–11.92,  $P = 0.88$ ) and 0.85 (95% CI: 0.10–7.05,  $P = 0.88$ ), respectively. The corresponding estimates at 6 weeks were 0.53 (95% CI: 0.06–4.93,  $P = 0.58$ ) and 0.45 (95% CI: 0.04–4.84,  $P = 0.51$ ), respectively.

In children undergoing anesthesia, the mean BIS were similar between those who had POCD ( $53 \pm 8$ , n = 6) and those with no POCD ( $54 \pm 7$ , n = 103) on Day 1 ( $P = 0.75$ ). Similar mean BIS were found between those who had POCD ( $58 \pm 10$ , n = 3) and those with no POCD ( $54 \pm 7$ , n = 106) at 6 weeks ( $P = 0.37$ ). Of the 12 desaturations, 2 occurred in children with POCD on Day 1 and none at 6 weeks. Hypotension did not occur in children with POCD at both follow-up times. There was no difference in pain scores between children with no change in cognitive function, POCD or POCI on Day 1 ( $P = 0.31$ ) and at 6 weeks ( $P = 0.29$ ).

## DISCUSSION

This prospective cohort of Hong Kong children aged 5 to 12 years undergoing GA showed the risk of POCD on Day 1 and at 6 weeks after surgery were 1 in 20 and 1 in 30, respectively. It should be noted that there were similar low incidences ( $< 10\%$ ) of cognitive impairment and improvement for all tests in both groups at each time point except visual matching in the anesthesia group on Day 1. When using the criterion of at least 2 tests with 2 SD decline, there was no association between GA and POCD. However, the results were imprecise when the combined Z-score criterion was adopted, with the POCD



**FIGURE 2.** Adjusted serial changes in mean scores (95% confidence interval) of the 4 cognitive function tests: Hong Kong List Learning (HKLL), Visual Matching, Visual Memory, and General Comprehension (GC). The control group is represented by blue circle with solid lines and the anesthesia group is represented by magenta triangle with long dash lines.

identified in the few children likely to be random variation than true deterioration. Measurement errors are unlikely to bias these results as our choice of cognitive function tests had an acceptable to high level of test–retest reliabilities. Pain score, depth of anesthesia, desaturation, and hypotensive episodes were not associated with POCD.

Our study provides weak evidence for the association between GA and visual matching, a measure of processing speed, on Day 1. For every 10 children undergoing GA, a decline in visual matching will occur in 1 in the early postoperative period. This is likely related to general discomfort from surgery, postoperative analgesic effects and the residual effects of longer GA. A post hoc analysis showed that children with a decline in visual matching scores had longer GA (median 159 min, IQR 130–288) than those with no decline (median 116 min, IQR 71–187) ( $P=0.03$ ). All children with visual matching impairment recovered before the 6-week follow-up assessment. In other studies, reaction time returned to baseline levels at 24 to 48 h after midazolam premedication, propofol, isoflurane, or sevoflurane-nitrous oxide anesthesia for dental procedures.<sup>11,22,23</sup> Compared with sevoflurane, propofol was associated with visual memory impairment at 1 week, but not at 3 months, after elective hernia surgery but the study did not control for a practice learning effect.<sup>12</sup> Taking all these results together, it appears that GA is associated with transient subtle effects on cognitive function in school-age children.

Our age appropriate panel of neuropsychological tests took 15 to 20 min to complete. Although more tests, such as those measuring executive function, would cover other areas of cognitive functions, too large a test battery would increase the rate of patient withdrawal because of fatigue. Our noncompliance rate of follow-up tests was acceptable and similar

between groups, suggesting that attrition bias was small and unlikely to affect the results. There is no consensus on the optimum size of a panel of neuropsychological tests.<sup>7</sup> Our focus on basic processes of memory, speed of processing, and comprehension covered several major areas of particular concern among parents of children undergoing GA.

Compared with previous studies in school-age children with a control group,<sup>13,22,24</sup> our study is the largest with the longest duration of anesthesia and follow-up data. While the use of a control group helped adjust for improved performance from learning and extraneous variables,<sup>7</sup> we found significant baseline differences between groups in half the panel of neuropsychological tests undertaken. This suggests that some selection bias was present despite comparable baseline characteristics described in Table 1. As children undergoing surgery were more likely to be anxious in an unfamiliar hospital environment than at school, this may have affected their baseline tests performance. Nevertheless, our results are generally consistent with a previous study showing no effect of halothane–nitrous oxide GA on reasoning, motor or memory functions at 24 h after myringotomy in children aged between 5 and 8 years old.<sup>13</sup>

There are several limitations in this study. Our study included children with relatively high IQs; the mean IQ in another Hong Kong study of similar age children was estimated to be 115.<sup>17</sup> The results have some generalizability to current pediatric anesthesia practice even if our data are old and the type of GA was not always standardized between anesthesiologists. Apart from intravenous thiopentone induction, our GA used current anesthetic agents namely midazolam premedication, propofol or sevoflurane induction, maintenance with nitrous oxide, oxygen, sevoflurane or isoflurane, neuromuscular blockade, and mechanical ventilation. Nevertheless, we believe that

the publication of this data may give further assurance to parents on the safety of GA in this patient age group.

In conclusion, this prospective cohort study with an age-matched control group of school children found weak evidence to support an association between GA and visual matching impairment on the first day of surgery. The incidences of POCD on Day 1 and at 6 weeks after surgery were low. We found no anesthesia-related POCD per se when using the widely accepted Z-score definition and relative risk ratio methodology. Any POCD found on Day 1 was likely to be a random event that resolved before the follow-up assessment at 6 weeks.

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