ANESTHESIOLOGY

Intravenous *versus* Volatile Anesthetic Effects on Postoperative Cognition in Elderly Patients Undergoing Laparoscopic Abdominal Surgery

A Multicenter, Randomized Trial

Yujuan Li, M.D., Ph.D., Dongtai Chen, M.D., Ph.D., Hanbing Wang, M.D., Zhi Wang, M.D., Ph.D., Furong Song, M.D., Hui Li, M.D., Li Ling, Ph.D., Zhiwen Shen, M.D., Chuwen Hu, M.D., Jun Peng, M.D., Ph.D., Weixing Li, M.D., Wei Xing, M.D., Jiahao Pan, M.D., Hua Liang, M.D., Qiaoling Zhou, M.D., Jun Cai, M.D., Ziqing He, M.D., Ph.D., Shuling Peng, M.D., Ph.D., Weian Zeng, M.D., Ph.D., Zhiyi Zuo, M.D., Ph.D.

ANESTHESIOLOGY 2021; 134:381–94

EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Postoperative neurocognitive disorders are common in older surgical patients
- It is unclear whether there are differences in neurocognitive outcomes between propofol-based intravenous anesthesia and the use of volatile anesthetics

What This Article Tells Us That Is New

- This prospective randomized study found no differences in neurocognitive disorder at postoperative days 5 to 7 between patients anesthetized with a propofol-based compared to a sevoflurane-based anesthetic
- Elevated interleukin-6 concentrations 1 h after skin excision may be predictive of the development of a postoperative neurocognitive disorder on postoperative days 5 to 7

ABSTRACT

Background: Delayed neurocognitive recovery after surgery is associated with poor outcome. Most surgeries require general anesthesia, of which sevoflurane and propofol are the most commonly used inhalational and intravenous anesthetics. The authors tested the primary hypothesis that patients with laparoscopic abdominal surgery under propofol-based anesthesia have a lower incidence of delayed neurocognitive recovery than patients under sevoflurane-based anesthesia. A second hypothesis is that there were blood biomarkers for predicting delayed neurocognitive recovery to occur.

Methods: A randomized, double-blind, parallel, controlled study was performed at four hospitals in China. Elderly patients (60 yr and older) undergoing laparoscopic abdominal surgery that was likely longer than 2 h were randomized to a propofol- or sevoflurane-based regimen to maintain general anesthesia. A minimum of 221 patients was planned for each group to detect a one-third decrease in delayed neurocognitive recovery incidence in propofol group compared with sevoflurane group. The primary outcome was delayed neurocognitive recovery incidence 5 to 7 days after surgery.

Results: A total of 544 patients were enrolled, with 272 patients in each group. Of these patients, 226 in the propofol group and 221 in the sevoflurane group completed the needed neuropsychological tests for diagnosing delayed neurocognitive recovery, and 46 (20.8%) in the sevoflurane group and 38 (16.8%) in the propofol group met the criteria for delayed neurocognitive recovery (odds ratio, 0.77; 95% CI, 0.48 to 1.24; $P = 0.279$). A high blood interleukin-6 concentration at 1 h after skin incision was associated with an increased likelihood of delayed neurocognitive recovery (odds ratio, 1.04; 95% CI, 1.01 to 1.07; $P = 0.007$). Adverse event incidences were similar in both groups.

Conclusions: Anesthetic choice between propofol and sevoflurane did not appear to affect the incidence of delayed neurocognitive recovery 5 to 7 days after laparoscopic abdominal surgery. A high blood interleukin-6 concentration after surgical incision may be an independent risk factor for delayed neurocognitive recovery.

(ANESTHESIOLOGY 2021; 134:381–94)

More than 50 and 60 million patients have surgery annually in the United States and in China, respectively.[1,2] Studies have shown acute and delayed onset postoperative cognitive dysfunction.[3–5] Postoperative cognitive dysfunction is associated with an increased mortality, length and cost of hospital stay, and dropout from job market.[4,6] Aging is identified as a risk factor for postoperative cognitive dysfunction.[3,4] About 40 and 10% of elderly (60

This article is featured in "This Month in Anesthesiology," page 1A. Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org). This article has a visual abstract available in the online version. Y.L. and D.C. contributed equally to this article.

Submitted for publication March 20, 2020. Accepted for publication December 11, 2020. Published online first on January 13, 2021. From the Department of Anesthesiology, Sun Yat-sen Memorial Hospital (Y.L., Z.W., H. Li, Z.S., C.H., J.P., W.L., S.P.), the Guangdong Province Key Laboratory of Brain Function and Disease, Zhongshan School of Medicine (Y.L.), the Department of Anesthesiology, The Third Affiliated Hospital (F.S., J.C., Z.H.), the Guangdong Provincial Key Laboratory of Malignant Tumor Epigenetics and Gene Regulation, Sun Yat-sen Memorial Hospital (H. Li), and the Department of Medical Statistics, School of Public Health (L.L.), Sun Yat-sen University, Guangzhou, China; the Department of Anesthesiology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovator Center for Cancer Medicine, Guangzhou, China (D.C., W.X., J.P., W.Z.); the Department of Anesthesiology, The First People's Hospital of Foshan City, Foshan, China (H.W., H. Liang, Q.Z.); and the Department of Anesthesiology, University of Virginia Health System, Charlottesville, Virginia 22908 (Z.Z.).

 Anesthesiology 2021; 134:381–94. DOI: 10.1097/ALN.0000000000003680

<zdoi;. DOI: 10.1097/ALN.0000000000003680>

yr and older) patients have this syndrome 7 days and 3 months, respectively, after noncardiac surgery.[3,4] Recently, the term "delayed neurocognitive recovery" was adopted for cognitive impairment in the interval from 0 to 30 days postoperatively.[7]

Because the majority of patients require general anesthesia during surgery, the possible role of general anesthetics, especially volatile anesthetics, in postoperative cognitive dysfunction is proposed based on animal study findings.[8–10] However, whether general anesthesia contributes to postoperative cognitive dysfunction development in humans is controversial. Patients having general anesthesia had a worse cognition function than patients having regional anesthesia at 1 week after surgery in some studies,[11,12] but this difference was not revealed in other studies.[13,14] Also, there was no difference in cognitive functions 3 or 6 months after surgery between patients receiving general and regional anesthesia.[11,13,14]

Because general anesthesia is often necessary in surgical patients, one important issue is whether anesthetic choice will influence postoperative cognitive dysfunction occurrence. Two types of general anesthetics are used: intravenous and inhalational anesthetics. Recent animal studies have been focused on identifying possible toxic effects of volatile anesthetics including inducing cell injury and inflammation.[9,15,16] Neuroinflammation may be a critical pathologic process for postoperative cognitive dysfunction.[16,17] These findings have prompted some anesthesiologists to propose reducing the use of volatile anesthetics.[18,19] However, the intravenous anesthetic propofol can also induce cell injury.[20] Although volatile anesthetics may induce inflammatory responses,[8,21] extensive research has shown that volatile anesthetics can inhibit various insult-induced neuroinflammation and brain cell injury.[22–25] Because surgery is an insult and induces neuroinflammation,[26,27] volatile anesthetics may inhibit surgery-induced neuroinflammation. Thus, volatile anesthetics may not be a "bad player" in terms of postoperative cognitive dysfunction.[28]

In fact, the role of intravenous and volatile anesthetics in delayed neurocognitive recovery/postoperative cognitive dysfunction in humans remains unclear. Although many studies have investigated this issue, most studies are small in sample size, used substandard methods to diagnose the syndrome, or were not designed primarily to determine this issue.[29–32] There is no multicenter study to address this issue. Because anesthetic choice can be effectively managed by anesthesiologists, determining the role of anesthetic choice in delayed neurocognitive recovery/postoperative cognitive dysfunction is important. The primary aim of our study was to compare the effects of propofol *versus* sevoflurane on the incidence of delayed neurocognitive recovery in elderly patients undergoing laparoscopic abdominal surgery. A secondary aim was to determine whether there were blood biomarkers for delayed neurocognitive recovery. These studies aimed to test the hypotheses that general anesthesia maintained mainly by propofol reduces delayed neurocognitive recovery compared with sevoflurane-based general anesthesia and that there are early blood biomarkers for predicting whether delayed neurocognitive recovery will occur.

Materials and Methods

Study Design and Participants

A multicenter, double-blind, randomized controlled trial was performed at Sun Yat-sen Memorial Hospital (Sun Yat-sen University, Guangzhou, China), the Sun Yat-sen University Cancer Center (Guangzhou, China), the First People's Hospital of Foshan (Foshan, China), and the Third Affiliated Hospital of Sun Yat-sen University (Guangzhou, China). The trial protocol was approved by the Clinical Research Ethics Committee of the leading hospital (Sun Yat-sen Memorial Hospital) and then the committee of each hospital (approval No. 2012-25). The study was registered with ClinicalTrials.gov (identifier NCT01809041; principal investigator: Zhiyi Zuo) on March 12, 2013. Initially, eight hospitals agreed to participate and were on the register. However, four hospitals dropped out due to insufficient manpower. The remaining four hospitals have about 7,500 beds and perform 140,000 surgeries annually.

Written informed consent was obtained from each participant enrolled in the study, which occurred between March 23, 2013, and March 11, 2019. Inclusion criteria included that patient's age was 60 yr or older and that the patient was scheduled to undergo elective major laparoscopic abdominal surgery (*e.g.*, gastrointestinal and gynecologic surgery). Additional inclusion criteria were that surgery was expected to last 2 h or longer and that patients did not have serious hearing and vision impairment and were able to read. The exclusion criteria included: (1) severe diseases in cardiovascular, respiratory, liver, kidney, or central nervous systems and having a life span of less than 3 months; (2) a mini-mental status examination score of less than 23; (3) a history of dementia or psychiatric illness; (4) current use of sedatives, antidepressants or corticosteroids; (5) alcoholism and drug dependence; (6) previous inclusion in this study; (7) difficulty with follow-up or poor compliance; and (8) uncontrolled hypertension (more than 180/100 mmHg).

Each participating hospital had at least one investigative team composed of two people. One person evaluated the eligibility of the patients, enrolled patients, received group randomization codes from the leading center, and made sure that the management of the patients was in compliance with the study design. The second person was responsible for performing neuropsychological assessment without knowing the group assignment of the patients.

Randomization and Masking

A study statistician in the leading center generated random numbers without restriction (simple randomization)

by using a computer. The randomization codes were sealed in sequentially numbered envelopes and sent to a research coordinator of the research team the day before surgery by a research nurse. The coordinator communicated the group assignment to the anesthesiologist caring for the patient and assigned participants to study groups according to the random codes.

The patients were randomized at 1:1 ratio to receive propofol-based (propofol group) or sevoflurane-based (sevoflurane group) general anesthesia. This trial used a parallel design to test the hypothesis that propofol-based anesthesia reduced the incidence of delayed neurocognitive recovery compared with sevoflurane-based anesthesia (superiority in nature). Preoperative interview, evaluation of eligibility, obtaining written informed consent, and enrolled the participants and postoperative follow-up were performed by investigators who did not participate in perioperative patient care and had been trained to perform neuropsychological assessment before the study (all were trained and certified by Yujuan Li). Both patients and investigators were blinded to study group assignment.

To adjust the practice effect from repeated neuropsychological tests used in this study, we enrolled 184 control subjects who were not exposed to surgery. They were volunteers from the community who were 60 yr old or older (similarly aged to patients with surgery) and were not patients evaluated in the hospitals or clinics. The inclusion and exclusion criteria for control subjects were identical to those of surgical patients. The evaluation dates of control subjects overlapped with those of surgical patients in the study. These control subjects were recruited exclusively for this study.

Anesthesia and Perioperative Care

No preoperative anxiolytic medication was administered. Intraoperative monitoring included the American Society of Anesthesiologists (ASA) mandatory monitoring, Bispectral Index (BIS), and end-tidal gas monitoring. Anesthesia was induced intravenously with fentanyl, lidocaine, propofol, and cisatracurium for both groups of patients. Anesthesia was maintained with inhaled sevoflurane (1.0 to 1.5 minimum alveolar concentrations) and intravenous remifentanil infusion (0.1 to 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) for patients in the sevoflurane group. For the other group, anesthesia was maintained with intravenous propofol infusion (50 to 150 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and remifentanil infusion (0.1 to 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$). There were no limitations for the use of muscle relaxant and vasoactive medications. However, glucocorticoid drugs, nonsteroidal analgesics, and dexmedetomidine were avoided during surgery.

During the operation, blood pressure was maintained within the range of ± 30% of the baseline, nasopharyngeal temperature was between 36 to 37.5°C, end-tidal pressure of carbon dioxide was between 35 and 45 mmHg, and blood glucose was in a range of 3.9 to 11.1 mM. The BIS values were maintained between 40 and 60 by adjusting propofol or sevoflurane dosages. Postoperative analgesia during the first 48 h was provided with a patient-controlled analgesia pump, which infused fentanyl or sufentanil. Pain relief was by tramadol or meperidine hydrochloride when needed 2 days after surgery. Hormones, nonsteroidal anti-inflammatory drugs, and long-acting sedatives were avoided after surgery.

Data Collection

Preoperative evaluation was performed within 3 days of surgery. The functional effects of comorbid diseases were evaluated with the New York Heart Association functional classification. Fitness and functionality before surgery were assessed with the ASA physical status classification and instrumental activities of daily living scores.[33] Cognitive function was evaluated with mini-mental status examination.[34] The presence and severity of depression were assessed by the Beck depression inventory.[35] State anxiety and trait anxiety were measured by the State–Trait Anxiety Inventory.[36] Adverse events during and after surgery until the patient was discharged were recorded. A data safety–monitoring board was not formed for this study because propofol and sevoflurane have been commonly used in clinical practice.

Venous blood (5 ml) was drawn before anesthesia (T1), 15 min after endotracheal intubation (T2), 1 h after operation had started (T3), at the end of surgery (T4), and 24 h after surgery (T5) for measuring biomarkers possibly related to delayed neurocognitive recovery/postoperative cognitive dysfunction. Delirium was assessed in the postanesthesia care unit when patients were awake by using the intensive care delirium screening check inventory.[37]

Enzyme-linked Immunosorbent Assay

Blood was maintained for 30 min at room temperature. Serum was obtained by centrifugation of blood at 4,000*g* for 20 min at 4°C and stored at –80°C. The concentrations of tumor necrosis factor-α, interleukin-6, interleukin-1β, interleukin-10, vascular endothelial growth factor, β-melanocyte–stimulating hormone, interferon-γ, intercellular adhesion molecule, transforming growth factor-β1, apolipoprotein E, complement C3a, advanced glycation end products, and myeloperoxidase were measured using enzyme-linked immunosorbent assay kits. Malondialdehyde was measured using a lipid peroxidation malondialdehyde assay kit.

Neuropsychological Assessment

Neuropsychological tests for patients were carried out the day before and 5 to 7 days after surgery with only the patient and an investigator present in a quiet room. Similarly, the second neuropsychological test time for control subjects was 6 to 9 days after the first time. The test was also done with a control subject and an investigator in a quiet room.

All tests were administered and scored in a standardized manner to minimize differences between investigators.

The neuropsychological test battery included the tests used to evaluate patients for delayed neurocognitive recovery in the International Study of Post-Operative Cognitive Dysfunction 1[3,4]: (1) word learning: visual verbal learning test based on the Rey's auditory recall of words[38]; (2) word recall: the number or words recalled from visual verbal learning trials after a 20-min delay; (3) cognitive flexibility: including trail making test A and B[39]; (4) distractibility: Stroop color word interference test[40]; and (5) working memory: letter–digit coding.[41] If a patient exhibited delirium at a testing time, neuropsychological evaluation was postponed 3 days.

Delayed neurocognitive recovery was diagnosed using the International Study of Post-Operative Cognitive Dysfunction 1 definition.[3,4] In brief, the average practice effect ($\Delta X_{control}$) and standard deviation ($SD[\Delta X_{control}]$) of each neuropsychological test were determined by comparing the test scores of control subjects at baseline with those 1 week later. For each patient, a Z score for each test was calculated by determining the difference between postoperative and preoperative scores (ΔX), subtracting $\Delta X_{control}$ from ΔX, and then dividing it by $SD(\Delta X_{control})$ as shown by this equation: $Z = (\Delta X - \Delta X_{control})/SD(\Delta X_{control})$. A combined Z score ($Z_{combined}$) was obtained by summation of the Z scores of all tests (ΣZ) in an individual patient divided by the standard deviations for this sum of Z scores in control subjects ($SD[\Sigma Z_{control}]$) as shown by the equation: $Z_{combined} = (\Sigma Z)/(SD[\Sigma Z_{control}])$. $SD(\Sigma Z_{control})$ was calculated based on ΣZ of all participants in the control group. A patient was diagnosed to have delayed neurocognitive recovery if the Z scores on two individual tests or $Z_{combined}$ was 1.96 or greater.

Statistical Analysis

The sample size estimate of this study was predetermined and posted on a publicly accessible server (ClinicalTrials.gov, identifier NCT01809041). The principal of data analysis and the statistical plan were decided before the initiation of the study. However, imputation strategies for missing data were decided after the data was accessed for *post hoc* sensitivity analyses.

Sample Size Calculation. The incidence of delayed neurocognitive recovery in comparable patient populations was about 40% at 1 week after noncardiac surgery.[4] We planned to detect 33% reduction in delayed neurocognitive recovery incidence in the propofol group compared with sevoflurane group or vice versa. Per group, 221 patients would provide 80% power to detect this difference based on a two-tailed significance level at 0.05. The sample size in the control group would be 164, assuming 4% incidence of decreased cognitive functions over time, and the estimated error range was 3% (δ = 3%, $z_{\alpha/2}$ = 1.96). Considering a 10% loss-to-follow-up rate, the final sample size was determined to be 250 patients in each surgery group and 184 nonsurgery elderly people in the control group. Additional patients were planned if the dropout rate was more than 10% to maintain minimally 221 patients per group. When this sample size was achieved, the enrollment would cease.

Outcome Analysis. The primary outcome of this study was delayed neurocognitive recovery incidence at postoperative 5 to 7 days. This outcome was analyzed using chi-square with both intention-to-treat and per-protocol principles. Patients who were enrolled, did not violate the research protocol, and completed all needed neuropsychological tests were included in the analysis with per-protocol principle. All enrolled patients were included in the analysis with intention-to-treat principle. Three strategies for managing missing data were taken in the intention-to-treat analyses: (1) no imputation of missing data, (2) imputing the missing data with last observation carried forward strategy, and (3) hot-deck imputation strategy. The data of patients who were enrolled and completed all needed neuropsychological tests were analyzed with the first strategy. Missing values were imputed from preoperative values with last observation carried forward strategy. For hot-deck imputation strategy, a patient with missing data was matched with patient(s) who had complete set(s) of data and similar characteristics including age, ASA physical status, education level, mini-mental state examination score, Beck depression inventory score, and insurance status. The missing Z scores of the patients with missing data were imputed with the Z scores of the matched subject. If there were two or more matched subjects, the average Z scores of these matched subjects were used to impute the Z scores of the patient with missing data.

The secondary outcomes were the changes of serum concentrations of inflammation-related cytokines (interleukin-10, interleukin-1β, interleukin-6, and tumor necrosis factor-α), oxidative stress biomarkers (myeloperoxidase, malondialdehyde, advanced glycation end products, and apolipoprotein E), and immune modulators (vascular endothelial growth factor, intercellular adhesion molecule, β-melanocyte–stimulating hormone, transforming growth factor-β1, interferon-γ, and C3a)[42,43] at various time points in patients with or without delayed neurocognitive recovery. These data were analyzed by two-way (between group comparisons with the time and group as two factors to be analyzed) repeated-measures ANOVA followed by Bonferroni multiple comparison correction.

Categorical data were reported as frequencies (percentage) and analyzed using the chi-square or Fisher exact test. Continuous variables are presented as means ± SD or median (25th, 75th percentiles) and were compared with independent *t* test or Mann–Whitney U test depending on the distribution of data. Univariate logistic regression analysis was used as an initial step to identify possible prognostic factors for delayed neurocognitive recovery, and these variables with a *P* value of <0.05 from this analysis were

included in the multiple regression analysis with forced entry. Variance inflation factor was used to evaluate multicollinearity of enrolled variables, the Hosmer–Lemeshow test was used to examine the goodness of fit of model, and the discrimination of the models was estimated by using analysis of the area under the curve. No analyses were adjusted for additional variables or stratification variables. Two-tailed tests were performed whenever appropriate, and a P value of <0.05 was considered statistically significant. The SPSS 25.0 for Windows (SPSS Inc., USA) software was used for all statistical analyses.

Results

Patient Characteristics

In total, 580 patients were screened for this study from March 23, 2013, to March 11, 2019. Among them, 36 patients did not meet the inclusion criteria, and 544 subjects were enrolled. Among the enrolled patients, 12 patients did not receive allocated intervention (surgery was changed to open procedure in 8 patients and 4 patients withdrew their consents to participate), 52 patients were lost to follow-up, and 33 patients were excluded because of incompletion of the tests (7 patients) or receiving medications that should be avoided (26 patients). Therefore, 221 patients in the sevoflurane group and 226 patients in the propofol group completed the study per protocol (fig. 1). In addition, 184 subjects were enrolled in the control group. The trial was ended because the planned number of patients was achieved.

The baseline characteristics of the patients were listed in table 1 and were well balanced between the sevoflurane and propofol groups. The age was 64 (62 to 68) years in the propofol group and 65 (62 to 69) years in the sevoflurane group ($P = 0.023$ per protocol principle and $P = 0.056$ per intention-to-treat principle). The sex distribution was different between the two groups ($P = 0.034$) in the per-protocol data set but was not different between the two groups in the intention-to-treat data set ($P = 0.139$). The education level distributions were different between the two groups in both data sets (table 1). The perioperative variables were comparable between the two groups (table 2). One patient each in the propofol and sevoflurane groups had an intensive care delirium screening check score of 4 or higher (the threshold to indicate delirium) in the postanesthesia care unit. The incidence of adverse events was similar between two groups except that more patients in the sevoflurane group developed intraoperative hypotension requiring intravenous vasopressors (table 3).

Primary Outcome

No patient exhibited delirium at a preset testing time. Therefore, neuropsychological evaluation was not postponed for any patient. Delayed neurocognitive recovery rates were not different between sevoflurane and propofol groups when the analysis was performed with per-protocol principle (20.8% *vs.* 16.8%, $P = 0.279$; table 4). We also analyzed the data of patients who were enrolled and completed the study with intention-to-treat principle. This analysis included the data of patients with per-protocol principle plus the data of patients receiving additional medications (13 in the sevoflurane group and 13 in the propofol group). The delayed neurocognitive recovery rates were also not different between sevoflurane and propofol groups: 21.4% *versus* 17.2% ($P = 0.245$; table 4). There were 12 patients who did not receive allocated intervention (9 in the sevoflurane group and 3 in the propofol group) because the surgery was changed to an open procedure, 22 patients in the sevoflurane group and 24 patients in the propofol group who were lost to follow-up because of earlier discharge, 6 patients (3 in the sevoflurane group and 3 in the propofol group) who declined to have postoperative neuropsychological tests, and 7 patients (4 in the sevoflurane group and 3 in the propofol group) who had incomplete data. When missing values were imputed with last observation carried forward strategy, there was no difference in the delayed neurocognitive recovery rates between sevoflurane and propofol groups: 18.7% *versus* 15.1% (n = 272 for each group, $P = 0.253$; table 4). When missing values were imputed with hot-deck imputation strategy, delayed neurocognitive recovery rates between sevoflurane and propofol groups were also not different: 20.2% *versus* 17.3% (n = 272 for each group, $P = 0.380$; table 4). However, the delayed neurocognitive recovery incidences in propofol or sevoflurane groups were higher than that in control subjects (3.8% [4 of 184]; $P < 0.001$; table 4).

Secondary Outcome

We planned to draw blood samples from all enrolled patients. However, some patients declined to have blood drawn or missed some time points of blood samples. Some samples had hemolysis. Therefore, for each biomarker, there were 53 to 66 patients who had a full set of blood samples for analysis. The basic characteristics of patients with blood biochemical measurements were similar to those of patients without blood biochemical measurements except for mini-mental status examination scores, number of patients with coronary arterial diseases, and number of patients with smoking history (Supplemental Digital Content 1, http://links.lww.com/ALN/C534). Our analysis showed that only interleukin-6 concentrations were higher in patients with delayed neurocognitive recovery than patients without nondelayed neurocognitive recovery ($P = 0.020$) and had a significant difference among the values from T1 to T5 within the same group of patients ($P < 0.001$; fig. 2). The interaction between time and group was significant ($P = 0.013$). Further analysis showed that interleukin-6 concentrations at T3 between patients with or without delayed neurocognitive recovery were significantly different (odds

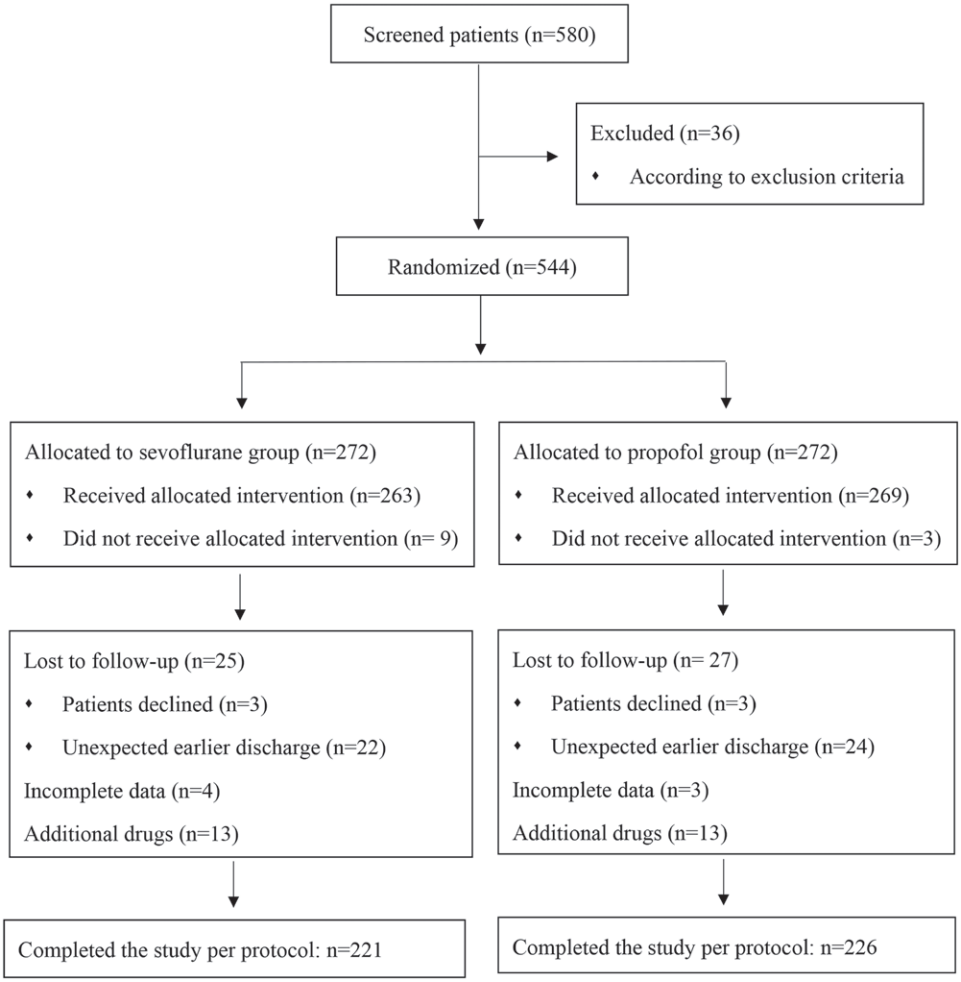

Fig. 1. Consolidated standards of reporting trial diagram.

ratio, 1.04 [1.01 to 1.08]; $P = 0.007$; table 5). Although some other blood indicators had time-dependent changes (such as vascular endothelial growth factor, intercellular adhesion molecule, transforming growth factor-β1, C3a, myeloperoxidase, apolipoprotein E, and advanced glycation end products), there were no differences in these indicators between patients with and without delayed neurocognitive recovery at various times (fig. 2).

Prognostic Factors for Delayed Neurocognitive Recovery

The univariate logistic regression analysis showed that risk factors for delayed neurocognitive recovery were age ($P = 0.044$), mini-mental status examination scores ($P = 0.001$), ASA physical status classification ($P = 0.018$), insurance status ($P = 0.042$), duration of hospitalization ($P = 0.005$), and interleukin-6 concentrations at T3 ($P = 0.007$; table 5). Elder age, ASA physical status classification III, a long hospitalization time, and a high interleukin-6 concentration at T3 increased delayed neurocognitive recovery incidence. Better mini-mental status examination scores and employer's medical insurance were associated with a lower delayed neurocognitive recovery rate.

The variables, such as age and ASA physical status classification, that were reported as risk factors for delayed neurocognitive recovery in previous studies[4,44] also had a P value of <0.05 in the univariate logistic regression analysis of the present study. Therefore, we chose these variables with a P value of <0.05 in this analysis to be enrolled into multiple regression analysis with forced entry. In the regression model, age, mini-mental status examination scores, interleukin-6 concentration at T3, and duration of hospitalization were analyzed as continuous variables; insurance was analyzed as a categorical variable; and ASA physical status classification was analyzed as a ranked variable. Variance inflation factor was used to evaluate multicollinearity between these factors. We found that the variance inflation factor values were less than 2 for all predictors enrolled into the multiple

Table 1. Basic Characteristics

	Per Protocol			Intention to Treat		
	Propofol	Sevoflurane	*P* Value*	Propofol	Sevoflurane	*P* Value*
	(n = 226)	(n = 221)		(n = 272)	(n = 272)	
Age, yr	64 (62–68)	65 (62–69)	**0.023**	64 (62–68)	65 (62–69)	0.056
Body mass index, kg/m^2	22.5 (20.2–24.3)	22.3 (20.3–24.7)	0.968	22.5 (20.2–24.5)	22.4 (20.3–24.7)	0.911
SBP, mmHg	130 (120–144)	130 (120–147)	0.395	130 (120–146)	132 (121–148)	0.844
Mini-mental state examination score	29 (29–30)	29 (28–30)	0.123	29 (28–30)	29 (28–30)	0.223
Instrumental activities of daily living score	5 (5–5)	5 (5–5)	0.031	5 (5–8)	5 (5–8)	0.072
Beck depression inventory score	2 (0–4)	2 (0–4)	0.723	2 (0–4)	2 (0–5)	0.550
State-anxiety inventory score	30 (26–35)	30 (25–38)	0.843	31 (26–35)	30 (26–38)	0.657
Trait-anxiety inventory score	29 (25–33)	29 (24–37)	0.340	29 (25–34)	30 (25–36)	0.241
Sex						
Female	57 (25.2)	76 (34.4)	**0.034**	72 (26.6)	88 (32.4)	0.139
Male	169 (74.8)	145 (65.6)		199 (73.4)	184 (67.6)	
Preoperative comorbidities						
Hypertension	65 (28.8)	66 (29.9)	0.798	88 (32.4)	71 (26.1)	0.109
Coronary artery disease	1 (0.4)	2 (0.9)	0.620	6 (2.2)	4 (1.5)	0.752
Diabetes mellitus	18 (8.0)	22 (10.0)	0.461	29 (10.7)	27 (9.9)	0.888
Arrhythmia	3 (1.3)	3 (1.4)	> 0.999	4 (1.5)	3 (1.1)	> 0.999
COPD	0 (0.0)	2 (0.9)	0.499	0 (0.0)	2 (0.9)	0.499
Chronic smoking	62 (27.4)	53 (24.0)	0.404	89 (32.7)	82 (30.1)	0.518
New York Heart Association classification						
I	181 (80.1)	181 (81.9)	0.763	215 (79.0)	213 (78.3)	0.834
II	44 (19.5)	40 (18.1)		56 (20.6)	59 (21.7)	
III	1 (0.4)	0 (0.0)		1 (0.4)	0 (0.0)	
Education						
Elementary school	42 (18.6)	70 (31.7)	**0.013**	54 (19.9)	81 (29.8)	**0.019**
Middle school	80 (39.4)	65 (29.4)		98 (36.0)	82 (30.1)	
High school	89 (39.4)	66 (29.9)		105 (38.6)	84 (30.9)	
University/above	11 (4.9)	14 (6.3)		11 (4.0)	18 (6.6)	
Unknown	4 (1.8)	6 (2.7)		4 (1.5)	7 (2.6)	
Residence						
Urban	130 (57.5)	132 (59.7)	0.893	146 (53.7)	151 (55.5)	0.974
Town	72 (31.9)	67 (30.3)		89 (32.7)	86 (31.6)	
Rural	24 (10.6)	22 (10.0)		29 (10.7)	28 (10.3)	
Unknown				8 (2.9)	7 (2.6)	
Insurance status						
Rural medical insurance	42 (18.6)	48 (21.6)	0.753	60 (22.1)	57 (21.0)	0.706
Employer's medical insurance	92 (40.7)	80 (36.2)		92 (33.8)	86 (31.6)	
Free medical service	11 (4.9)	11 (5.0)		12 (4.4)	12 (4.4)	
Self-pay	81 (35.8)	81 (36.7)		91 (33.5)	91 (33.5)	
Unknown	0 (0.0)	1 (0.5)		17 (6.3)	26 (9.6)	

The data are presented as the number of patients and percentage (%) or median (25th to 75th percentiles). Boldface values indicate $P < 0.05$.

*The *P* values were calculated by the Mann–Whitney U test, chi-square test, or Fisher exact test.

COPD, chronic obstructive pulmonary disease; SBP, systolic blood pressure.

regression analysis (ranging from 1.079 to 1.356), suggesting that there was minimal collinearity among predictors in the regression analysis. The Hosmer–Lemeshow test was used to examine the goodness of the fit of a model and showed a *P* at 0.815, suggesting that our model predictions match well with the observed data. The discrimination of the models was performed by using analysis of the area under the curve. The area under the curve of our model was 0.780 (95% CI, 0.654 to 0.906). The blood interleukin-6 concentrations at T3 were an independent risk factor for delayed neurocognitive recovery at 5 to 7 days after surgery (table 6). The other factors were not independent risk factors for delayed neurocognitive recovery by our analysis (table 6).

Discussion

Propofol and sevoflurane are the most frequently used inhalational and intravenous anesthetics. It has been a recent focus to determine whether anesthetic choice plays a role in delayed neurocognitive recovery/postoperative cognitive dysfunction, a syndrome whose importance is well recognized now.[17,19] This determination is necessary because it will define whether anesthetic choice is a modifiable risk factor for delayed neurocognitive recovery/postoperative

Table 2. Perioperative Variables

	Per Protocol			Intention to Treat		
	Propofol	Sevoflurane	*P* Value*	Propofol	Sevoflurane	*P* Value*
	(n = 226)	(n = 221)		(n = 272)	(n = 272)	
Surgery						
Upper abdomen/stomach	21 (9.3)	20 (9.0)	0.065	23 (8.5)	28 (10,6)	0.159
Middle abdomen/colorectum	200 (88.5)	186 (84.2)		238 (88.1)	219 (83.0)	
Lower abdomen/uterus	5 (2.2)	15 (6.8)		9 (3.3)	17 (6.4)	
ASA physical status						
I	18 (8.0)	21 (9.5)	0.836	26 (9.8)	21 (8.1)	0.762
II	178 (78.8)	170 (76.9)		196 (74.2)	198 (76.4)	
III	30 (13.3)	30 (13.6)		42 (15.9)	40 (15.4)	
Operation time, h	3.3 (2.6–4.2)	3.4 (2.6–4.2)	0.427	3.3 (2.6–4.3)	3.3 (2.6–4.1)	0.939
Anesthesia time, h	4.0 (3.3–4.7)	4.3 (3.4–5.2)	0.096	3.7 (2.9–4.5)	3.6 (2.8–4.4)	0.991
Intraoperative infusion, ml	2,000 (1,500–2,425)	2,000 (1,500–2,500)	0.255	2,000 (1,500–2,300)	2,000 (1,500–2,475)	0.045
Estimated blood loss, ml	50 (50–100)	50 (50–100)	0.837	50 (50–100)	50 (50–100)	0.734
Blood transfusion cases	9 (4.0)	17 (7.7)	0.094	14 (5.1)	22 (8.1)	0.168
Duration of hospitalization, days	15 (12–18)	14 (11–16)	0.090	15 (12–17)	14 (11–16)	0.118
Intensive care delirium screening check score	0 (0–1)	0 (0–1)	0.768	0 (0–1)	0 (0–1)	0.716

The data are presented as the number of patients and percentage (%) or median (25th to 75th percentiles).

*The *P* values were calculated by the Mann–Whitney U test, chi-square test, or Fisher exact test.

ASA, American Society of Anesthesiologists.

cognitive dysfunction. Our study showed that delayed neurocognitive recovery incidences in patients with sevoflurane- or propofol-based general anesthesia after a laparoscopic abdominal surgery were not different no matter whether the analysis was performed with per-protocol principle or intention-to-treat principle with various imputation strategies for missing data, suggesting that anesthetic choice is not a modifiable risk factor for delayed neurocognitive recovery. This finding is consistent with that in our animal study.[28]

Table 3. Adverse Events

Characteristics	Propofol (n = 272)	Sevoflurane (n = 272)	*P* Value*
Intraoperative events			
Hypotension†	75 (27.6)	123 (46.4)	< 0.001
Hypertension‡	29 (10.7)	24 (9.1)	0.533
Allergic reaction	2 (0.7)	0 (0)	0.499
Postoperative events			
Postoperative nausea and vomiting	165 (75.0)	174 (77.7)	0.507
Intestinal obstruction	1 (0.4)	0 (0)	> 0.999
Pneumonia	0 (0)	1 (0.4)	0.494
Hypotension	1 (0.4)	0 (0)	> 0.999
Hypertension	0 (0)	1 (0.4)	0.494
Myocardial ischemia	0 (0)	1 (0.4)	0.494

The data are presented as the number of patients and percentage (%).

*The *P* values were calculated by the Fisher exact test. †Systolic blood pressure less than 90 mmHg or a decrease of systolic blood pressure more than 30% from the baseline (average value in the ward) and required intravenous vasopressors, such as ephedrine, dopamine, norepinephrine, or aramine. ‡Systolic blood pressure more than 180 mmHg or an increase of systolic blood pressure more than 30% from the baseline (average value in the ward) and required intravenous agents to decrease blood pressure, such as urapidil, perdipine, metoprolol, or nitroglycerin; Postoperative complications were those that occurred during the whole hospitalization period after anesthesia recovery.

Many clinical studies have determined the role of anesthetic choice in delayed neurocognitive recovery. A meta-analysis analyzed seven studies with a total of 869 patients published before November 2017 and has concluded that there is evidence with low certainty that propofol-based anesthesia may reduce delayed neurocognitive recovery compared with volatile anesthetic-based anesthesia (odds ratio, 0.52 [0.31 to 0.87]).[29] However, the certainty of the evidence was classified to be low by the authors because some studies had insufficiently reported methods of randomization, and one study might have a high risk of attrition bias. In addition, the majority of these previous studies only used the decrease of the mini-mental status examination score to diagnose delayed neurocognitive recovery.[29] Three randomized studies were published after this meta-analysis. A prespecified subanalysis of one center's data of a clinical trial designed to determine anesthetic choice on the outcome of patients after cancer surgery has shown that patients anesthetized with propofol have a lower delayed neurocognitive recovery incidence than those anesthetized with sevoflurane,[32] a finding that is different from our study. Our study is a multicenter randomized study designed specifically to determine whether there was a difference in delayed neurocognitive recovery incidence between patients whose general anesthesia was maintained mainly by propofol or sevoflurane. The type of surgery in our study is laparoscopic abdominal surgery, whereas the previous study included laparoscopic and open

Table 4. Incidence of Delayed Neurocognitive Recovery in Patients Who Received Different Types of General Anesthetics

	Per Protocol				Intention to Treat*			
	Propofol	Sevoflurane	Odds Ratio (95% CI)	*P* Value	Propofol	Sevoflurane	Odds Ratio (95% CI)	*P* Value
	(n = 226)	(n = 221)			(n = 239)	(n = 234)		
Nondelayed neurocognitive recovery	188 (83.2)	175 (79.2)	0.77 (0.48–1.24)	0.279	198 (82.8)	184 (78.6)	0.76 (0.48–1.21)	0.245
Delayed neurocognitive recovery	38 (16.8)	46 (20.8)			41 (17.2)	50 (21.4)		
	Intention to Treat†				Intention to Treat‡			
	Propofol	Sevoflurane	Odds Ratio (95% CI)	*P* Value	Propofol	Sevoflurane	Odds Ratio (95% CI)	*P* Value
	(n = 272)	(n = 272)			(n = 272)	(n = 272)		
Nondelayed neurocognitive recovery	231 (84.9)	221 (81.3)	0.77 (0.49–1.21)	0.253	225 (82.7)	217 (79.8)	0.82 (0.54–1.27)	0.380
Delayed neurocognitive recovery	41 (15.1)	51 (18.7)			47 (17.3)	55 (20.2)		

The data are presented as the number of patients and percentage (%). The *P* value was calculated by the chi-square test. The percentage of delayed neurocognitive recovery in control group was 3.8% (7 of 184), which was significantly different from propofol group and sevoflurane group ($P < 0.001$ for both comparisons).

*The data of patients were analyzed without imputing the missing data. †The data of patients were analyzed with last observation carried forward strategy to impute the missing data. ‡The data of patients were analyzed with the hot-deck imputation strategy for the missing data.

thoracic/abdominal surgery for patients with cancer. In addition, some medications, such as midazolam, dexmedetomidine, glucocorticoids, and nonsteroidal analgesics, that may affect cognitive functions were not permitted in our study but were used in the previous study. These major differences may have led to the different findings between our study and the previous study.[32] Another study showed no difference in delayed neurocognitive recovery incidence in patients with spinal surgery under sevoflurane-based or propofol-based anesthesia.[30] The third study showed that patients anesthetized by sevoflurane had a lower delayed neurocognitive recovery incidence than those anesthetized by propofol after carotid endarterectomy.[45] It is important to note that most of the previous studies have small patient samples (15 to 100 patients per group), are not registered in a publicly accessible server, do not include a nonsurgery control group to adjust the practice effects of repeated testing, and use inappropriate neuropsychological tests to diagnose delayed neurocognitive recovery.[29,30,45,46] Our study is a multicenter study designed to avoid these weaknesses to determine whether anesthetic choice plays a role in delayed neurocognitive recovery.

Associated with the issue of anesthetic choice is the question of whether the depth of general anesthesia plays a role in postoperative cognitive dysfunction. A meta-analysis that included four small studies published before August 2017 did not show a difference in delayed neurocognitive recovery/postoperative cognitive dysfunction rates between patients maintained at deep or light general anesthesia.[47] This meta-analysis combined the information of cognitive impairment assessed within 1 month or at a time point longer than 1 month after surgery. Two studies have published after this meta-analysis. One showed that light anesthesia had advantages,[48] and the other showed that deep anesthesia reduced delayed neurocognitive recovery.[49] Thus, there is no evidence to indicate that the depth of general anesthesia plays a role in delayed neurocognitive recovery/postoperative cognitive dysfunction development.

Interestingly, patients with delayed neurocognitive recovery had a lower mini-mental status examination score than patients without delayed neurocognitive recovery, suggesting that patients with delayed neurocognitive recovery have lower cognitive functions. Also, patients with delayed neurocognitive recovery had worse ASA physical status classification. These results suggest that patients with worse physical status are more likely to have delayed neurocognitive recovery, similar to the finding reported previously.[4] Patients with delayed neurocognitive recovery stayed longer in the hospital, again as shown previously.[4,50] Univariate logistic regression analysis showed that age, ASA physical status classification, mini-mental status examination scores, and duration of hospitalization were predictors for delayed neurocognitive recovery, similar to that reported before.[4] Also, we found that patients with employer's health insurance had a lower delayed neurocognitive recovery incidence, indicating that less financial burden on the family for health care reduces delayed neurocognitive recovery. Finally, a high blood interleukin-6 concentration at 1 h after surgical incision is a risk factor for developing delayed neurocognitive recovery. In fact, interleukin-6 concentration in the blood at this time is the only independent risk factor for delayed neurocognitive recovery as determined by multiple regression model analysis. Surgery-induced interleukin-6 increase has been shown in multiple studies.[51,52] However, its concentration as a risk factor for delayed neurocognitive recovery has not been reported.

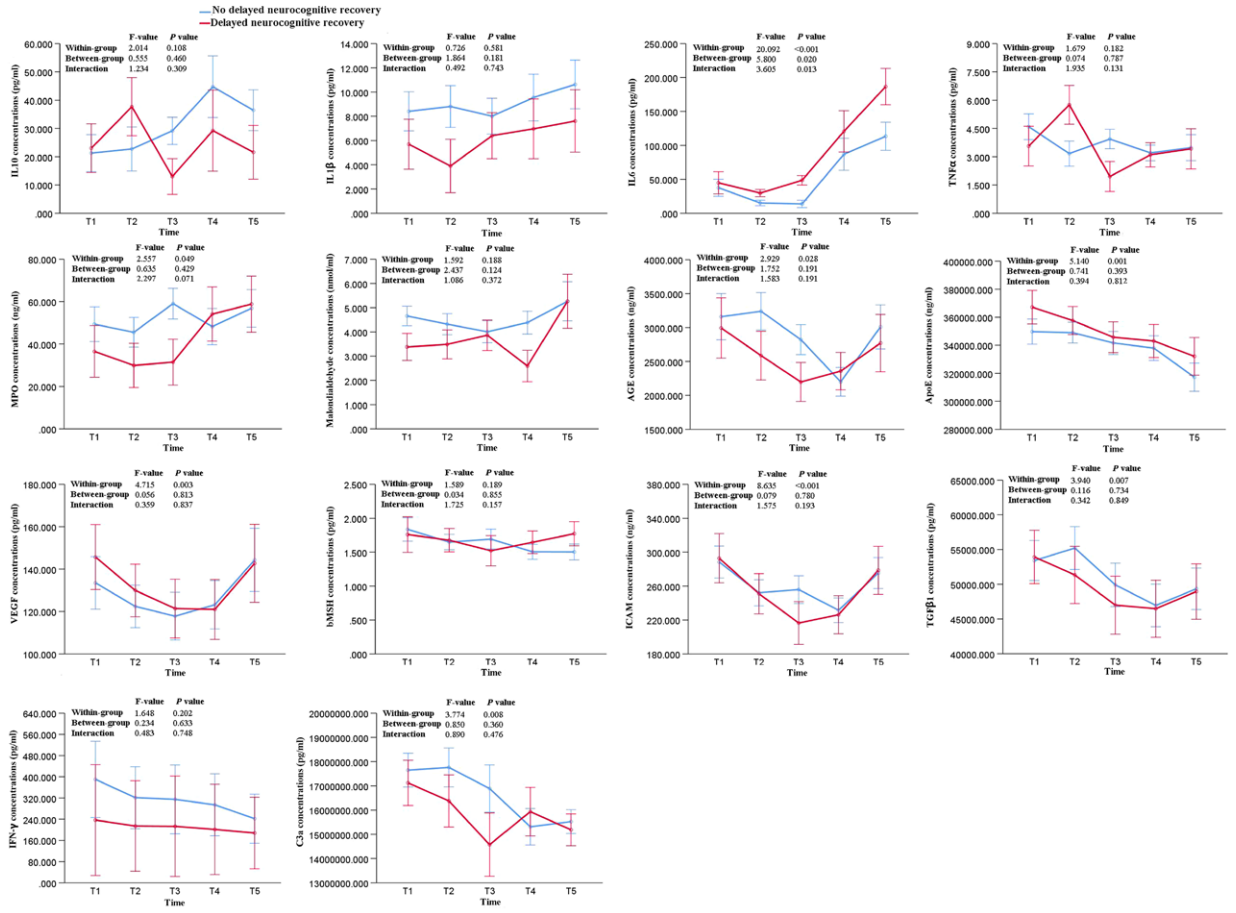

Fig. 2. Comparison of serum cytokines, oxidative stress biomarkers, or immune modulators between patients with or without delayed neurocognitive recovery. The data are presented as the means ± SD. The *P* values are the results from two-way repeated-measures ANOVA with time and group as two factors to be analyzed. The serum concentrations of interleukin (IL)–6 were significantly higher in patients with delayed neurocognitive recovery than those in patients without nondelayed neurocognitive recovery ($P = 0.020$) and had a significant difference among the times from T1 to T5 within the same group of patients ($P < 0.001$). There was a significant interaction between time and group in interleukin-6 changes ($P = 0.013$). T1, before anesthesia; T2, 15 min after endotracheal intubation; T3, 1 h after surgical incision; T4, at the end of surgery; T5, 24 h after surgery. ApoE, apolipoprotein E; AGE, advanced glycation end product; C3a, complement C3a; ICAM, intercellular adhesion molecule; IFN-γ, interferon-γ; MPO, myeloperoxidase; bMSH, β-melanocyte–stimulating hormone; TGF-β1, transforming growth factor β1; TNFα, tumor necrosis factor α; VEGF vascular endothelial growth factor.

Neuroinflammation is considered a critical neuropathological process for postoperative cognitive dysfunction.[17] This consideration is mostly based on results from animal studies.[17] We have shown that surgery on peripheral tissues causes systemic inflammation that then induces neuroinflammation in rodents.[16,28] Consistent with this finding, serum interleukin-6 concentrations were increased after surgery in patients with or without delayed neurocognitive recovery, but the interleukin-6 concentrations were higher in patients with delayed neurocognitive recovery than that in patients without delayed neurocognitive recovery, providing initial evidence that heightened inflammation may be a pathologic process for delayed neurocognitive recovery in humans. There were no changes in the serum interleukin-1β, interleukin-10, and tumor necrosis factor-α within 24 h after the surgery. These results suggest that only selected cytokines, like interleukin-6 in this surgical population, are induced after surgery. Interestingly, the serum concentrations of vascular endothelial growth factor, intercellular adhesion molecule, transforming growth factor-β1, C3α, and advanced glycation end products were first decreased and then recovered after surgery. The first four factors can modulate immune functions. Advanced glycation end products are an oxidative stress marker.[42,43] The reasons for this pattern of change are not known but may indicate a decreased immune function at the end of surgery, which recovers with time after surgery.

Table 5. Univariate Logistic Regression Analysis of Possible Predictive Factors for Delayed Neurocognitive Recovery

Variables	Delayed Neurocognitive Recovery (n = 84)	Nondelayed Neurocognitive Recovery (n = 363)	Univariate Odds Ratio (95% CI)	*P* Value*
Age, yr	65 (62–69)	65 (62–68)	1.05 (1.00–1.10)	**0.044**
Body mass index, kg/m^2	23.4 (20.8–24.8)	22.3 (20.2–24.4)	1.00 (0.97–1.03)	0.904
Mini-mental state examination score	29 (28–30)	29 (29–30)	0.81 (0.71–0.92)	**0.001**
Instrumental activities of daily living score	5 (5–5)	5 (5–8)	0.86 (0.72–1.04)	0.118
Beck depression inventory score	2 (0–5)	2 (0–4)	1.05 (0.99–1.11)	0.089
State-anxiety inventory score	29 (24–35)	30 (26–37)	0.99 (0.97–1.02)	0.710
Trait-anxiety inventory score	29 (25–34)	29 (25–35)	0.98 (0.96–1.01)	0.200
Sex				
Female	23 (27.4)	110 (30.3)	Reference	
Male	61 (72.6)	253 (69.7)	1.15 (0.68–1.96)	0.598
Education				
Elementary	19 (22.6)	93 (25.6)	Reference	
Middle school	24 (28.6)	121 (33.3)	0.97 (0.50–1.88)	0.930
High school	32 (38.1)	123 (33.9)	1.27 (0.68–2.39)	0.451
University/above	6 (7.1)	19 (5.2)	1.55 (0.55–4.4)	0.413
Unknown	3 (3.6)	7 (1.9)	2.10 (0.50–8.9)	0.313
Residence				
Urban	47 (56.0)	215 (59.2)	Reference	
Town	24 (28.6)	115 (31.7)	0.96 (0.56–1.64)	0.892
Rural	13 (15.5)	33 (9.1)	1.80 (0.88–3.68)	0.107
New York Heart Association classification				
I	64 (76.2)	298 (82.1)	Reference	
II	20 (23.8)	64 (17.6)	1.46 (0.82–2.57)	0.435
III	0 (0.0)	1 (0.3)	Not applicable	
Insurance status				
Rural medical insurance	23 (27.4)	67 (18.5)	Reference	
Employer's medical insurance	26 (31.0)	146 (40.2)	0.52 (0.276–0.98)	**0.042**
Free medical service	3 (3.6)	19 (5.2)	0.46 (0.125–1.70)	0.244
Self-pay	32 (38.1)	130 (35.8)	0.72 (0.389–1.32)	0.286
Unknown	0 (0.0)	1 (0.3)	Not applicable	
Surgery				
Upper abdomen/stomach	12 (14.3)	29 (8.0)	Reference	0.059
Middle abdomen/colorectum	66 (78.6)	320 (88.2)	0.50 (0.242–1.03)	0.953
Lower abdomen/uterus	6 (7.1)	14 (3.9)	1.04 (0.322–3.34)	
ASA physical status				
I	5 (6.0)	34 (9.4)	Reference	
II	58 (69.0)	290 (79.9)	1.36 (0.51–3.62)	0.539
III	21 (25.0)	39 (10.7)	3.66 (1.25–10.8)	**0.018**
Anesthesia time, h	4.4 (3.6–5.2)	4.1 (3.3–4.9)	1.07 (0.93–1.23)	0.351
Postoperative PCA				
With fentanyl	35 (41.7)	193 (53.2)	Reference	0.059
With sufentanil	49 (58.3)	170 (46.8)	0.63 (0.389–1.02)	
Duration of hospitalization, day	16 (13–19)	14 (11–17)	1.05 (1.01–1.08)	**0.005**
Interleukin-6 concentration at T3, pg/ml	25.8 (11.2–75.6)	10.9 (6.2–20.3)	1.04 (1.01–1.08)	**0.007**

The data are presented as the number of patients and percentage (%) or median (25th to 75th percentiles). Boldface values indicate $P < 0.05$.

*The *P* values were calculated by the univariate logistic regression analysis.

ASA, American Society of Anesthesiologists; PCA, patient-controlled analgesia.

Perioperative neurocognitive disorder including delayed neurocognitive recovery (the subject of our current study), postoperative delirium, and longer-lasting postoperative cognitive dysfunction has been a focus of recent studies.[17,19] Identifying modifiable risk factors, intervention, and biomarkers for perioperative neurocognitive disorder in humans and determining the mechanisms for this syndrome in animal and human studies will help reduce its occurrence and ultimately improve the outcome of perioperative patients.

One obvious limitation of our study is the unintended low power. A landmark study has shown that 41% of patients who were 60 yr of age or older developed delayed neurocognitive recovery at 7 days after various noncardiac surgeries including minimally invasive surgery.[4] The sample size was calculated assuming a 40% delayed neurocognitive recovery rate and an 80% power to detect a one-third decrease in delayed neurocognitive recovery incidence in one group of patients compared with the other group. Because our study had

Table 6. Multiple Logistic Regression Analysis of Potential Risk Factors for Delayed Neurocognitive Recovery

Characteristics	Multivariate Odds Ratio (95% CI)	*P* Value
Age, yr	1.05 (0.91–1.21)	0.542
Mini-mental state examination score	0.91 (0.66–1.26)	0.555
Insurance	1.16 (0.65–2.05)	0.615
ASA physical status (II/III)	1.75 (0.41–7.41)	0.448
Duration of hospitalization, days	1.02 (0.90–1.16)	0.746
Interleukin-6 concentration at T3, pg/ml	1.04 (1.01–1.07)	**0.007**

Boldface values indicate $P < 0.05$.
ASA, American Society of Anesthesiologists.

20.8% patients with delayed neurocognitive recovery in one group, the power to detect the same magnitude of decrease is decreased to 0.499 with the number of our patients. To achieve 80% power with the incidence in one group, we will need 430 patients in each study group to detect a one-third decrease in delayed neurocognitive recovery incidence in another group. Nevertheless, our study did not show the magnitude of one-third decrease in the propofol-based general anesthesia group, and the delayed neurocognitive recovery incidences were not different between patients anesthetized with propofol or sevoflurane. Thus, our study does not support that the general anesthetic choice may play an important role in delayed neurocognitive recovery development.

Although the incidence of delayed neurocognitive recovery in our study is lower than that in the study using the same method and criteria to diagnose delayed neurocognitive recovery,[4] our incidence is similar to those in other well designed studies. The incidence of delayed neurocognitive recovery for noncardiac surgery patients (60 yr or older) in International Study of Post-Operative Cognitive Dysfunction 1 is 25.8% 7 days after the surgery.[3] The other two very recent studies showed 14.8 to 23.2% of patients to have delayed neurocognitive recovery 7 days after surgery.[32,53]

In summary, our study showed that patients with laparoscopic abdominal surgery under propofol-based anesthesia had a delayed neurocognitive recovery incidence similar to that of patients under sevoflurane-based anesthesia. Anesthetic choice may not be a modifiable factor for delayed neurocognitive recovery. Our study has identified that a high concentration in serum interleukin-6 is an independent risk factor for delayed neurocognitive recovery. This finding provides clinical evidence for the role of inflammation in delayed neurocognitive recovery. Finally, our study has shown that delayed neurocognitive recovery is associated with an increased hospitalization length in Chinese patients, similar to patients in the United States and Australia.[4,50]

Research Support

Supported by grant No. 17ykjc26 from the fundamental research fund for the central universities, an internal fund from each participating institute, and the Baxter International Chinese Branch (Shanghai, China). The fund of the Baxter International Chinese Branch was used to print the data collection form and purchase blood sample collection tubes and a freezer to store blood samples.

Competing Interests

This study was partly sponsored by Baxter International Chinese Branch (Shanghai, China). The company had no role in the study design, data collection, data analysis, data interpretation, or writing of the article. The authors declare no competing interests.

Reproducible Science

Full protocol available at: zz3c@virginia.edu or liyuj@mail.sysu.edu.cn. Raw data available at: zz3c@virginia.edu or liyuj@mail.sysu.edu.cn.

Correspondence

Address correspondence to Dr. Zuo: Department of Anesthesiology, P.O. Box 800710, University of Virginia Health, Charlottesville, Virginia 22908. zz3c@virginia.edu. This article may be accessed for personal use at no charge through the Journal Web site, www.anesthesiology.org.

References

1. Hall M, Schwartzman A, Zhang J, Liu X: Ambulatory surgery data from hospitals and ambulatory surgery centers: United States, 2010. Natl Health Stat Report 2017; 1–15
2. China Health Statistics Yearbook. Beijing, China, Peking Union Medical College Press, The National Health Commission of the People's Republic of China, 2019
3. Moller JT, Cluitmans P, Rasmussen LS, Houx P, Rasmussen H, Canet J, Rabbitt P, Jolles J, Larsen K, Hanning CD, Langeron O, Johnson T, Lauven PM, Kristensen PA, Biedler A, van Beem H, Fraidakis O, Silverstein JH, Beneken JE, Gravenstein JS; ISPOCD Investigators: Long-term postoperative cognitive dysfunction in the elderly ISPOCD1 study: International study of post-operative cognitive dysfunction. Lancet 1998; 351:857–61
4. Monk TG, Weldon BC, Garvan CW, Dede DE, van der Aa MT, Heilman KM, Gravenstein JS: Predictors of cognitive dysfunction after major noncardiac surgery. Anesthesiology 2008; 108:18–30
5. Newman MF, Kirchner JL, Phillips-Bute B, Gaver V, Grocott H, Jones RH, Mark DB, Reves JG, Blumenthal JA; Neurological Outcome Research Group and the Cardiothoracic Anesthesiology Research Endeavors Investigators: Longitudinal assessment of neurocognitive function after coronary-artery bypass surgery. N Engl J Med 2001; 344:395–402

6. Steinmetz J, Christensen KB, Lund T, Lohse N, Rasmussen LS; ISPOCD Group: Long-term consequences of postoperative cognitive dysfunction. Anesthesiology 2009; 110:548–55
7. Evered L, Silbert B, Knopman DS, Scott DA, DeKosky ST, Rasmussen LS, Oh ES, Crosby G, Berger M, Eckenhoff RG; Nomenclature Consensus Working Group: Recommendations for the nomenclature of cognitive change associated with anaesthesia and surgery: 2018. Anesthesiology 2018; 129:872–9
8. Culley DJ, Baxter MG, Yukhananov R, Crosby G: Long-term impairment of acquisition of a spatial memory task following isoflurane-nitrous oxide anesthesia in rats. Anesthesiology 2004; 100:309–14
9. Xie Z, Culley DJ, Dong Y, Zhang G, Zhang B, Moir RD, Frosch MP, Crosby G, Tanzi RE: The common inhalation anesthetic isoflurane induces caspase activation and increases amyloid β-protein level *in vivo*. Ann Neurol 2008; 64:618–27
10. Cao L, Li L, Lin D, Zuo Z: Isoflurane induces learning impairment that is mediated by interleukin 1β in rodents. PLoS One 2012; 7:e51431
11. Rasmussen LS, Johnson T, Kuipers HM, Kristensen D, Siersma VD, Vila P, Jolles J, Papaioannou A, Abildstrom H, Silverstein JH, Bonal JA, Raeder J, Nielsen IK, Korttila K, Munoz L, Dodds C, Hanning CD, Moller JT; ISPOCD2 (International Study of Postoperative Cognitive Dysfunction) Investigators: Does anaesthesia cause postoperative cognitive dysfunction?: A randomised study of regional *versus* general anaesthesia in 438 elderly patients. Acta Anaesthesiol Scand 2003; 47:260–6
12. Edipoglu IS, Celik F: The Associations between Cognitive Dysfunction, Stress Biomarkers, and Administered Anesthesia Type in Total Knee Arthroplasties: Prospective, Randomized Trial. Pain Physician 2019; 22:495–507
13. Williams-Russo P, Sharrock NE, Mattis S, Szatrowski TP, Charlson ME: Cognitive effects after epidural *vs.* general anesthesia in older adults: A randomized trial. JAMA 1995; 274:44–50
14. Nielson WR, Gelb AW, Casey JE, Penny FJ, Merchant RN, Manninen PH: Long-term cognitive and social sequelae of general *versus* regional anesthesia during arthroplasty in the elderly. Anesthesiology 1990; 73:1103–9
15. Zhang J, Tan H, Jiang W, Zuo Z: Amantadine alleviates postoperative cognitive dysfunction possibly by increasing glial cell line–derived neurotrophic factor in rats. Anesthesiology 2014; 121:773–85
16. Zheng B, Lai R, Li J, Zuo Z: Critical role of P2X7 receptors in the neuroinflammation and cognitive dysfunction after surgery. Brain Behav Immun 2017; 61:365–74
17. Eckenhoff RG, Maze M, Xie Z, Culley DJ, Goodlin SJ, Zuo Z, Wei H, Whittington RA, Terrando N, Orser BA, Eckenhoff MF: Perioperative neurocognitive disorder: State of the preclinical science. Anesthesiology 2020; 132:55–68
18. Baranov D, Bickler PE, Crosby GJ, Culley DJ, Eckenhoff MF, Eckenhoff RG, Hogan KJ, Jevtovic-Todorovic V, Palotás A, Perouansky M, Planel E, Silverstein JH, Wei H, Whittington RA, Xie Z, Zuo Z; First International Workshop on Anesthetics and Alzheimer's Disease: Consensus statement: First International Workshop on Anesthetics and Alzheimer's Disease. Anesth Analg 2009; 108:1627–30
19. Berger M, Schenning KJ, Brown CH 4th, Deiner SG, Whittington RA, Eckenhoff RG, Angst MS, Avramescu S, Bekker A, Brzezinski M, Crosby G, Culley DJ, Eckenhoff M, Eriksson LI, Evered L, Ibinson J, Kline RP, Kofke A, Ma D, Mathew JP, Maze M, Orser BA, Price CC, Scott DA, Silbert B, Su D, Terrando N, Wang DS, Wei H, Xie Z, Zuo Z; Perioperative Neurotoxicity Working Group: Best practices for postoperative brain health: Recommendations from the Fifth International Perioperative Neurotoxicity Working Group. Anesth Analg 2018; 127:1406–13
20. Pearn ML, Hu Y, Niesman IR, Patel HH, Drummond JC, Roth DM, Akassoglou K, Patel PM, Head BP: Propofol neurotoxicity is mediated by p75 neurotrophin receptor activation. Anesthesiology 2012; 116:352–61
21. Zuo Z, Johns RA: Inhalational anesthetics up-regulate constitutive and lipopolysaccharide-induced inducible nitric oxide synthase expression and activity. Mol Pharmacol 1997; 52:606–12
22. Xu X, Kim JA, Zuo Z: Isoflurane preconditioning reduces mouse microglial activation and injury induced by lipopolysaccharide and interferon-γ. Neuroscience 2008; 154:1002–8
23. Lee JJ, Li L, Jung HH, Zuo Z: Postconditioning with isoflurane reduced ischemia-induced brain injury in rats. Anesthesiology 2008; 108:1055–62
24. Li H, Yin J, Li L, Deng J, Feng C, Zuo Z: Isoflurane postconditioning reduces ischemia-induced nuclear factor-κB activation and interleukin 1β production to provide neuroprotection in rats and mice. Neurobiol Dis 2013; 54:216–24
25. Archer DP, Walker AM, McCann SK, Moser JJ, Appireddy RM: Anesthetic neuroprotection in experimental stroke in rodents: A systematic review and meta-analysis. Anesthesiology 2017; 126:653–65
26. Cibelli M, Fidalgo AR, Terrando N, Ma D, Monaco C, Feldmann M, Takata M, Lever IJ, Nanchahal J, Fanselow MS, Maze M: Role of interleukin-1β in postoperative cognitive dysfunction. Ann Neurol 2010; 68:360–8
27. Zhang J, Jiang W, Zuo Z: Pyrrolidine dithiocarbamate attenuates surgery-induced neuroinflammation and cognitive dysfunction possibly via inhibition of nuclear factor κB. Neurosci 2014; 261:1–10
28. Zhang J, Tan H, Jiang W, Zuo Z: The choice of general anesthetics may not affect neuroinflammation and

impairment of learning and memory after surgery in elderly rats. J Neuroimmune Pharmacol 2015; 10:179–89
29. Miller D, Lewis SR, Pritchard MW, Schofield-Robinson OJ, Shelton CL, Alderson P, Smith AF: Intravenous *versus* inhalational maintenance of anaesthesia for postoperative cognitive outcomes in elderly people undergoing non-cardiac surgery. Cochrane Database of Syst Rev 2018; 8:CD012317
30. Kletecka J, Holeckova I, Brenkus P, Pouska J, Benes J, Chytra I: Propofol *versus* sevoflurane anaesthesia: Effect on cognitive decline and event-related potentials. J Clin Monit Comput 2019; 33:665–73
31. Hanning CD: Postoperative cognitive dysfunction. Br J Anaesth 2005; 95:82–7
32. Zhang Y, Shan GJ, Zhang YX, Cao SJ, Zhu SN, Li HJ, Ma D, Wang DX; First Study of Perioperative Organ Protection (SPOP1) investigators: Propofol compared with sevoflurane general anaesthesia is associated with decreased delayed neurocognitive recovery in older adults. Br J Anaesth 2018; 121:595–604
33. Lawton MP, Brody EM: Assessment of older people: Self-maintaining and instrumental activities of daily living. Gerontologist 1969; 9:179–86
34. Folstein MF, Folstein SE, McHugh PR: "Mini-mental state": A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12:189–98
35. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J: An inventory for measuring depression. Arch Gen Psychiatry 1961; 4:561–71
36. Bieling PJ, Antony MM, Swinson RP: The state-trait anxiety inventory, trait version: Structure and content re-examined. Behav Res Ther 1998; 36:777–88
37. Bergeron N, Dubois MJ, Dumont M, Dial S, Skrobik Y: Intensive care delirium screening checklist: Evaluation of a new screening tool. Intensive Care Med 2001; 27:859–64
38. Brand N, Jolles J: Learning and retrieval rate of words presented auditorily and visually. J Gen Psychol 1985; 112:201–10
39. Reitan RM: Trail making test results for normal and brain-damaged children. Percept Mot Skills 1971; 33:575–81
40. Bohnen N, Twijnstra A, Jolles J: Performance in the Stroop color word test in relationship to the persistence of symptoms following mild head injury. Acta Neurol Scand 1992; 85:116–21
41. Houx PJ, Shepherd J, Blauw GJ, Murphy MB, Ford I, Bollen EL, Buckley B, Stott DJ, Jukema W, Hyland M, Gaw A, Norrie J, Kamper AM, Perry IJ, MacFarlane PW, Meinders AE, Sweeney BJ, Packard CJ, Twomey C, Cobbe SM, Westendorp RG: Testing cognitive function in elderly populations: The PROSPER study. PROspective Study of Pravastatin in the Elderly at Risk. J Neurol Neurosurg Psychiatry 2002; 73:385–9
42. Brenner DR, Scherer D, Muir K, Schildkraut J, Boffetta P, Spitz MR, Le Marchand L, Chan AT, Goode EL, Ulrich CM, Hung RJ: A review of the application of inflammatory biomarkers in epidemiologic cancer research. Cancer Epidemiol Biomarkers Prev 2014; 23:1729–51
43. Llibre A, Duffy D: Immune response biomarkers in human and veterinary research. Comp Immunol Microbiol Infect Dis 2018; 59:57–62
44. Needham MJ, Webb CE, Bryden DC: Postoperative cognitive dysfunction and dementia: What we need to know and do. Br J Anaesth 2017; 119:i115–25
45. Kuzkov VV, Obraztsov MY, Ivashchenko OY, Ivashchenko NY, Gorenkov VM, Kirov MY: Total intravenous *versus* volatile induction and maintenance of anesthesia in elective carotid endarterectomy: Effects on cerebral oxygenation and cognitive functions. J Cardiothorac Vasc Anesth 2018; 32:1701–8
46. Tang N, Ou C, Liu Y, Zuo Y, Bai Y: Effect of inhalational anaesthetic on postoperative cognitive dysfunction following radical rectal resection in elderly patients with mild cognitive impairment. J Int Med Res 2014; 42:1252–61
47. Lu X, Jin X, Yang S, Xia Y: The correlation of the depth of anesthesia and postoperative cognitive impairment: A meta-analysis based on randomized controlled trials. J Clin Anesth 2018; 45:55–9
48. Hou R, Wang H, Chen L, Qiu Y, Li S: POCD in patients receiving total knee replacement under deep *vs.* light anesthesia: A randomized controlled trial. Brain Behav 2018; 8:e00910
49. Quan C, Chen J, Luo Y, Zhou L, He X, Liao Y, Chou J, Guo Q, Chen AF, Wen O: BIS-guided deep anesthesia decreases short-term postoperative cognitive dysfunction and peripheral inflammation in elderly patients undergoing abdominal surgery. Brain Behav 2019; 9:e01238
50. Silbert BS, Scott DA, Evered LA, Lewis MS, Kalpokas M, Maruff P, Myles PS, Jamrozik K: A comparison of the effect of high- and low-dose fentanyl on the incidence of postoperative cognitive dysfunction after coronary artery bypass surgery in the elderly. Anesthesiology 2006; 104:1137–45
51. Xie X, Xu L, Liu H, Chen W, Zhuang D, Zhang J, Duan S, Zhou W: Positive association between–1021TT genotype of dopamine β hydroxylase gene and progressive behavior of injection heroin users. Neurosci Lett 2013; 541:258–62
52. Zhu Y, Yao R, Li Y, Wu C, Heng L, Zhou M, Yan L, Deng Y, Zhang Z, Ping L, Wu Y, Wang S, Wang L: Protective effect of celecoxib on early postoperative cognitive dysfunction in geriatric patients. Front Neurol 2018; 9:633
53. Cheng XQ, Mei B, Zuo YM, Wu H, Peng XH, Zhao Q, Liu XS, Gu E; POCD Study Group: A multicentre randomised controlled trial of the effect of intra-operative dexmedetomidine on cognitive decline after surgery. Anaesthesia 2019; 74:741–50