

STUDY PROTOCOL

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Effect of intravenous versus inhaled anesthetics on blood-brain barrier dysfunction and neuroinflammation in elderly patients undergoing major surgery: study protocol of a randomized controlled trial

Wongook Wi¹, Hyo-Jin Kim¹, Sira Bang¹, Oh Joo Kweon², Doyeon Kim³ and Eun Jung Oh^{1*} 

Abstract

Background Postoperative cognitive dysfunction (POCD) is one of the major complications after surgery, with devastating clinical outcomes. Although POCD is a condition with a multifactorial pathophysiology, blood-brain barrier (BBB) dysfunction and neuronal injury have been shown to play a critical role, especially in the elderly. Previous studies have demonstrated that the choice of anesthetics affect BBB permeability and neuroinflammation. However, most studies are carried out on animals, with limited research undertaken on humans. Therefore, we will compare the effect of intravenous anesthetics and inhaled anesthetics on BBB dysfunction and the change of inflammatory markers after surgery.

Methods One hundred and fifty-four patients who are 60 years of age or older undergoing major surgery for more than 2 h will be randomly allocated to two anesthetics groups (intravenous, inhaled) in a 1:1 ratio. In the intravenous anesthetics group (group P), propofol will be infused with a target-controlled infusion (TCI) system throughout the entire surgery. In the inhaled anesthetics group (group G), bolus injection of propofol will be administered for loss of consciousness, and simultaneously sevoflurane will be initiated for the maintenance of anesthesia. The primary outcome is the change in serum S100 calcium binding protein β (S100 β) at four time points: before induction of anesthesia, at the end of surgery, 4 h after surgery, postoperative day 1. Secondary outcomes include changes in the inflammatory markers, serum interleukin (IL)-6, IL-8, tumor necrosis factor (TNF)- α , and C-reactive protein; the incidence of delirium; and the change in the cognitive function between groups. In patients pre-scheduled for postoperative intensive care unit admission, the cerebrospinal fluid/serum albumin quotient (Qalb) between the two groups will be compared before and after surgery, and change in inflammatory markers in serum and CSF will be analyzed in relation to the Qalb.

Discussion The current study will compare the effect of intravenous versus inhaled anesthetics on blood-brain barrier permeability and, as a result, the difference in neuroinflammation in elderly patients. Also, the study results will provide additional information to develop intraoperative anesthetic strategies to reduce POCD.

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Trial registration The trial was prospectively registered at Clinical Trials protocol registration with identifier 2310-117-126 on April 9, 2024.

Keywords Blood-brain barrier, Cerebrospinal fluid, Inhaled anesthetics, Intravenous anesthetics, Neuroinflammation, Postoperative cognitive dysfunction, Postoperative delirium, S100 calcium binding protein β (S100 β)

Administrative information

Note: The numbers in curly brackets in this protocol refer to SPIRIT checklist item numbers. The order of the items has been modified to group similar items (see <http://www.equator-network.org/reporting-guidelines/spirit-2013-statement-defining-standard-protocol-items-for-clinical-trials/>).

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Name and contact information for the trial sponsor {5b}	The National Research Foundation (NRF) of Korea. 201 Gajeong-ro, Yuseong-gu, Daejeon 34113 Korea / TEL.82-42-869-6114 / FAX.82-42-869-6777 The Chung-Ang University Research Grants of Korea. 84 Hukseok-ro, Dongjak-gu, Seoul 06974 Korea / TEL.81-2-820-6460
Role of sponsor {5c}	The trial sponsors are not involved in the design, proposal, protocol of the study; collection, analysis, interpretation of data; and in writing and submission of the article.

Introduction

Background and rationale {6a}

Among patients undergoing anesthesia, up to 65% may develop postoperative cognitive dysfunction (POCD) [1, 2] and delirium [3]. Although surgeries are done to increase quality of life, development of postoperative

neurocognitive dysfunction is associated with increased 1-year mortality, comorbidity, functional decline (frailty), prolonged hospital stay, and consequently decreased quality of life [4–6]. Given the high incidence of POCD and its potentially devastating postoperative clinical outcomes, there is a need to understand the pathophysiology and prevent POCD.

POCD is a condition with a multifactorial pathophysiology [7]. The one pathophysiology that may underlie POCD is neuroinflammation [8]. Several studies support that higher levels of postoperative inflammatory cytokine in serum and cerebrospinal fluid (CSF) of patients are associated with postoperative neurocognitive dysfunction [8, 9]. Usually, the blood-brain barrier (BBB) serves as a physical and chemical barrier that separates the brain from systemic inflammation. However, an animal study has shown that dysfunction of the BBB commonly occurs after surgery, causing peripheral immune cells to migrate to the brain, leading to neuroinflammation [10]. Therefore, recent studies have shown that increased permeability of the BBB after surgery plays a critical role in the development of POCD, especially in the elderly [11, 12].

In addition, some studies show that the choice of anesthetics affect BBB permeability and neuroinflammation [13, 14]. However, the effect of the type of anesthetics on BBB dysfunction and neuroinflammation are mostly studied in animal studies and human studies are still limited. In the present study, we designed a randomized controlled clinical study to compare the effect of intravenous anesthetics (propofol) and inhaled anesthetics (sevoflurane) on BBB dysfunction and neuronal injury in relation to the change of inflammatory markers after surgery. Furthermore, we will analyze the association between anesthetics and delirium or POCD.

Objectives {7}

The aim of the present study is to compare the blood-brain barrier injury marker S100 β between the intravenous anesthetics group and the inhaled anesthetics group in patients aged 60 years and over undergoing major surgery for more than 2 h. Also, we will investigate the difference in markers of neuronal injury and inflammation in blood or CSF within 24 h after surgery and compare the perioperative neurocognitive test scores

between baseline and 3 months after surgery between the two groups.

Trial design {8}

This is a prospective, parallel-arm, double-blinded, randomized controlled superiority trial. Participants will be randomly assigned into intravenous anesthetics group or inhaled anesthetics group in 1:1 ratio.

Methods: participants, interventions and outcomes **Study setting {9}**

The present study will be conducted in the Chung-Ang University Gwangmyeong Hospital (academic hospital), Gwangmyeong, Gyeonggi-do, South Korea.

Eligibility criteria {10}

We will enroll patients 60 years of age or older who are scheduled for major surgery under general anesthesia for more than 2 h. The exclusion criteria are as follows: history of dementia, history of mental disorder, history of cerebrovascular disease, history of brain surgery, patient taking psychiatric medications, and patient refusal.

Who will take informed consent? {26a}

The investigators will judge the eligibility of the patient at the time when the surgery schedule is registered. One of the research team members (EJO) will instruct on the study protocol and obtain informed consent from the participants.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

Blood sample (3 mL) will be obtained at predetermined time points (BL-1, before induction of anesthesia; BL-2, at the end of surgery; BL-3, 4 h after the end of surgery; BL-4, postoperative day 1). CSF samples will be obtained for patients scheduled for postoperative intensive care unit (ICU) admission after the surgery. CSF samples (3 mL) will be obtained at predetermined time points (CSF-1, before induction of anesthesia; CSF-2, at the end of surgery). We will explain the amount, timing, and storage plan of the biological specimens and obtain informed consent from all participants in advance.

Interventions

Explanation for the choice of comparators {6b}

The intravenous anesthetics (propofol) and the inhaled anesthetics (sevoflurane) are the commonly used anesthetics. However, the effects of the two anesthetics on the

neuronal and blood-brain barrier injuries are still controversial. Therefore, we want to compare the effect of the intravenous anesthetics (propofol) and the inhaled anesthetics (sevoflurane) on the neuronal and the blood-brain barrier injuries.

Intervention description {11a}

The study participants from both groups will follow the same study protocol, except for the type of anesthetics used during the surgery. The study protocol is as follows. Study participants will be prohibited from using any pre-medication on the day of surgery, including anesthetics such as midazolam, remimazolam, and dexmedetomidine, as well as psychiatric medications. After applying standard intraoperative monitoring devices including electrocardiography (ECG), pulse oximetry, non-invasive blood pressure (NIBP), and electroencephalography (EEG) with Sedline patient status index (PSI) monitors (Masimo, Irvine, CA), the first blood sample will be collected in both groups (BL-1).

For induction of anesthesia, propofol (Fresofol MCT/LCT 2%; Fresenius Kabi Korea) will be infused with a target-controlled infusion (TCI) system at the effect-site concentration of $5.0 \mu\text{g}\cdot\text{mL}^{-1}$ in the intravenous anesthetics group (group P). In the inhaled anesthetics group (group G), propofol ($1.5\text{--}2 \text{ mg}\cdot\text{kg}^{-1}$) will be administered in bolus for loss of consciousness, and simultaneously sevoflurane would be initiated. Remifentanyl will be infused from the beginning of the induction of general anesthesia, at an effect-site concentration of $3.0 \text{ ng}\cdot\text{mL}^{-1}$ in both groups. TCI will be performed on the basis of a pharmacokinetic model developed by Schneider for propofol [15] and Minto for remifentanyl [16]. After loss of consciousness, $0.6\text{--}0.8 \text{ mg}\cdot\text{kg}^{-1}$ of rocuronium will be administered to achieve neuromuscular blockade and patient's airway will be secured using endotracheal intubation. For maintenance of general anesthesia, the target effect-site concentration of propofol will be adjusted in group P and sevoflurane will be adjusted in group G. In both groups, the depth of anesthesia will be guided by Sedline PSI value between 25 and 50. For analgesia, remifentanyl will be infused at an effect-site concentration adjusted between 0 and $5.0 \text{ ng}\cdot\text{mL}^{-1}$ throughout the surgery. If the Sedline PSI value remains within the target range, remifentanyl could be increased, or the infusion could be halted temporarily based on the vital signs. Fluid administration will be controlled based on pulse pressure variation. Vasoactive or inotropic drugs will be administered, if necessary, in order to maintain mean arterial pressure of higher than 65 mmHg.

For postoperative pain control, fentanyl ($0.5 \mu\text{g}\cdot\text{kg}^{-1}$) will be administered 30 min before the end of surgery, and remifentanyl infusion will be immediately stopped.

At the end of the surgery, neuromuscular blockade will be reversed with 4 mg·kg⁻¹ of sugammadex, and the endotracheal tube will be extubated after confirming the patient's ability to obey and to recover self-respiration. The patient will be monitored for 30 min at post-anesthesia care unit (PACU) and will be transferred to the general ward. Postoperative pain management will be provided by a patient-controlled analgesia pump, which is established with only fentanyl (Fentanyl, Hana Pharmaceutical, Seoul, South Korea) and antiemetics.

The blood samples will be collected at four predetermined time points: before induction of anesthesia (BL-1), at the end of surgery (BL-2), 4 h after the end of surgery (BL-3), and postoperative day 1 (BL-4). In patients who are pre-scheduled for ICU admission postoperatively, CSF samples will be collected before induction of anesthesia (CSF-1) and at the end of surgery (CSF-2) in addition to the blood samples described above. For each patient, we will collect a total of 3 ml of CSF samples at each time point. All lumbar punctures will be performed using a 25-gauge Quincke needle in the lumbar intervertebral space (L3–4 or L4–5) with sterile technique. The CSF samples will be used for biochemical analysis, including albumin counts and biomarkers.

Criteria for discontinuing or modifying allocated interventions {11b}

The study protocol will be suspended in cases of unexpected surgery cancelation, inability to finish the preoperative baseline neurocognitive assessment, violation of the study protocol, serious adverse events, and voluntary withdrawal of informed consent.

Strategies to improve adherence to interventions {11c}

Not applicable. The interventions will be carried out during general anesthesia and without the patients' recognition.

Relevant concomitant care permitted or prohibited during the trial {11d}

No premedication is allowed on the day of surgery. Also, midazolam, remimazolam, and dexmedetomidine which are known to affect the postoperative neurocognitive function will be prohibited during the study period.

Provisions for post-trial care {30}

Not applicable. The interventions applied to participants in both groups are anesthesia methods currently used in daily clinical practice. Thus, the patients will be strictly managed according to our institutional standard protocol.

Outcomes {12}

The primary outcome is the change of serum S100 calcium binding protein β (S100 β) at predetermined time points (BL-1, before induction of anesthesia; BL-2, at the end of surgery; BL-3, 4 h after surgery; BL-4, postoperative day 1) between the two groups. Secondary outcomes include concentration change of serum interleukin-6 (IL-6), interleukin-8 (IL-8), tumor necrosis factor- α (TNF- α), and C-reactive protein (CRP) between the two groups. In patients who are pre-scheduled for postoperative ICU admission, the CSF-serum albumin ratio (Qalb) will be compared between groups from CSF samples collected before induction of anesthesia (CSF-1) and at the end of surgery (CSF-2). Also, the changes of the inflammatory markers in serum and CSF were compared in relation to the value of Qalb.

Also, the incidence of delirium within the first 7 postoperative days or until discharge and change in neurocognitive function between before and 3 months after surgery will be compared between groups.

Participant timeline {13}

The timeline of enrollment, intervention, and assessment for the study participants are presented in Figs. 1 and 2.

Sample size {14}

The sample size was calculated based on a previous randomized controlled study result. In a study evaluating the difference of plasma S100 β between propofol and sevoflurane in patients receiving laparoscopic cholecystectomy [17], postoperative S100 β at the end of surgery were 261.93 ± 44.31 pg·mL⁻¹ and 282.67 ± 38.67 pg·mL⁻¹, respectively. Based on the result, we calculated an effect size of 0.499. With a significance level of 0.05 on both-sides and a power of 0.8, the number of cases needed would be 65 per group. Considering the dropout rate of 15%, we planned to recruit 77 cases in each group for a total of 154 cases. The sample size was calculated using the PASS (NCSS, LLC, Kaysville, UT, USA).

Recruitment {15}

Patients will be informed of the study objectives, procedural protocols, potential risks, and benefits of each intervention in the pre-anesthesia evaluation clinic. The principal investigator (EJO) will screen patients 60 years of age or older who are scheduled for major surgery under general anesthesia for more than 2 h at Chung-Ang University Gwangmyeong Hospital. Enrollment will be carried out in a consecutive fashion using a preassigned randomization table.

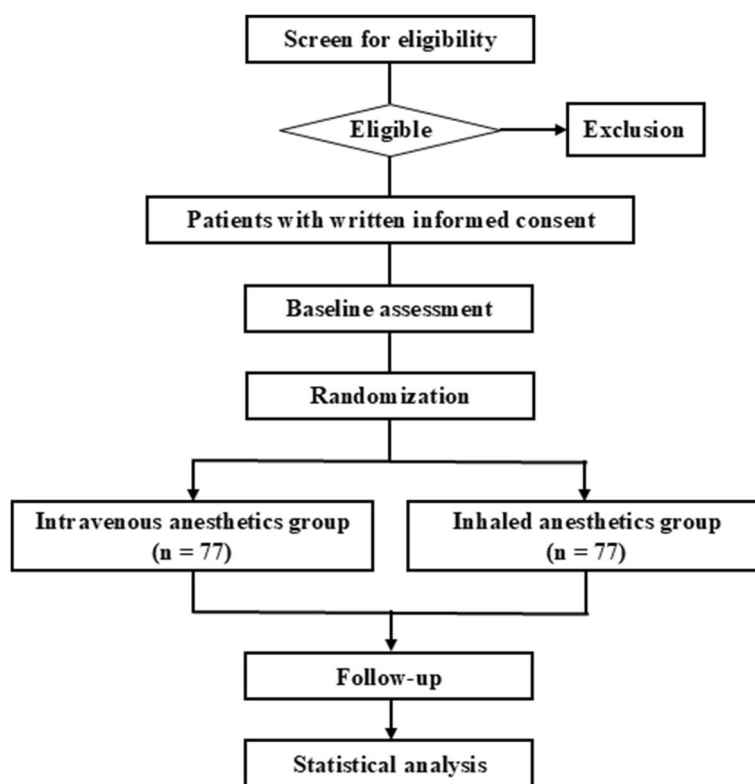


Fig. 1 Study flow diagram

Assignment of interventions: allocation

Sequence generation {16a}

The eligible patients will be randomly assigned to either the group P or the group G, using computer-generated block randomization sequence (PASS, version 2023) with an allocation ratio of 1:1.

Concealment mechanism {16b}

The allocation information will be sealed in an opaque envelope and stored in a cabinet with lock in the research office. Only the independent statistician has access to the randomization list and allocation concealment. Randomization information will be managed confidentially, so it is not disclosed to the blinded assessor.

Implementation {16c}

After obtaining written informed consent, an investigator (EJO) will assign the participants to one of the two groups according to the randomization table. Only the enrolment information will be shared with the research team members without the group allocation

information. On the day of surgery, the attending anesthesiologist will open the sealed envelope with the allocation information to prepare the anesthetic medication according to the study protocol.

Assignment of interventions: blinding

Who will be blinded {17a}

The attending anesthesiologist who is in charge of the intraoperative management of the study participants and the principal investigator (EJO) who is in charge of enrollment, randomization, and adverse event monitoring related to the study protocol will not be blinded. Registered clinical research coordinator (CRC), other researchers, and study participants will be blinded.

Procedure for unblinding if needed {17b}

Not applicable. Attending anesthesiologists are not blinded and will deal with the adverse events related to the study procedure with the principal investigator (EJO).

Data collection and management

Plans for assessment and collection of outcomes {18a}

All outcome assessments will be carried out by the blinded research team personnel. Intraoperative blood

STUDY PERIOD								
	Enrollment	Allocation	Post-Allocation					
Time Points	T(-1)	Surgery day	T0	T1	T2	T3	T4 or D	T5
ENROLLMENT:								
Eligibility Screen	X							
Informed Consent	X							
Allocation		X						
INTERVENTIONS:								
Inhaled Anesthetics			X					
Intravenous Anesthetics			X					
ASSESSMENTS								
Serum Collection			X	X	X	X		
CSF Collection			X	X				
KT-MoCA	X							X
Delirium					X	X	X	

Fig. 2 Timeline of enrollment, interventions, and assessments. T(-1), within 1 week before surgery; T0, before induction of anesthesia; T1, at the end of surgery; T2, 4 h after surgery; T3, postoperative day 1; T4, postoperative day 7; D, discharge; T5, 3 months after surgery; CSF, cerebrospinal fluid; KT-MoCA, Korean version of Telephone-Montreal Cognitive Assessment

samples and CSF samples will be collected by dedicated investigators (HJK and WW), and postoperative blood samples will be collected by a registered CRC (YNM). All biological specimens will be aliquoted and stored in an appropriate fashion described in the collection plan section by dedicated investigators (OJK) in the department of laboratory medicine for analysis. The BBB dysfunction and the neuronal injury marker, serum S100 β , are measured by an electrochemiluminescence immunoassay, and the inflammation cytokines in serum, such as IL-6, IL-8, and TNF- α , are measured by enzyme-linked immunosorbent assay [18]. The measurement of the albumin levels in CSF and serum was performed by an immunonephelometry. The neurocognitive function will be assessed by a trained clinical research coordinator (YNM) using the Korean version of Telephone-Montreal Cognitive Assessment (KT-MOCA) [19] within 1 week before the surgery and 3 months after the surgery. KT-MOCA is a simple and validated cognitive screening tool which is scored on a scale of 0 to 22, with higher scores indicating better cognitive function. Cognitive impairment is defined as a KT-MOCA score less than

18. Also, the incidence of delirium will be assessed using the Confusion Assessment Method [20] and Confusion Assessment Method for the Intensive Care Unit [21] by a formally trained blinded nurse during the first 7 postoperative days or until discharge.

Plans to promote participant retention and complete follow-up {18b}

During the pre-anesthesia evaluation clinic visit, researchers will explain the intraoperative intervention and postoperative follow-up in detail. The 3-month follow-up KT-MOCA schedule will be informed to the study participants prior to discharge, and an additional text message will be sent 1–2 days prior to the phone call. The dedicated investigator (YNM) will conduct KT-MOCA test with careful consideration of their individual status.

Data management {19}

Patient consent, human material research consent, and paper case report form (CRF) will be stored in a cabinet

with lock in the research office. Once the enrollment is finished, paper CRF will be converted to an electronic CRF (DK). Only the research team members have access to the electronic CRF. All process of data acquisition, conversion, and storage will be supervised for consistency by a blinded independent researcher (SB).

Confidentiality {27}

Personal data, including name and phone number, will be anonymized and identified by a predetermined numeric code assigned for each study participant. The predetermined numeric code will be recorded in the subject identification log, and only the principal investigator (EJO) has access to the key to the subject identification log. All study-related forms will be securely stored in a locked filing cabinet in the custody of the principal investigator.

Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

Three milliliters of blood samples will be collected using standard venepuncture or an indwelling line for each predetermined time points (before induction of anesthesia, at the end of the surgery, 4 h after the surgery, postoperative day 1). Three milliliters of CSF samples will be additionally collected for predetermined time points (before induction of anesthesia, at the end of the surgery) in patients who are scheduled for postoperative ICU admission. All blood samples and CSF samples will be collected, labeled with predetermined numeric code, and sent to the department of laboratory medicine right after acquisition. Researcher (OJK) will centrifuge and store aliquots at -80°C until the unified determination. All human materials collected for research purposes will be analyzed for markers of BBB dysfunction and neuroinflammation.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

The normality of data distribution will be examined using the Shapiro-Wilk test. Continuous variables will be presented as mean $\pm$ standard deviation or median with an interquartile range, as appropriate. Categorical variables will be presented as numbers with percentages.

The primary outcome, effect of anesthetics on changes in S100 β from preoperative level, will be tested using the repeated-measures one-way analysis of variance (ANOVA), and Student's *t*-test will be used to compare the significant change between the preoperative level and

the level at specific postoperative time point between groups. Other inflammatory markers of serum and CSF acquired at predetermined time points will be compared using the same statistical method. The incidence of POCD and delirium will be presented as a categorical variable, and to compare between two intervention groups, the Chi-square test or the Fisher's exact test will be used as appropriate. All analysis will be analyzed using NCSS 2023 (LLC. Kaysville, UT, USA).

Interim analyses {21b}

Not applicable. No interim analyses are to be performed.

Methods for additional analyses (e.g., subgroup analyses) {20b}

Subgroup analysis will be performed based on age (older vs. younger) [22] and preoperative neurocognitive function (cognitive impairment vs. normal) [23]. Statistical tests will be adjusted for multiple comparisons using Bonferroni correction.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

All randomized participants will be included in the main analyses. An intention-to-treat analysis will be carried out relating to any protocol non-adherence or dropouts. There is possibility of missing blood or CSF samples due to procedural difficulties. In these cases, missing data will not be replaced.

Plans to give access to the full protocol, participant-level data, and statistical code {31c}

The present study protocol is publicly available on <https://clinicaltrials.gov>. Individual participant data that underlies the results of this study can be considered by the corresponding author upon reasonable request.

Oversight and monitoring

Composition of the coordinating center and trial steering committee {5d}

The coordinating center is the Department of Anesthesiology and Pain Medicine of the Chung-Ang University Gwangmyeong Hospital, Gwangmyeong, Korea. The trial steering committee consists of the principal investigator (EJO) and sub-investigators (HJK, WW, OJK) who are responsible for recruiting participants, conducting day-to-day study, and organizing data. Any decisions needing to be taken regarding the study will be done with the consensus of the entire research team.

Composition of the data monitoring committee, its role and reporting structure {21a}

The data will be monitored by an independent data monitoring committee composed of the IRB of the Chung-Ang University Gwangmyeong Hospital. The IRB is independent of the sponsor and competing interests of the study.

Adverse event reporting and harms {22}

The interventions performed in the current study include selecting one of the anesthetic drugs commonly used in daily clinical practice. As a result, there will be no increased risk for the study participants related to the intervention. However, adverse events that can occur during the blood and the CSF sample collection process will be monitored. Any adverse events will be treated immediately according to the routine practice, and the patients will be followed up until they are completely resolved, or the therapy is terminated. Severe adverse events will be reported to the ethical committee as soon as possible.

Frequency and plans for auditing trial conduct {23}

Regular auditing will not be conducted for the present study. Instead, protocol adherence and data management will be monitored by the IRB committee on a regular basis. Also, the National Research Foundation (NRF) of Korea, the funder of this study, may audit at any time.

Plans for communicating important protocol amendments to relevant parties (e.g., trial participants, ethical committees) {25}

Any amendments to the protocol will be posted in the trial registry after approval by the IRB.

Dissemination plans {31a}

The study results will be disseminated via conference presentation and peer-reviewed journal publication.

Discussion

Recently, the age of patients undergoing surgery has increased, following the increase in the elderly population. In this elderly population, perioperative neurocognitive disorders, encompassing delirium and POCD, are a major challenge after surgery. Despite the advances in surgical technology and anesthesia care, surgery usually induces systemic inflammation. Systemic inflammation activates cellular and humoral signaling, leading to a transient increase in BBB permeability and inducing inflammatory mediators to rapidly reach the brain [10, 24, 25]. This activation of inflammation in the brain, so called neuroinflammation, may be one of the key

processes in the development of POCD, especially in the elderly patients [8].

Previous studies have demonstrated a positive correlation between POCD and neuroinflammation biomarkers in serum [18, 26] and CSF [10, 12, 18]. Moreover, an increase in biomarkers indicating BBB dysfunction in the perioperative period was associated with postoperative delirium and the severity of delirium [12]. Therefore, avoiding BBB dysfunction and neuroinflammation may be the potential therapeutic target to reduce the incidence of POCD. However, the preceding relationship between BBB dysfunction and neuroinflammation has not been elucidated.

In some human studies, neuroinflammation was influenced by the choice of anesthetics [17, 27, 28]. Furthermore, in animal studies, the protective effect of propofol on neuroinflammation was demonstrated via either decreasing BBB breakdown [13, 14, 29] or enhancing astrocyte function [30]. Although a recent meta-analysis showed that the postoperative inflammatory response did not change significantly depending on the anesthetic drugs [31], the studies included in the meta-analysis were studies with relatively small sample sizes and a wide range of ages. To our knowledge, no prior human study has investigated the impact of anesthetic drugs on temporal changes in BBB permeability and whether it is a determinant for the differences in response to neuroinflammation. Therefore, in the present study, we will compare the effect of two types of anesthetics, intravenous (propofol) versus inhaled anesthetics (sevoflurane), on the BBB dysfunction and neuroinflammation based on immediate postoperative serum and CSF biochemical markers.

In this regard, the primary outcome of the present study is the change of serum 100 calcium binding protein β (S100 β) between the two groups. S100 β is a neuronal injury marker which is thought to precisely reflect the degree of both BBB dysfunction and neuronal injury [32]. Under normal physiologic conditions, S100 β is primarily produced by astrocytes in the brain and does not cross the BBB, maintaining a concentration of CSF about 100 times higher than that of blood [33]. Once the BBB is disrupted, S100 β diffuses into the bloodstream, increasing the plasma levels of S100 β . However, as the elimination half-life of S100 β is relatively short [32], the plasma levels of S100 β would reflect the rapid changes in BBB permeability. Moreover, this marker has been validated in predicting neuronal injury in various situations, including circulatory arrest [34], major surgery [18], and minor surgery [17]. Taylor et al. demonstrated that changes in plasma S100 β level after surgery are directly associated with the incidence and the severity of postoperative delirium [12]. In a recent meta-analysis, it was

found that the POCD group had a notably higher postoperative plasma S100 β level compared to the control group [35]. Therefore, in the current study, we selected S100 β as the marker of BBB dysfunction and neuronal injury in the immediate postoperative period.

Additionally, to better understand the effect of anesthetics on BBB permeability, we will evaluate whether the BBB permeability changes in patients exposed to the specific anesthetics for more than 2 h by the changes in Qalb before and after surgery. Moreover, we will evaluate the changes in inflammatory markers in serum and CSF following surgery using designated anesthetics to each group. We hypothesized that all inflammatory markers would be higher at postoperative period compared to baseline and is proportionate to the degree of BBB permeability. As a consequence, patients with BBB dysfunction identified with Qalb or S100 β would exhibit disproportionately higher increase in inflammatory markers in CSF compared to plasma.

The present study has several limitations. First, the type of surgical procedure is not restricted. Although we include patients undergoing surgery for more than 2 h, the inflammatory response may appear differently depending on the type of surgery. To minimize the surgery-related confounders, we will limit surgeries to major surgeries. Second, CSF samples are not collected in all participants. For patient safety, only patients who will be admitted to the intensive care unit will be included for CSF sample collection and analysis. The number of patients in each group may ultimately be small. Third, since this is a single center study, external validation is required for generalization.

Despite the limitations of the current study, the design and the method to compare the effect of intravenous versus inhaled anesthetics on blood-brain barrier permeability and neuroinflammation in elderly patients are appropriate and will provide additional information to develop intraoperative anesthetic strategies to reduce POCD.

Trial status

The study is in the recruitment stage at the time of the manuscript submission. The protocol described in this paper was approved by the IRB on January 3, 2024 (version 1.0). Recruitment started in April 2024 and is expected to be completed around September 2024.

Abbreviations

POCD	Postoperative cognitive dysfunction
CSF	Cerebrospinal fluid
BBB	Blood-brain barrier
ICU	Intensive care unit
ECG	Electrocardiography
NIBP	Non-invasive blood pressure

EEG	Electroencephalography
PSI	Patient status index
TCI	Target-controlled infusion
PACU	Post-anesthesia care unit
IL-6	Interleukin-6
IL-8	Interleukin-8
TNF- α	Tumor necrosis factor- α
CRP	C-reactive protein
Qalb	CSF-serum albumin ratio
CRC	Clinical research coordinator
KT-MOCA	Korean version of Telephone-Montreal Cognitive Assessment
CRF	Case report form
ANOVA	Analysis of variance
IRB	Institutional review board
NRF	National Research Foundation

Acknowledgements

Not applicable.

Authors' contributions {31b}

EJ Oh is the principal investigator. She conceived the study and led the proposal and protocol development. HJ Kim, W Wi, and S Bang contributed to the study design and to the development of the proposal. OJ Kwon contributed to the protocol development. D Kim contributed to organizing and managing collected data. EJ Oh and W Wi drafted the manuscript, and HJ Kim, OJ Kwon, and S Bang critically reviewed the manuscript. All authors read and approved the final manuscript.

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Data availability {29}

The data supporting the findings of the present study will be made available upon reasonable request from the corresponding author, after deidentification.

Declarations

Ethics approval and consent to participate {24}

The IRB of Chung-Ang University Gwangmyeong Hospital approved the study protocol on January 3, 2024 (No. 2023–0214). Written informed consent will be obtained from all participants.

Consent for publication {32}

The participant information materials and informed consent form are available from the corresponding author on request.

Competing interests {28}

The authors declare that they have no competing interests.

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