International Journal of General Medicine

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STUDY PROTOCOL

Effect of $rScO_2$-Guided Blood Pressure Management on Postoperative Complications in Elderly Patients After Major Noncardiac Surgery: Protocol for a Randomized Controlled Trial

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Background: Postoperative complications are common after major surgical procedures, leading to increased morbidity and mortality. Regional cerebral oxygen saturation ($rScO_2$) reflects cerebral and global perfusion, and thus it can be used to guide hemodynamic management. We aim to explore the effect of $rScO_2$-guided blood pressure management strategy on postoperative major complications in older adults who undergo major noncardiac surgery.

Methods: This randomized controlled clinical trial includes a total of 400 elderly patients receiving major noncardiac surgery and general anesthesia. Patients will be randomized (1:1) to one of two blood pressure management groups: a standard care group (targeting mean arterial pressure >65 mmHg or within 20% of baseline value), and a $rScO_2$-guided group (absolute value of $rScO_2$ >60% or decrease in $rScO_2$ <10% of baseline). The primary outcome is the composite outcome of major complications (including infectious, respiratory, neurologic, cardiovascular, renal, thromboembolic gastrointestinal, and surgical complications) and deaths within the first 7 days after surgery. Secondary outcomes include the individual components of the primary outcome by day 7 after surgery and 30-day mortality. Data will be analyzed in the modified intention-to-treat population.

Discussion: This study will provide evidence for improving postoperative outcomes using the $rScO_2$-guided blood pressure management among older adults who undergo major noncardiac surgery.

Trial Registration: Chinese Clinical Trial Registry (Identifier: ChiCTR2200060816).

Plain Language Summary: This is a protocol for a prospective, randomized, controlled clinical trial to evaluate the use of intraoperative individualized regional cerebral oxygen saturation ($rScO_2$) optimization for blood pressure management in older adults undergoing major noncardiac surgery.

The primary focus of this trial is the composite outcome of major complications (including infectious, respiratory, neurologic, cardiovascular, renal, thromboembolic gastrointestinal, and surgical complications) and deaths within the first 7 days after surgery. The secondary outcomes are the individual components of the primary outcome by day 7 after surgery and 30-day mortality.

The findings of this trial will provide clinical evidence for the $rScO_2$-guided blood pressure management to improve postoperative outcomes in older patients who are scheduled for major noncardiac surgery.

Keywords: regional cerebral oxygen saturation, blood pressure management, postoperative major complications, major noncardiac surgery, elderly patients

Received: 18 June 2023
Accepted: 18 August 2023
Published: 25 August 2023

Introduction

With the increase in life expectancy and improved medical technology, more elderly patients are receiving major surgical procedures that undoubtedly increase the risk of postoperative morbidity and mortality.[1,2] However, postoperative complications are common, which lead to prolonged hospitalization, increased healthcare costs, compromised quality of life, and increased deaths after surgery.[3,4] Perioperative hemodynamic management is crucial for patient outcomes after surgery. Previous studies have suggested that optimizing fluid therapy, increasing cardiac output and oxygen delivery, and appropriate blood pressure management may reduce postoperative complications.[5–7]

Regional cerebral oxygen saturation ($rScO_2$) monitoring by non-invasive near-infrared spectroscopy has been used recently to illustrate the balance between oxygen demand and supply in brain. Low $rScO_2$ values were associated with perioperative low hemoglobin concentration, cognitive dysfunction, prolonged recovery, and increased complications and deaths after cardiac and noncardiac surgery.[8–11] With the index organ of brain, $rScO_2$ has been considered to reflect global perfusion, and thus strategies that optimize $rScO_2$ may improve perfusion in vital organs and patients' clinical outcomes.[12,13]

In this context, we design this randomized clinical study to evaluate the use of $rScO_2$-guided blood pressure management strategy through individualized $rScO_2$ optimization among older adults who undergo major noncardiac surgery. We hypothesize that the $rScO_2$-guided blood pressure management would reduce postoperative major complications in this patient population.

Methods

Study Design

This prospective randomized controlled trial is carried out at two medical centers of the First Affiliated Hospital of Soochow University, China. A total of 400 elderly patients undergoing major noncardiac surgery will be recruited. Figure 1 shows the study flowchart. We report this protocol according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guideline (Table S1).[14]

Ethics and Dissemination

This trial was approved by the Ethics Committee of the First Affiliated Hospital of Soochow University (Approval No. 2022-044) on April 28, 2022, and then registered on the Chinese Clinical Trial Registry (http://www.chictr.org.cn, ChiCTR2200060816) on June 12, 2022. Due to the COVID-19 pandemic and shortage of staff, we only recruited 70 patients (17.5% of total) by the time of this submission. We expect to complete patient recruitment before December 31, 2024. All patients will provide their written informed consent. Patients can withdraw their consent at any time during the study. This study follows the Declaration of Helsinki. The study results will be published in a peer-reviewed journal.

Inclusion Criteria

1. Older patients aged 60−90 years;
2. ASA classification II or III;
3. Undergoing major noncardiac surgery under general anesthesia.

Major noncardiac surgical procedures include abdominal, urologic, gynecologic, and orthopedic procedures, with an estimated surgical duration ≥2 hours and hospital stay ≥2 days.

Exclusion Criteria

1. Emergent surgery;
2. Use of spinal and/or epidural anesthesia only;
3. Uncontrolled hypertension, which is defined as systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥110 mmHg;
4. Acute cardiovascular events including acute or decompensated heart failure, acute coronary syndrome;

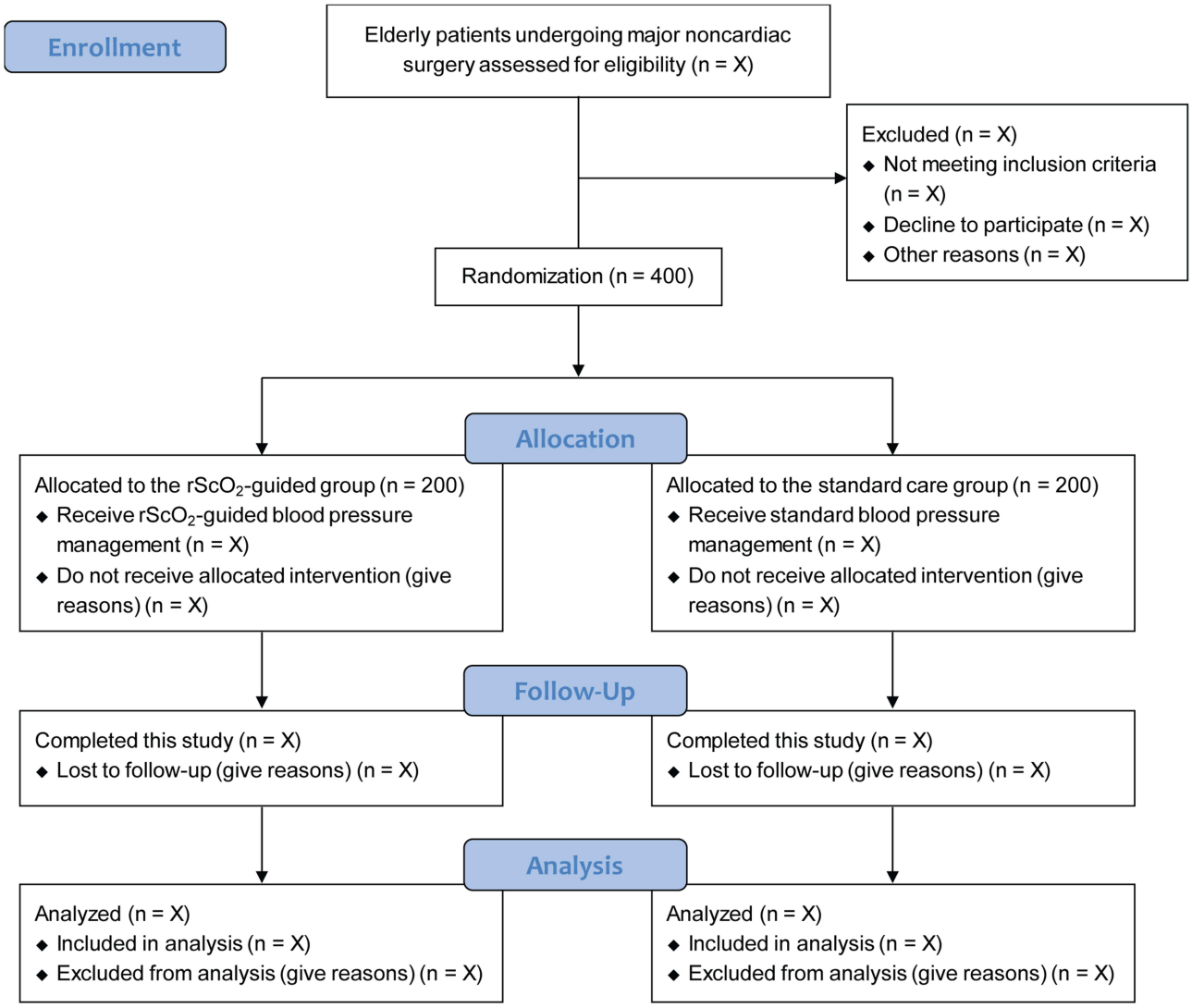

Figure 1 Study flowchart.
Abbreviation: $rScO_2$, regional cerebral oxygen saturation.

5. Acute phase of cerebrovascular disease or cerebrovascular accident within 1 month of onset;
6. Liver function insufficiency, ie, Child-Pugh grade ≥B;
7. Chronic renal disease with creatinine ≥200 μmol/L or end-stage renal disease which is defined as requirement for renal replacement therapy;
8. Preoperative sepsis;
9. Declined to provide consent.

Randomization and Blinding

An independent research personnel will use the online randomization service (www.91trial.com) to generate a random allocation list, in a 1:1 ratio with stratification according to surgical type (abdominal or nonabdominal surgery) and study center. Patients will be randomly allocated into either a standard care group or a $rScO_2$-guided group. The details of randomization and allocation will be concealed by password protection. It is impossible to mask the group allocation to the anesthesiologists who provide anesthesia, due to obvious differences in the clinical practice of these strategies. All participants, surgeons, data collectors, outcome assessors, perioperative care staff, statisticians, and data monitoring committee will be unaware of the allocation details throughout the study.

Anesthesia

Baseline data such as mean arterial pressure (MAP) and heart rate (HR) are documented in surgical ward before surgery. In the operating room, the routine monitoring includes noninvasive cuff blood pressure, electrocardiography, and pulse oximetry. The radial artery is cannulated after local anesthesia for continuous monitoring of arterial blood pressure. The $rScO_2$ monitoring (ELITE01-06-300, Foresight) will be applied on both sides of the forehead in all patients. Before anesthesia induction, the baseline $rScO_2$ value is obtained when patients breathe room air in the supine position.

Anesthesia is induced using i.v. propofol 1.5–2 mg/kg or etomidate 0.2–0.3 mg/kg, sufentanil 0.2–0.4 μg/kg, and rocuronium 0.6 mg/kg. After endotracheal intubation, anesthesia is maintained with 1–3% sevoflurane or propofol infusion 50–150 μg/kg/min. Boluses of sufentanil and rocuronium are given if needed. The lungs are mechanically ventilated using tidal volume of 6–8 mL/kg (predicted body weight), fraction of inspired oxygen (FIO_2) of 50%, and respiratory rate of 12–20 breaths/minute, positive end-expiratory pressure of 5 cm H_2O to maintain end-tidal carbon dioxide between 35 and 45 mmHg. Lactated Ringer's solution of 4 mL/kg/h is infused as basal fluid repletion, and boluses of 6% hydroxyethyl starch (130/0.4) 200 mL over 10 minutes will be given to treat hypovolemia. A warming blanket and/or a fluid warming device are used to maintain nasopharyngeal temperature at 36–37°C. Wound infiltration or nerve blocks can be used at the clinicians' discretion.

Study Interventions

Table 1 presents the process of enrollment, intervention, and assessment conforming to the SPIRIT statement. For the standard care group, the target is MAP ≥65 mmHg or within ±20% of the baseline value. For the $rScO_2$-guided group, the target is

Table 1 Schedule of Enrollment, Intervention, and Assessment

	Study Period							
	Enrollment	Allocation	Post-Allocation					Close-Out
Timepoint	**Preanesthetic Visit**	**Prior to Surgery**	**During Surgery**	**PACU**	**POD1**	**POD 7**	**Hospital Discharge**	**POD 30**
Enrollment								
Inclusion criteria	×							
Exclusion criteria	×							
Informed consent	×							
Demographics	×							
Comorbidities	×							
Randomization		×						
Allocation		×						
Intervention								
rSO_2-oriented blood pressure management			×					
Standard blood pressure management			×					
Assessment								
Blood pressure and $rScO_2$		×	×					
Hemodynamic events			×	×				
Fluids and vasoactive agents			×	×				
Major complications				×	×	×		
ICU admission and duration							×	
Length of postoperative stay							×	
Postoperative recovery							×	
Mortality						×		×
Lab tests		×	×		×	×		

Notes: According to SPIRIT 2013 statement of defining standard protocol items for clinical trials.
Abbreviations: PACU, postanesthesia care unit; POD, postoperative day; $rScO_2$, regional cerebral oxygen saturation; ICU, intensive care unit.

$rScO_2$ ≥60% (the absolute value) or decrease in $rScO_2$ <10% of baseline.[15,16] For patients who do not reach the $rScO_2$ target, those who have coexisting hypotension (MAP <65 mmHg or reduction of MAP >20% of baseline that persists for ≥1 min) will be treated with continuous infusion of norepinephrine (10 μg/mL); if patients already show hypertension (increasement of MAP >20% above baseline that persists for ≥1 min), the following interventions will be applied: increasing FIO_2 to 100%, maintaining $PaCO_2$ close to 40 mmHg, and erythrocytes transfusion when hematocrit <28%.[12,17]

Outcome Measures

The primary outcome is the incidence of composite outcome of major complications and deaths within the first 7 days postoperatively. The secondary outcome measures are the individual components of the primary outcome by day 7 after surgery and 30-day mortality.

The definitions of the major complications are listed in Table S2, including infectious complications (systemic inflammatory response syndrome or sepsis), respiratory complications (hypoxemia, pneumonia, acute respiratory distress syndrome, or need for mechanical ventilation), neurologic complications (altered consciousness, postoperative delirium [POD], or stroke), cardiovascular complications (myocardial ischemia or infarction, acute heart failure, new-onset arrhythmia, or cardiac arrest), renal complications (acute kidney injury or need for renal replacement therapy), thromboembolic complications (deep venous thrombosis or pulmonary embolism), gastrointestinal complications (ileus, intestinal ischemia, acute mesenteric ischemia, or gastrointestinal bleeding), and surgical complications (anastomotic dehiscence or leak, surgical site infection, bleeding, or need for reoperation).

The perioperative data and exploratory outcomes include MAP values, left and right $rScO_2$ values, low $rScO_2$ events ($rScO_2$ <80% of baseline), intraoperative volume of fluids, use of vasopressors, hemodynamic events including hypotension, hypertension, bradycardia (HR <45 beats/min for ≥1 min), and tachycardia (HR >100 beats/min for ≥1 min), postoperative nausea and vomiting, recovery time of bowel function, admission to intensive care unit, duration of intensive care unit stay, length of postoperative hospital stay. In addition, we will collect perioperative blood sample lab results (hemoglobin, hematocrit, red blood cell distribution width [RDW], white blood cells, platelets, prothrombin time, activated partial thromboplastin time, blood urea nitrogen, creatinine, lactate, etc.). Increased RDW has been shown to predict poor outcomes in patients with heart failure or coronary artery disease as well as in the general population.[18]

Data Collection

An independent investigator screens patients according to the eligibility criteria and collects the demographics and baseline characteristics. The outcome measurements and perioperative data are documented by independent research investigators via postoperative patient visits and reviewing electronic medical records. The 30-day mortality data are acquired by telephone calls. All data are recorded in the case report forms and registered in the electronic database. An independent data monitoring committee conducts an ongoing data review throughout this study. Patients' confidentiality will be ensured and deidentified data will be analyzed.

Sample Size Estimation

The required sample size was estimated using the PASS software (version 21.0.3, NCSS, LCC, USA). According to the previous study, the incidence of composite outcome of major complications by day 7 after major noncardiac surgery was about 40% in elderly patients receiving a standard blood pressure management.[7] We expect that the $rScO_2$-guided blood pressure management strategy would reduce the incidence of composite outcome by 35% (ie, an absolute reduction of 14%). To detect such a difference at two-sided $\alpha = 0.05$ and power = 80%, 176 patients in each group are needed. By considering that 10% of patients may drop out from this study, we plan to recruit 200 in each group (ie, a total of 400 patients).

Statistical Analysis

The normality of continuous data will be checked by the Shapiro–Wilk test. These data are presented as mean ± standard deviation and median with interquartile ranges and compared with the independent *t*-test, repeated measures analysis of

variance, Mann–Whitney rank-sum test or Kruskal–Wallis test, as appropriate. Categorical data will be presented as numbers (percentages) and compared with the Chi-square test or Fisher's exact test.

For the study outcomes, the between-group difference will be analyzed using the odds ratio with 95% confidence interval. For the primary outcome, a multivariate logistic regression will be used to adjust for age, surgical type, and study center. Subgroup analyses will be performed based on the stratification. Multiple comparisons of the secondary outcomes will be adjusted using the Benjamini–Hochberg procedure. Survival analysis and Kaplan–Meier curves will be plotted for 30-day mortality using the Cox proportional hazards model. For the exploratory outcomes, no statistical inference should be made.

Data will be analyzed in the modified intention-to-treat population, consisting of all patients after randomization with outcome data available. In addition, we will perform a sensitivity analysis in the per-protocol population, including patients who receive planned interventions without significant protocol violation. Imputation of missing data is not planned. An interim analysis after recruiting 50% of patients is planned, with the stopping rule of $\alpha = 0.00305$ using the Lan–DeMets method. An independent statistician will analyze all data with the use of SPSS software (version 25.0; IBM SPSS, USA). A two-sided $P < 0.05$ indicate a statistically significant difference.

Discussion

This randomized controlled clinical trial will enroll 400 elderly patients undergoing major noncardiac surgery to compare the $rScO_2$-guided blood pressure management strategy with the standard care strategy. The primary focus is to assess the incidence of composite outcome of major complications by day 7 postoperatively. In addition, we investigate the mortality during the 30-day follow-up. This study will be conducted following the guideline of Consolidated Standards of Reporting Trials.[19]

Previous studies reported that intraoperative $rScO_2$ reduction was significantly correlated with the development of postoperative cognitive decline, such as POD and postoperative cognitive dysfunction (POCD), in patients undergoing cardiac and noncardiac surgery.[20–22] Moreover, a reduction in $rScO_2$ has been used to predict postoperative neurological complications after various types of surgery (such as total hip arthroplasty and carotid endarterectomy).[22,23]

Interventional studies using $rScO_2$-guilded anesthesia have yielded mixing results. Colak et al reported that maintaining $rScO_2$ >50% (the absolute value) or >80% of baseline reduced cognitive impairment following coronary artery bypass surgery.[24] Uysal et al maintained the intraoperative $rScO_2$ value >60% to improve postoperative memory outcome in cardiac surgical patients.[16] Recently, another study suggested that the $rScO_2$-guilded management stabilized hemodynamics and reduced the POCD incidence in older patients with hypertension after shoulder arthroscopy.[25] However, Lei et al showed that restoration of $rScO_2$ to ≥75% of baseline did not reduce POD in elderly patients following cardiac surgery, while preoperative value of $rScO_2$ ≤50% was associated with higher risk of POD.[12] Similarly, a recent meta-analysis suggested that $rScO_2$ monitoring helped to reduce POCD after cardiac and major noncardiac surgical procedures but may have no impact on the development of POD.[26]

For surgical patients, the primary aim of intraoperative hemodynamic management is to ensure adequate tissue oxygenation and organ perfusion. Mixed venous oxygen saturation monitoring reflects systemic oxygen balance, but this invasive technique cannot be routinely applied in daily practice. The $rScO_2$ monitoring reflects acute hemodynamic fluctuations and tissue perfusion without time delay, which is more reliable than mixed venous oxygen saturation.[27] When cardiac output decreases progressively, brain perfusion is preserved preferentially via cerebral autoregulation and blood flow redistribution.[28] Low $rScO_2$ reflects cerebral desaturation, providing the clinicians important information when anemia-related impaired oxygenation is still compensated or transfusion may be indicated, especially in patients at lower pretransfusion hemoglobin level.[11] Hence, low $rScO_2$ is accompanied by a decreased systemic perfusion, providing an early-warning indicator of regional and global oxygen desaturation. Specifically, low preoperative $rScO_2$ values were associated with cardiopulmonary dysfunction and short- and long-term complications and deaths in patients following cardiac surgical procedures,[13,29] and low intraoperative $rScO_2$ was an independent predictor of acute kidney injury.[30]

To our knowledge, this is the first study to determine whether the $rScO_2$-guided blood pressure management strategy, as compared to the standard, would reduce major postoperative complications in older adults following major noncardiac

surgery. The limitations include the lack of longer-term outcomes and exclusion of patients with ASA classification IV. The results of this study would inform future investigations on the very elderly and vulnerable surgical patients.

In summary, the findings of this prospective, randomized, controlled clinical trial will provide clinical evidence for the $rScO_2$-guided intraoperative blood pressure management strategy to improve postoperative outcomes in older patients who are scheduled for major noncardiac surgery.

Data Sharing Statement

Data will be available from the corresponding author on reasonable request.

Funding

This work will be supported by Suzhou Youth Science and Technology Project (KJXW2021008 to YFY), Jiangsu Medical Association Anesthesia Research Project (SYH-32021-0036 (2021031) to KP), Suzhou Medical Health Science and Technology Innovation Project (SKY2022136 to KP), Natural Science Foundation of Jiangsu Province (BK20200195 to WWH), National Natural Science Foundation of China (82072130 to FHJ), Six Talent Peaks Project in Jiangsu Province (WSN-022 to FHJ), Key Medical Research Projects in Jiangsu Province (ZD2022021 to FHJ), Suzhou Clinical Medical Center for Anesthesiology (Szlcyxzxj202102 to FHJ).

Disclosure

The authors have no conflicts of interest to declare.

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