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Impact of multimodal warming during general anaesthesia on postoperative cognitive dysfunction in elderly patients with gynaecological cancer: study protocol for a single-blinded randomised controlled trial

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ABSTRACT

Background Cognitive impairment after anaesthesia and surgery is a recognised consequence. This often leads to poor health outcomes and increases healthcare resource utilisation and associated costs, especially in elderly people. However, thus far, there have not been any effective therapies for managing postoperative cognitive dysfunction (POCD). Furthermore, research on the association of multimodal warming with POCD and the clinical outcomes in older patients after gynaecological surgery has not been rigorous. For these reasons, our investigation aims to evaluate whether perioperative multimodal warming would reduce the incidence of POCD and improve prognosis in elderly patients with gynaecological cancer.

Methods and analysis This is a single-centre, prospective, single-blinded randomised controlled trial. One hundred and fifty patients for gynaecological cancer surgery and 16 non-surgical controls aged 65 years or older will be studied in this trial. A series of neuropsychological tests will be completed to evaluate cognitive function in surgery patients before, at day 7 and 3 months after gynaecological cancer surgery. In addition, POCD and cognitive decline will be assessed using the reliable change index using the control group's results. The primary outcome is the prevalence of POCD in elderly gynaecological cancer surgery patients and association between perioperative multimodal warming and POCD.

Ethics and dissemination The protocol for this prospective observational study was approved by the ethics committee of the West China Second University Hospital, Sichuan University (NO. KX215). Recruitment will commence in April 2021 and continue to April 2022. The findings of this trial will be disseminated in peer-reviewed journals and scientific meetings.

Trial registration number ChiCTR2100041663.

Strengths and limitations of this study

- Observational, randomised, single-blinded design only examining association, not causation.
- A series of neuropsychological evaluations will be used for cognitive function in patients before and after surgery and can adequately reflect the changes of patients' condition.
- We will use simple paper-and-pencil tests which are more convenient and agreeable to the elderly population in this study.
- We will also assess the elderly patients' quality of life 3 months after surgery.
- The small sample size of this single-centre study is a limitation of the study design.

INTRODUCTION

Postoperative cognitive dysfunction (POCD), denoting a subtle decline in cognitive function following anaesthesia and surgery. It is a severe complication associated with increased morbidity and mortality, especially for seniors needing major surgery under general anaesthesia at high risk.[1–4] Most patients exhibiting POCD naturally recover from the condition within 6 months after surgery, nearly 2% of POCD cases last until the end of life.[5] Aside from directly impacting patient prognosis, POCD considerably increases treatment costs for patients and their families.[6]

Although the aetiology and pathogenesis of POCD remain inconclusive, advanced age seems to be the single established independent risk factor in 3 months postsurgery.[7] Additionally, there is a growing appreciation for the link between perioperative management and POCD. Anaesthetists usually choose a variety of warming techniques to regulate patient temperature during anaesthesia and surgery. Some experiments[8] showed that various complications such as blood loss, postoperative infection, cardiac morbidity and delaying hospital discharge could be

increased by hypothermia. In contrast, Ginsberg[9] indicated that perioperative temperature is associated with the development of POCD and that the incidence would be reduced if hypothermia had occurred. Extensive studies have indicated that therapeutic hypothermia is a potent neuroprotectant attenuating the detrimental effects of cerebral ischaemia.[10–13]

Over the past 20 years, with the increased number of older people undergoing surgery, the incidence of POCD has continued to rise.[14 15] However, a very few studies have been conducted on multimodal warming during anaesthesia to enhance postsurgery cognitive functions in an elderly population. Currently, monitoring temperature during general anaesthesia to maintain temperature homeostasis is standard practice.[8] It is well reported that a decrease in body temperature by 2°C–3°C is known to reduce the risk of various neurological diseases and protect the brain from ischaemia and hypoxaemia. Nevertheless, none of the clinical studies have distinguished patients who benefited from intraoperative warming and the avoidance of warming. Taken together, we could not find any studies focusing on perioperative body temperature recorded to evaluate the possible associations with the development of POCD after non-cardiac surgery.

The overreaching hypothesis of this study is that elderly patients receiving multimodal warming during gynaecological cancer surgery have a lower incidence of POCD. Therefore, we predict that these patients will have better short-term outcomes than those receiving no warming. Second, we will record the perioperative body temperature to assess the association to cognitive impairment.

METHODS

This single-blinded randomised controlled trial will be conducted at the West China Second University Hospital, Sichuan University. Patient recruitment will commence in April 2021 and is expected to last for 12 months. Before participant recruitment, we have obtained ethics committee approval from West China Second University Hospital, Sichuan University (NO. KX215). In addition, written informed consent will be obtained from each participant prior to enrolment in the study. Recruitment and consenting of study participants by members of the research team is in-line with Good Clinical Practice (GCP).[16] All research personnel will receive mandatory training in GCP prior to participant recruitment.

Study participants

The flow chart of this study procedure is shown in figure 1. Eligible patients will be identified by screening the daily list of visits in the preoperative anaesthesia clinic. The duration of the complete surgical procedure will be expected to last more than 2 hours with an in-hospital recovery period of at least 7 days. Study inclusion and exclusion criteria are described in table 1. Control participants (Group C) are healthy volunteers whose characteristics matched those of the study groups but will not undergo surgery during the study period. Control participants will be recruited via advertisements in the local community.

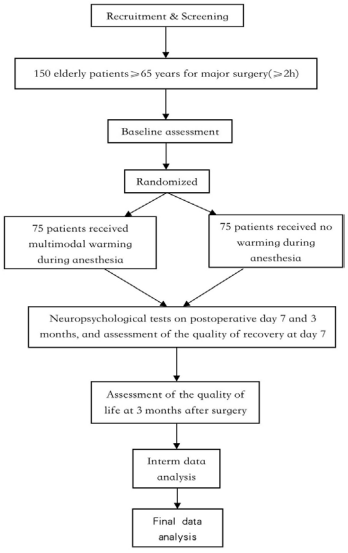


Figure 1 Flow chart of the study.

Randomisation and blinding

Participants will be allocated into study groups by computer-generated randomisation using Microsoft Excel random number generator. Numbers will be enclosed in sealed envelopes which will be opened when patients enter the operating room. Patients will be randomly assigned to receive multimodal warming regimen (group M, patients will be administered an infusion of fluids warmed with a Hotline Fluid Warmer (Smiths Medical ASD, Rockland, Massachusetts, USA) and forced-air warming will be applied using an Equator Convective Warming Blanket (Smiths Medical ASD.)) or no warming (group N, patients will be covered with a sheet and no active warming method will be applied). To obtain a similar size for both groups, blocked randomisation is applied with an allocation ratio of 1:1. The anaesthetists managing the patient will be not involved in data collection, and patients will not know the group allocation.

Perioperative interview

For convenience, all original test scales will be translated into Chinese. Patients will be fully informed about the anaesthesia protocol during the preoperative consultation. The demographic data, including age, gender, body mass index and level of education, and patients' clinical characteristics, including ASA grade, tumour status, medical history and current medication will be recorded. Psychological and mental data will be collected by using Mini-Mental State Examination (MMSE), Beck Depression Inventory and the State-Trait Anxiety Inventory (STAI)-Y-2. Example testing scales are shown in figure 2. The MMSE scale is an important screening tool that can reflect patients' mental state and the degree of cognitive

Table 1 Inclusion and exclusion criteria for study participation

Inclusion criteria	Exclusion criteria
Aged ≥65 years	Refusal to participate in the study
ASA grade I or II	A score of ≤23 on the Mini-Mental State Examination
Elective tumour resection under general anaesthesia	History of neurosurgery or cardiosurgery
Fluent in Chinese	Use of tranquillisers or antidepressants
Able to independently complete the neuropsychological tests	Severe anxiety disorder or severe hearing and visual decline
	Severe hepatic dysfunction (Child-Pugh stage C) or renal dysfunction
	Parkinson disease, Alzheimer disease or coma
	Alcoholism or drug dependence
	Tumour metastasis or cancer cachexia
	Canceled surgery

ASA, American Society of Anesthesiologists physical status classification system.

decline comprehensively and quickly.[17] The Beck Depression Inventory is a widely used 21-item self-report inventory designed to measure the presence and severity of depressive symptoms. The STAI -Y-2 is a commonly used measure to assess trait and state anxiety.[18 19]

Neuropsychological assessment

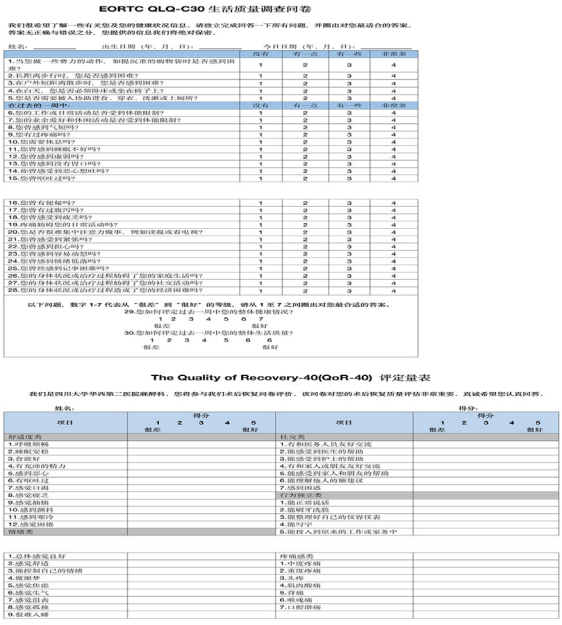
A series of neuropsychological tests, including the Visual Verbal Learning Test, the Concept Shifting Test, the Stroop Colour Word Interference Test and the Letter-digit Coding Test, will be performed preoperatively as well as at 7 days and 3 months postoperatively and at the corresponding time points in group C (Baseline day 1, 7 days and 3 months later). Standard neuropsychological tests will be carried out by two investigators trained at West China Second University Hospital. All neuropsychological tests will be translated into Chinese and conducted

Figure 2 Sample simple neuropsychological evaluations which are more simple paper pencil tests will be given to the participants assigned to the study.

in a quiet environment. A correction for short-term practice effects will be carried out based on previous work.[20] The Visual Verbal Learning Test is based on Rey's auditive recall of words and evaluates learning and memory in this study.[21] A 15-word list will be presented at intervals of two seconds; participants are instructed to read them aloud, after which they will be asked to repeat all words they remember to evaluate short-term memory. Investigators will record and calculate the total number of correct words. After 30 min, participants will be asked to recall as many of the original 15 words as possible to evaluate long-term memory. Concept shifting and executive functioning will be measured by The Concept Shifting Test which is based on Halstead and Reitan's neuropsychological test battery.[22] Participants will be asked to cross out a specific target number as quickly as possible. The Stroop Colour Word Interference Test consists of three conditions: word reading (Word), colour reading (Colour) and colour-word reading (colour-word) are used to test distributed attentional processing.[23] Participants will be asked to name colour patches, then to read colour words and in the third condition to name the colour of colour-words printed in an ink of a different colour as fast as possible. The Letter-digit Coding Test evaluates mental processing speed and concentration.[24] According to a printed key, participants will be required to match as many of the symbols with the digits as they can in 90 s. Evaluations will be conducted as specified by the International Study of Post-operative Cognitive Dysfunction 1.[1 3] The total assessment will take no longer than 60 min as not to intervene in the daily routine clinical management of the patients.

Anaesthetic management

Patients will not receive any medication prior to surgery. After 5 min of preoxygenation, intravenous propofol and sufentanil will be used for induction of general anaesthesia, atracurium or rocuronium for neuromuscular blockade. Patients will be intubated and mechanically


EORTC QLQ-C30 生活质量调查问卷

The Quality of Recovery-40(QoR-40) 评定量表

Figure 3 The example scale of QoR-40 and EORTC QLQ-C30 for evaluating the participants' postoperative recovery. EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; QoR-40, Quality of Recovery-40.

ventilated with an air/oxygen mixture to maintain end-tidal carbon dioxide at 4.6±0.6 kPa. The temperature of all patients will be monitored using a nasopharyngeal temperature probe. Inhalational sevoflurane, intravenous sufentanil or remifentanil will be used to maintain anaesthesia. Dexmedetomidine,[25] midazolam[1] or scopolamine[26] will not be administered, as no consensus can be reached with their impacts on patients' cognition. Intraoperatively, the depth of anaesthesia will be monitored by bispectral index (target range 40–60). Nasopharyngeal temperature, MAP and HR will be recorded at five specific time points: the day before surgery (baseline), skin incision, maximum trauma end of surgery and extubation.

Postoperative analgesia

At the end of the surgery, analgesia will be provided with bilateral ultrasound-guided transversus abdominis plane block (20 mL of 0.375% ropivacaine will be administered on each side) and patient-controlled intravenous analgesia (sufentanil 3 µg/kg, granisetron 12 mg and butorphanol 12 mg in 0.9% normal saline with a total volume of 200 mL; 2 mL/hour as the background infusion with a 0.5 mL bolus at a 15 min lockout period).

Evaluation of postoperative recovery profiles

Figure 3 shows the example scale for evaluating the postoperative recovery. The Quality of Recovery-40 (QoR-40) questionnaire, which is a global measure of patient-assessed QoR, will be given to patients to evaluate the functional recovery of patients in the first 7 days after surgery. The QoR-40 consists of 40 checklist items assessing the quality of postoperative recovery: physical comfort (12 items); emotional status (9 items); psychological support (7 items); physical independence (5 items) and pain (7 items).[27] Each item is graded on a five-point Likert scale from 1, poor performance, to 5, good performance and the QoR-40 scores range from 40 (inferior QoR) to 200 (excellent QoR).

The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) will be administered to assess the quality of life (QoL) at 3 months postoperation. The EORTC QLQ-C30 is a widely used 30-item instrument for assessing the QoL in patients with cancer. The questionnaire consists of multi-item scales and single-item measures including five functional scales (physical, role, emotional, cognitive and social), three symptom scales (fatigue, nausea/vomiting and pain) and a global health status/QoL scale and six single items. The six single items are dyspnoea, insomnia, loss of appetite, constipation, diarrhoea and financial difficulty.[28] Each item is graded on a four-point Likert scale, and the global health/QoL scale is evaluated with a seven-point Likert scale. According to the EORTC QLQ-C30 Scoring Manual, subscale scores are transformed to standard scores that vary from 0 to 100, where a higher score indicates a better QoL.

Patient and public involvement

There is no active involvement of patients or the public in the development of this protocol. However, the patients and their families will be fully debriefed and informed about the study results at the end of the trial.

STATISTICS

Sample size calculation

The sample size required for this study will be calculated based on a clinical trial that reported an incidence of POCD 7 days after major elective noncardiac surgery approximately 17%.[29] The morbidity of POCD will be expected to decrease from 22% in group N to 5% in Group M. Using the means and SD for the analyses, the two-sided nominal significance level α is set to be 5%, and the statistical power is designed to be 80%, at least the proportion of samples assigned to each group is 65. In addition, with a foreseeing lost to follow-up rate of about 15% at 7 days postoperation,[29] we determined a sample size of 75 patients per group. The ratio of enrolled surgical patients to healthy volunteers is 4:1.

Outcomes analyses

The primary study outcomes are the incidence of POCD at 7 days and 3 months postsurgery. Secondary outcomes include the following: recovery (QoR-40) and length of hospital stay, all-cause mortality at 30 and 90 days after surgery, and QoL (EORTC QLQ-C30) at 3 months after surgery.

POCD will be assessed using an established formula.[30] A Z score will be calculated for each neurophysiological test according to the following formula: $Z=(X-X_{reference})/(SD_{control})$, in which X presents the different baseline and

neuropsychological tests score after surgery at 7 days or 3 months after surgery between group M and group N. At the corresponding time point, $X_{reference}$ in the formula represents the difference between the baseline and the neuropsychological test scores in group C and $SD_{control}$ represents the variations of SD in the group C. Patients with Z score ≥1.96 on each test will be classified as suffering from cognitive decline or POCD.[1 4]

We will use one-way analysis of variance to analyse the continuous variables with normal distributions and the Kruskal-Wallis H test to analyse variables that do not meet normality criteria. Numerical data will be expressed as proportions and compared using Fisher's exact, correction for continuity or Pearson's χ^2 tests as appropriate. ORs and 95% CI will be calculated using a logistic regression model. A $p<0.05$ is considered a statistically significant difference. An interim analysis will be performed to assess the quality of data after primary data acquisition from 20 participants. We will follow the Strengthening Reporting of Observational Studies in Epidemiology statement[31] for all future reports related to this study. All statistical analyses will be performed using SPSS V.22.0 (SPSS).

Data monitoring

The Department of Research and Clinical Investigation of our institution will monitor all written informed consent, inclusion and exclusion criteria, and follow-up on all serious adverse events.

Safety

All serious adverse events will be documented and reviewed by the principal investigator and reported to the trial sponsor and Department of Anaesthesiology, West China Second University Hospital.

Ethics and dissemination

The study has been approved by the ethics committee of the West China Second University Hospital, Sichuan University (No. KX215) and will follow the International Conference Guideline for Good Clinical Practice to ensure that the data and the results are credible. In this study, all neuropsychological tests will not interfere with other participant activities, and most assessments will be completed during the inpatient period. In addition, a short telephone follow-up will be carried out respectively at 3 months after surgery. Before beginning the study, investigators will make relevant information available to patients, including the potential benefits and possible harms associated with this clinical trial. All the information provided from patients, such as personal health information and cognitive assessment results, would be kept confidential.

Knowledge translation of the results of this study will be presented in an open-access peer-reviewed journal and the presentation at an academic conference. At the same time, an open-access version of the study results will be made available through the website of Chinese Clinical Trial Registry, and the participants will also be informed of the results.

DISCUSSION

This study is designed to investigate the beneficial effects of multimodal warming during general anaesthesia in elderly surgical patients. The primary hypothesis of this investigation is that multimodal warming during general anaesthesia can decrease the incidence of POCD. As previously mentioned, age has been indicated as a significant risk factor for postoperative cognitive decline reported approximately 26% of individuals over 65 years old. Based on these findings,[32 33] we decided to set the inclusion criterion threshold for participants 65 years of age and older. The findings of this study may have the potential to provide guidelines to the medical community on how to apply preventative and early intervention approaches to POCD.

Our study will use a series of neuropsychological evaluations, which are more straightforward paper-and-pencil tests (reading and answering are relatively simple). Tasks previously conducted by researchers were using computers[34–38] and while computerised tasks make record and analyse data relatively quickly, using this test for an older population is often difficult.[39–42] When using computers, frustration, negative emotions, and decreased motivation towards the tests might be more easily accessible for elderly patients. The paper-and-pencil tests prove to be more convenient for the elderly population.[43]

POCD is a complex neuropsychological disorder presenting primarily as a decline in cognitive ability after surgery. There is no universal definition of POCD making the outcomes of clinical cognitive research complex to interpret. Assessment for POCD, therefore, needs to be evaluated by time-intensive combination of neurocognitive function tests.[44] Thus, we propose that to make the assessment simple and practical to perform, the diagnosis of POCD should be mainly based on an established formula calculation: $Z=(X-X_{reference})/(SD_{control})$.[30]

This study does include several limitations. Primarily, the clinical trial will be conducted at a single centre and the sample size is relatively small. The approach to recruitment may lead to bias for the yield of enrolled participates given the short period of active recruitment. The body of literature on this topic is very small, thus, we firmly believe that the small sample size of this study will be able to provide the essential groundwork for future investigations. Second, postoperative cognitive follow-up will be performed within 3 months but the long-term effects of multimodal warming group on older patients will not be evaluated.

In general, this study will explore the beneficial effects of intraoperative warming in elderly surgical patients and provide preliminary evidence to support the notion that multimodal warming during anaesthesia will be good on postoperative cognitive. The

proportion of older people undergoing surgical procedures has been increasing for the past two decades.[45 46] Therefore, the results of this study will have the potential for wide-ranging application to improve the QoL of the elderly population who have undergone surgery.

Contributors JZ and SS designed study protocol; JZ obtained funding, involved with study conduct and wrote first draft of manuscript; QZ is involved with study conduct, data analysis; All authors edited and approved the final manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

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