BMJ Open

Effect of different durations of preoperative computerised cognitive training on postoperative delirium in older patients undergoing cardiac surgery: a study protocol for a prospective, randomised controlled trial

Xinyuan Qiu, Lili Wang, Xinge Wen, Qingling Meng, Junwei Qi, Chuang Li, Hua Yin, Fei Ling, Qiao Yuhan, Wen Zhang, Yueying Zhang

To cite: Qiu X, Wang L, Wen X, *et al*. Effect of different durations of preoperative computerised cognitive training on postoperative delirium in older patients undergoing cardiac surgery: a study protocol for a prospective, randomised controlled trial. *BMJ Open* 2024;**14**:e088163. doi:10.1136/bmjopen-2024-088163

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2024-088163).

XQ and LW are joint first authors.

Received 29 April 2024
Accepted 18 October 2024

Department of Anesthesiology, The Affiliated Hospital of Xuzhou Medical University, Xuzhou, Jiangsu, China

Correspondence to
Dr Yueying Zhang;
zyy0218@126.com

ABSTRACT

Introduction Postoperative delirium (POD) is a common neurological complication after surgery among older patients, characterised by acute disturbances in consciousness, attention and cognition, usually occurring within 24–72 hours after surgery. POD has a significant impact on the prognosis of older patients undergoing major cardiovascular surgery, including increased length of hospital stay, hospital costs and readmission rates, with an incidence rate as high as 26%–52%. Computerised cognitive training (CCT) refers to difficulty-adaptive training in cognitive domains such as attention, memory and logical reasoning, using systematically designed tasks. Existing studies have shown that CCT has reduced the risk of delirium in non-cardiac surgery patients with at least minimal compliance. The purpose of this study is to investigate the effects of preoperative CCT on the incidence of POD in older patients undergoing elective cardiac surgery, to clarify the dose–effect relationship between different training time of preoperative CCT and POD and to explore the minimum effective time target that can significantly lower the incidence of POD.

Methods and analysis This is a prospective, single-blind, randomised controlled trial that aims to enrol 261 older patients scheduled for elective cardiac surgery at the Affiliated Hospital of Xuzhou Medical University. The patients will be randomised into three groups: group C will be the routine care group (no CCT prior to surgery); group L will be the low-dose time group (with a total of 5 hours of CCT prior to surgery) and group H will be the high-dose time group (with a total of 10 hours of CCT prior to surgery). The primary outcome is the incidence of delirium within 7 days after surgery. Secondary outcomes include postoperative mild neurocognitive disorder (NCD) and postoperative major NCD (30 days up to 1 year), time of onset and duration and severity of delirium, and all-cause mortality within 1 year after surgery. The results of this study are of significant importance for establishing effective, patient-centred and low-risk prevention strategies for POD/postoperative NCD.

Ethics and dissemination This study protocol has been approved by the Ethics Committee of the Affiliated Hospital of Xuzhou Medical University (Ethics Number: XYFY2023-KL149-01). All participants will provide written informed consent, and the results of the study will be published in international peer-reviewed academic journals and presented at academic conferences.

Trial registration number ChiCTR2300072806.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The study investigates the effects of computerised cognitive training on postoperative delirium among older patients undergoing elective cardiac surgery.
⇒ For the first time, this study will be divided into three groups to examine the effects of different durations of preoperative computerised cognitive training on postoperative delirium.
⇒ Although postoperative delirium typically occurs within 72 hours after surgery, we will follow patients for up to 1 year to assess their postoperative neurocognitive function.
⇒ This study is a single-centre clinical trial with older cardiac surgery patients as the subjects, which has inherent limitations. Further multicentre studies with larger sample sizes are needed.
⇒ The study uses subjective scales to quantify the research outcomes and lacks objective evidence such as laboratory indicators like S100β protein, neuron-specific enolase, which may reflect postoperative delirium to some extent.

INTRODUCTION

Postoperative delirium (POD) is defined as an acute brain dysfunction characterised by impaired attention, altered consciousness, and cognitive and orientation disturbances. It typically manifests as an acute onset, fluctuating severity and progressive course, often

occurring within the first week after surgery, with a peak incidence between 24 and 72 hours after surgery.[1] POD of cardiovascular surgery (PODOCVS) has a high incidence rate ranging from 26% to 52%, which is significantly higher than that observed in other surgical procedures, including spine surgery (3.3%–19.5%), abdominal surgery (10.7%–25%), urological surgery (8.8%–26%) and cataract surgery (5%).[2] Based on its clinical presentation, POD can be categorised into three types: hyperactive, inactive or mixed. Approximately 25% of cases are classified as hyperactive delirium, which is typified by discernible clinical symptoms such as restlessness, irritability, sudden aggression, hallucinations and incoherent speech. Inactive delirium, comprising about 50% of cases, presents with less overt clinical manifestations, including drowsiness, silence and reduced activity. This makes it susceptible to being overlooked. Mixed delirium, representing approximately 25% of cases, exhibits features of both hyperactive and inactive delirium.[3–5] The gold standard for diagnosing POD is based on the criteria set forth in the Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition, published by the American Psychiatric Association.[6] The primary diagnostic characteristics include an acute onset and fluctuating symptoms, a decline in cognitive function, a disruption of attention and an altered level of consciousness. Supportive features include an abnormal sleep-wake cycle, perceptual disturbances (hallucinations or illusions), mental disturbances (inactivity or hyperactivity) and behavioural and emotional disturbances. It is imperative to ascertain whether the current symptoms and severe reduction in the patient's level of consciousness (such as coma) are attributable to other potential causes. Research has demonstrated that POD has a significant impact on patient outcomes, including an extended hospital stay and increased hospital costs, elevated higher short-term and long-term mortality rates, an increased incidence of complications, a diminished capacity for self-care and a long-term decline in postoperative cognitive function,[7–9] particularly in patients who have undergone PODOCVS.[10]

Pharmacological and non-pharmacological approaches are the primary modalities used in the management of PODOCVS. Pharmacological prevention has been demonstrated to have limited efficacy in the prevention of POD, with some approaches even proving to be ineffective.[2 11] It is important to note that pharmacological prevention carries potential risks, including sedation, extrapyramidal symptoms, orthostatic hypotension and arrhythmias.[12] The use of pharmacotherapy for the prevention of PODOCVS is not recommended.[13–16] Cognitive training is regarded as a proactive and efficacious non-pharmacological intervention that may mitigate the risk of delirium and enhance postoperative neurocognitive function in surgical patients. Cognitive training is a method of cognitive intervention that employs a variety of cognitive tasks to enhance cognitive function. In recent years, there has been a gradual transition from traditional paper-and-pencil, instructional training methods to computerised cognitive training (CCT) that is adaptive in difficulty and focuses on skill enhancement.[17] A recent study by Humeidan *et al* indicates that preoperative cognitive training may reduce the incidence of delirium in patients aged 60 and above undergoing non-cardiac and non-neurological surgeries.[18] This randomised, single-blind clinical trial used electronic tablet-based cognitive exercises targeting memory, speed, attention, flexibility and problem-solving skills. Compared with the control group, the cognitive training group showed a significant reduction in delirium rates. Moreover, in the cognitive intervention group, the incidence of delirium was twice as high in those who played less than 5 hours as in those who played more than 10 hours. A study demonstrated the feasibility of perioperative cognitive training using mobile devices in older patients undergoing cardiac surgery. The study found that patients scheduled for elective cardiac surgery were most likely to adhere to the training programme and had sufficient time for such interventions prior to surgery.[19]

A structured preoperative CCT programme may have a more pronounced effect on reducing the incidence of POD. However, there are several challenges in current clinical practice. First, the quality of training is difficult to ensure without supervision and guidance, emphasised by the Cognitive Training Guidelines for China (2022),[20] which recommends that cognitive training be implemented in specialised centres for optimal efficacy. Second, for many elective surgeries, patients cannot be guaranteed sufficient preoperative training time before surgery, and the dose–response relationship between training time and cognitive improvement is unknown. Finally, some patients undergoing routine surgery may not prioritise cognitive training, leading to poor compliance, as demonstrated in previous studies. Therefore, we aim to find an efficient training programme that achieves optimal cognitive improvement in the shortest possible time, to facilitate its implementation in clinical practice. For these reasons, we have designed a randomised clinical trial in which older patients scheduled for elective cardiac surgery will receive different durations of preoperative CCT under the guidance of trained professionals, to evaluate the impact of different training durations on POD in this patient population.

METHODS AND ANALYSIS

Aims and hypothesis

Research hypotheses

Primary hypothesis

Preoperative CCT at the 5/10-hour dosage leads to statistically significantly greater improvements in the incidence of POD compared with group C.

Secondary hypothesis

Preoperative CCT at the 5/10-hour dosage leads to statistically significantly greater improvements in postoperative neurocognitive function compared with group C.

Study design

A prospective, single-centre, randomised controlled trial was designed to evaluate the impact of CCT on the incidence of POD in older patients undergoing elective cardiac surgery. It aims to clarify the dose-response relationship between different durations of preoperative CCT and POD and to explore the minimum effective duration that significantly improves POD. This trial is an innovative and low-risk intervention that has been registered in the Chinese Clinical Trial Registry (ChiCTR2300072806). The intervention programme will be administrated and supervised by trained research personnel to ensure that the participants complete at least one game in each cognitive category and reach the goal of 1 hour of training during each session. The study is scheduled to commence on 1 July 2023 and end on 1 October 2024. It includes three groups: the routine care group (group C), the low-dose time group (group L) and the high-dose time group (group H). Online supplemental figure 1 shows the patient flow chart for this RCT.

Study population

The CCT trial aims to enrol patients aged 60 years and above who are admitted to the Affiliated Hospital of Xuzhou Medical University and need cardiac surgery. Patients who meet the inclusion criteria will be informed about the details of the study and will be required to sign a written informed consent form prior to randomisation while respecting individual autonomy and ethical principles (the details of the informed consent form can be found in online supplemental file 1).

Inclusion and exclusion criteria

Inclusion criteria for the RCT are patients aged 60 years and older who will undergo coronary artery bypass grafting or valve surgery at least 5 days prior to their surgical procedure. We excluded patients with a history of psychiatric illness (anxiety or depression, stroke, dementia, epilepsy, Parkinson's disease, Alzheimer's disease or other forms of cognitive decline), dependence on alcohol and psychotropic drugs, presence of significant hearing or visual impairment and active depression (using the Geriatric Depression Scale, (GDS)). We also exclude patients who score less than 24 on the Mini–Mental Status Exam (MMSE) (20 for patients with less than a middle school education, 17 for illiterate patients).

Recruitment, randomisation and blinding

Recruitment of participants

All subjects will be recruited on the first day after admission. Trained researchers will perform baseline assessments, and recommend eligible patients who meet the inclusion criteria to participate in the study. Written informed consent will be obtained from patients and their families prior to randomisation and enrolment. Following the baseline assessment, eligible subjects (n=261) will be randomised by researchers who are blinded to the preoperative assessment tests. Outcomes will be measured at the following time points: on admission (T0), postoperative days 0–5 and day 7 (T1–T6, T7), postoperative 1 month (T8), postoperative 3 months (T9) and postoperative 1 year (T10).

Table 1 Schedule of visits and assessments

		Follow-up				
Variables	**T0**	**T1–6**	**T7**	**T8**	**T9**	**T10**
Written informed consent form	√					
MMSE	√			√	√	√
MoCA	√			√	√	√
GDS	√			√	√	√
CCI	√					
PQRS	√	√	√	√	√	√
PSQI	√					
CAM/CAM-ICU	√	√	√			
DRS-R-98 (If delirium occur)		√	√			
NRS		√				
Katz				√	√	√

CAM-ICU, Confusion Assessment Method for the Intensive Care Unit; CCI, Charlson Comorbidity Index; DRS-R-98, Delirium Rating Scale-Revised-98; GDS, Geriatric Depression Scale; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; NRS, Numerical Rating Scale; POD, postoperative day; PQRS, Postoperative Quality Recovery Scale; PSQI, Pittsburgh Sleep Quality Index; T0, the day of admission; T1, the day of surgery; T2, postoperative day 1; T3, postoperative day 2; T4, postoperative day 3; T5, postoperative day 4; T6, postoperative day 5; T7, postoperative day 7; T8, postoperative 1 month; T9, postoperative 3 months; T10, and postoperative 1 year.

Randomisation

The trial uses a computer-generated random number table to randomise eligible patients (as shown in table 1) into the routine care group (group C, no CCT prior to surgery), the low-dose time group (group L, a total of 5 hours of CCT prior to surgery) and the high-dose time group (group H, a total of 5 hours of CCT prior to surgery). Group allocation information will be stored in sealed, sequentially numbered envelopes, with strict sealing and blinding procedures to minimise selection bias. Randomisation will be performed by an unbiased and unaffiliated graduate student.

Blinding

Patients in this study cannot be blinded prior to surgery, but they are informed that they may be assigned to either the routine care group or the CCT group without knowledge of the specific design and training protocol of the study. Patients in the intervention group will be unblinded at the final follow-up (1 year) when they will be informed of the detailed research plan. Blinding for researchers will be maintained by separating preoperative cognitive training and postoperative follow-up activities.

Researchers who provide preoperative guidance and supervise the CCT will recuse themselves from subsequent follow-up of patients after surgery. Postoperative follow-up will be conducted by other researchers who are unaware of the group assignments. Data collection after discharge will avoid asking patients about preoperative training information, and if unblinding occurs inadvertently, the follow-up researcher will be replaced at the next follow-up.

Sample size

Previous studies have shown that the incidence of POD after cardiac surgery in older patients is approximately 50%.[2] A clinically significant reduction in the incidence of POD is defined as a reduction in the overall rate from 50% to 25%. The effect size is calculated by determining the difference in proportions between two of the three groups and pooling the data from the two comparison groups. Therefore, assuming a power of 90% and α=0.05, each group requires 78 participants, allowing for a 10% dropout rate, resulting in an actual sample size of 87 participants per group and a total sample size of 261 participants.[21]

Intervention

During hospitalisation, baseline assessments are performed using questionnaires after written informed consent is obtained from patients. The Postoperative Quality Recovery Scale (PQRS) will be used to quantify health-related quality of life and social activities of daily living (ADLs); the Pittsburgh Sleep Quality Index will be used to assess recent sleep quality; and the Montreal Cognitive Assessment (MoCA) will be used to assess baseline cognitive reserve. These assessments must be completed by the patients themselves. Patients who complete the assessments and meet the eligibility criteria will be randomly assigned to one of three groups. All three groups will undergo routine laboratory testing, preoperative preparation, health education promotion and ward safety management. On admission to the operating room, all patients will undergo routine monitoring of electrocardiography, blood pressure, pulse, oxygen saturation and bispectral index (BIS). After intravenous access is established, dexmedetomidine is administered at a rate of 0.5 µg/kg/hour. Invasive arterial blood pressure monitoring is performed under ultrasound-guided radial artery cannulation. General anaesthesia is induced with lidocaine 1–2 mg/kg, etomidate 0.2 mg/kg, rocuronium 0.6–0.9 mg/kg and sufentanil 7 µg/kg. Manual ventilation via a mask is performed for 3–5 min until adequate muscle relaxation is achieved for intubation, followed by the insertion of a cuffed endotracheal tube with a transesophageal echocardiography (TEE) probe. Maintenance of anaesthesia will include propofol infusion at 2–4 mg/kg/hour, continuous infusion of cisatracurium, adjustment of tidal volume to maintain $P_{ET}CO_2$ between 35 and 45 mm Hg, and BIS between 40 and 60. Heparinisation with 3 mg/kg of heparin is administered after sternotomy, reduced to 1.5 mg/kg if cardiopulmonary bypass (CPB) is not required, and protamine is used to reverse heparin after major procedures. After surgery, patients are transferred to the intensive care unit (ICU) while still intubated.

However, there are specific differences in non-pharmacological interventions among the three groups of patients before surgery.

Routine care group (group C)

Patients in group C will receive comprehensive standard care, including preoperative preparation, routine monitoring of vital signs and health education. No additional cognitive intervention will be provided to avoid the placebo effect.

CCT group (groups L and H)

In addition to receiving routine care, patients in group L will receive 1 hour of CCT daily for 5 days prior to surgery, for a total of 5 hours of training. Patients in group H will receive 1 hour of CCT twice daily (morning and evening) for 5 days prior to surgery, for a total of 10 hours of training. The CCT intervention tool in this trial is based on a brain training game called 'Memorado', which is available on tablets or smartphones and supports Chinese. The cognitive training consists of a series of computer games focusing on six categories: attention, memory, logic, reaction time, speed and language. Patients in the intervention groups are required to complete at least one game under each cognitive category during each session, and more if time permits. The intervention process is conducted under the full supervision of research personnel to ensure the effectiveness of the training. If participants fail to complete the training time dosage, they will be recorded as a dropout (see online supplemental figure 2).

Trained research personnel, who are not involved in preoperative cognitive intervention and are unaware of the grouping, will use the Confusion Assessment Method (CAM) and the the CAM for the ICU to assess the presence of delirium in patients both before surgery and during the postoperative period. Assessments will be conducted at approximately 24 hours postoperatively and then twice daily for the subsequent six postoperative days, between the hours of 08:00–10:00 and 18:00–20:00. In the event that a patient displays symptoms of delirium, the severity of the delirium will be quantified using the Delirium Rating Scale-Revised-98 (DRS-R-98). The duration of delirium was calculated as the cumulative number of days during which delirium was diagnosed on at least one assessment.[22] From postoperative days 1 to 5 (each afternoon), the PQRS will be employed to evaluate the quality of postoperative recovery, while the Numerical Rating Scale (NRS) will be used to assess the intensity of pain experienced at rest. On postoperative day 7, the CAM will be employed once more for the purpose of conducting a further patient assessment. Neurocognitive function will be evaluated using the MMSE and the MoCA, while postoperative recovery quality will be

assessed using the PQRS. For patients who are discharged earlier, follow-up will be conducted via telephone. Subsequent assessments will be conducted via telephone on postoperative days 30, 90 and 1 year, employing the GDS, MMSE, MoCA, Katz Index of Independence in ADLs and PQRS scales to evaluate patients' status comprehensively. Furthermore, the follow-up assessments will document whether patients have continued cognitive training after discharge, which will serve as a control variable to adjust for the postoperative training effect.

Retention and adherence

In order to optimise the retention of enrolled patients, a series of measures have been implemented. In order to optimise the retention of enrolled patients, a series of measures have been implemented. First, a comprehensive explanation of the research objectives is provided to potential participants who meet the criteria, addressing any queries they may have regarding the study prior to formal enrolment. Second, prior to randomisation, compliance screening is conducted to ascertain that enrolled participants are committed to cooperating with the training. Finally, we request the assistance of patients' family members, caregivers and bedside healthcare providers. Patients who are unable to adhere to the full requirements of the screening phase will be excluded from the randomisation process. Following randomisation, the research personnel responsible for the intervention will conduct one-on-one CCT with patients at specified times and locations to ensure that the training duration is met. At the time of enrolment, a minimum of two contact numbers are obtained from each patient in order to minimise the likelihood of loss to follow-up during subsequent assessments. Throughout the intervention process, participants are provided with encouragement and assistance. Communication with family members and caregivers is actively facilitated, with training effects and intervention progress shared when appropriate. This ensures that enrolled patients cooperate with the intervention in a smooth and effective manner.

Outcome measures

The data are collected by researchers with extensive training at the initial and subsequent assessment points through on-site evaluations and telephone follow-ups. The study results will be measured at the following time points: the day of admission (T0), the day of surgery (T1), postoperative day 1 (T2), postoperative day 2 (T3), postoperative day 3 (T4), postoperative day 4 (T5), postoperative day 5 (T6), postoperative day 7 (T7), postoperative 1 month (T8), postoperative 3 months (T9) and postoperative 1 year (T10) (see table 1 for details).

Primary outcome measures

The incidence of POD within 7 days

Assessed by the CAM[23]: The CAM assessment covers four principal domains as follows: (1) acute change or fluctuation in consciousness state; (2) lack of concentration; (3) disorganised thinking and (4) altered level of consciousness. A diagnosis of POD is made when both (1) and (2) are exhibited, along with either (3) or (4). In cases where the patient is located within the ICU, the CAM for the ICU is used for assessment.[24] Prior to using the CAM-ICU, the depth of sedation is assessed via the Richmond Agitation-Sedation Scale (RASS). Should the RASS score reach either −4 or −5, indicating a state of unconsciousness, the assessment is terminated. Nevertheless, if the RASS score is ≥−3, the CAM-ICU assessment for delirium status is continued.[25]

Secondary outcome measures

Delirium subtypes

The behavioural manifestations of delirium can be classified into three main categories according to their clinical presence: hyperactive delirium, which is characterised by restlessness and constant movement; inactive delirium, which is defined by a lack of movement, reduced speech output and unresponsiveness and mixed delirium, which presents with a rapid alternation between hyperactive and inactive signs and symptoms.

The incidence of postoperative mild neurocognitive disorder and postoperative major neurocognitive disorder (30 days up to 1 year)

Neurocognitive function is evaluated using the MoCA[26] and the MMSE[27] at 1 month, 3 months and 1 year postoperatively. The objective criteria are a decline of 1–2 SD relative to the preoperative period for mild neurocognitive disorder (NCD) and a decline of ≥2 SD for major NCD.[28] Telephone follow-ups are conducted for discharged patients. The MoCA and MMSE encompass a comprehensive range of cognitive domains, including memory, language, attention, calculation, abstract thinking, orientation, visuospatial abilities and executive function.

The time of onset, duration and severity of delirium

Assessed by using the DRS-R-98,[29] comprising 13 items pertaining to various aspects of the subject's condition, including disturbances of the sleep-wake cycle, perceptual disturbances (hallucinations), delusions, fluctuating emotions, language impairment, abnormal thought processes, agitation, orientation disturbances, impaired attention, short-term memory deficits, long-term memory deficits and visuospatial ability impairments. The DRS-R-98 is advantageous in that it allows for a comprehensive evaluation of patients from different perspectives and severity levels while also enabling differentiation from other mental disorders such as depression, dementia and schizophrenia.

Postoperative depression incidence

Prior to surgical intervention, patients will be evaluated using the GDS to ascertain the absence of active depressive symptoms.[30] Subsequently, at 1 month, 3 months and 1 year postoperatively, the GDS is employed to ascertain whether surgical patients have developed depression. The GDS score is composed of

30 items that represent the core symptoms of geriatric depression, including feelings of sadness, reduced activity, irritability, thoughts of withdrawal, negative evaluations of the past, present and future. The total score on the GDS ranges from 0 to 30, with a score of 0–10 indicating no clinically significant depressive symptoms, a score of 11–20 indicating mild symptoms, and a score of 21–30 indicating moderate to severe symptoms.

Postoperative recovery quality

The PQRS is employed for the assessment of patients' recovery status at multiple time points and across various domains following surgical procedures.[31] The scale is not designed to demonstrate cognitive decline; rather, it is employed to evaluate recovery in comparison to the baseline in a number of domains, including physiological, nociceptive, emotional, ADLs, cognitive and overall patient assessment.

The physiological domain encompasses a range of vital sign measurements, including systolic blood pressure, heart rate, temperature, respiratory rate and oxygen saturation. These assessments aim to gauge the patient's physiological recovery.

The nociceptive domain encompasses the assessment of pain and discomfort. It encompasses the assessment of pain and nausea, reflecting aspects of pain management and discomfort.

The emotional domain encompasses an evaluation of depressive and anxiety levels.

The ADLs domain assesses the ability to perform routine activities independently, including standing, walking, dressing and self-care.

The cognitive domain comprises five tests evaluating orientation, language memory, executive function, attention and concentration.

The overall patient assessment reflects the patient's recovery rates in daily activities, mental clarity, work ability and satisfaction with anaesthesia care. The term 'recovery' is defined as returning to baseline values or better.

Postoperative pain scoring

The NRS is employed to evaluate the intensity of postoperative pain in patients.[32] Patients are requested to indicate a number between 0 and 10, with 0 representing no pain and 10 signifying the most severe pain conceivable. Scores of 1–3 indicate mild pain, 4–6 indicate moderate pain and 7–10 indicate severe pain.

The 1-year overall postoperative mortality rate

The 1-year overall mortality rate of patients should be recorded through on-site follow-ups, electronic medical record system queries and telephone follow-ups.

Other secondary outcomes

Duration of ICU stay, length of hospital stay and time of extubation are recorded according to the electronic medical record.

Statistical analysis

The impact of the intervention will be assessed on a range of outcome measures, including binary, continuous and ordinal data. The statistical methods employed will be selected on the basis of the nature and distribution of each outcome, with due consideration given to the most appropriate approaches.

The data will be analysed using the statistical software package SPSS Statistics, V.26.0 (IBM). The normal distribution of data is evaluated using the Shapiro-Wilk test, and the Levene method is used to test the homogeneity of variance. Quantitative variables that obey a normal distribution are presented as mean±SD. Non-normal distribution data are represented by median (M) and IQR. Binomial variables are expressed as rates. The continuous data that follow a normal distribution are analysed by one-way analysis of variance. The continuous data that do not follow a normal distribution among the three groups are analysed using the Kruskal-Wallis rank-sum test. Categorical data are analysed using the χ^2 test, with the p value adjusted according to the Bonferroni method and fixed at 0.017 for pairwise comparison. A $p<0.05$ is considered to indicate statistical significance. Outcome analyses are conducted on the intention-to-treat population, and a per-protocol analysis is also performed for the primary endpoint. The primary outcome is analysed using a χ^2 test or Fisher's exact test, with the crude OR and 95% CI reported. The adjusted OR (aOR) and 95% CI are calculated for both the primary and secondary outcomes. To handle missing data, multiple imputations by chained equations are used, assuming that the missing data are missing randomly.

A post hoc subgroup analysis will also be conducted. The aim is to compare the effect of cognitive training on subgroups defined by baseline cognitive function, different levels of education, sex and the presence or absence of CPB. When all methods yield consistent conclusions, the results of the study are more credible.

The GraphPad Prism V.9.0 software will be used for the generation of graphical representations. A two-sided $p<0.05$ will be considered to be a significant difference.

Other variables

The preoperative data collection of patient basic information includes the following: gender, age, American society of Anesthesiologists (ASA) physical status classification, body mass index, education level, smoking history, alcohol consumption history, disability status, history of delirium, history of hypertension, history of diabetes, history of stroke or intracranial haemorrhage, albumin level, haemoglobin level and preoperative blood glucose level.

The intraoperative data set includes the following variables: surgical time, type of surgery, duration of CPB (if applicable), aortic clamping time, total CPB time, intraoperative blood glucose level, blood loss, fluid replacement volume, transfusion volume, partial anaesthesia drug use and vasoactive drug use.

The postoperative data collection encompasses the following: any additional sedative and analgesic drugs administered (with a record of the drug types and doses), and postoperative complications such as wound infection, postoperative bleeding, heart failure, pericardial effusion, arrhythmia, acute ischaemic stroke, atelectasis, pulmonary oedema and acute renal dysfunction.

Adverse events

Cognitive training is a patient-led non-pharmacological intervention, typically a brain game on a tablet or smartphone, with minimal physical exertion and non-invasive procedures. The intervention programme poses no additional risks to the patients, as it does not interfere with their surgery or their cardiac rehabilitation. Furthermore, there is no evidence in the literature of risks associated with cognitive training interventions. The physiological and psychological impact of the intervention on patients is minimal, and it may play a preventive role in postoperative cognitive impairment, reducing postoperative complications and improving long-term outcomes. Therefore, the risk to participants is minimal.

Data collection, management and monitoring

All data obtained during the study, including data from electronic medical records, are stored in a locked cabinet (hard copy) and on a password-protected server (electronic). Access to the data is restricted to members of the study team.

The clinical trial will establish data safety monitoring plans corresponding to the magnitude of risk. The principal investigator will conduct regular reviews of all adverse events, convene investigator meetings when necessary to assess the risks and benefits of the study and perform an unmasked strategy when required to ensure the safety and legal rights of subjects. Independent data monitoring personnel will be arranged to monitor the accumulated safety and efficacy data, determining whether the study should continue.

Patient and public involvement

Clinical partners are engaged in the study design process; however, neither patients nor the general public will be involved in the design, conduct, reporting or dissemination plans of the research.

Confidentiality

The confidentiality of data is of the utmost importance, and the collection of data will adhere to the guidelines set forth by the Ethics Committee of the Affiliated Hospital of Xuzhou Medical University. Digitised data devoid of any patient-identifying information will be stored in password-protected files in a secure digital repository. Access to the source data and files will be restricted to members of the research team and auditors/inspectors designated by the Ethics Committee, thereby ensuring complete confidentiality. The informed consent forms and other documents pertaining to the participants will be kept securely throughout the duration of the study.

ETHICS AND DISSEMINATION

The trial is being conducted in accordance with the tenets set forth in the Declaration of Helsinki, and all procedures have been approved by the Ethics Committee of the Affiliated Hospital of Xuzhou Medical University (Ethics number: XYFY2023-KL149-01). Participation is entirely voluntary, and participants are at liberty to withdraw from the study at any time. Should any amendments be made to the protocol, these will be communicated promptly to the research team, the Ethics Committee and the Chinese Clinical Trial Registry (ChiCTR) via email. This will include any changes to the eligibility criteria, the outcomes or the analysis procedures. Furthermore, any amendments to the protocol will be duly recorded in the ChiCTR.

The findings of this research will be disseminated through presentations at relevant academic conferences and publication in peer-reviewed journals. Moreover, efforts will be made to disseminate the study results, trial tools and other resources to supporting institutions, such as the Affiliated Hospital of Xuzhou Medical University.

Acknowledgements Furthermore, we extend our gratitude to all research personnel and participants for their invaluable assistance.

Contributors XQ and LW drafted the manuscript. YZ, XQ and LW conceived the idea for the project and contributed to the study's design. XW, QM, CL, JQ and HY were involved in the oversight of the data collection. FL, QY and WZ revised the manuscript. All authors approved the final manuscript. YZ is responsible for the overall content as guarantor.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

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 Consent obtained directly from patient(s).

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iD

Yueying Zhang http://orcid.org/0009-0009-6081-7008

REFERENCES

1 Silverstein JH, Timberger M, Reich DL, *et al*. Central nervous system dysfunction after noncardiac surgery and anesthesia in the elderly. *Anesthesiology* 2007;106:622–8.
2 Vasilevskis EE, Han JH, Hughes CG, *et al*. Epidemiology and risk factors for delirium across hospital settings. *Best Pract Res Clin Anaesthesiol* 2012;26:277–87.

3 Kostas TRM, Zimmerman KM, Rudolph JL. Improving delirium care: prevention, monitoring, and assessment. *Neurohospitalist* 2013;3:194–202.
4 Rudolph JL, Harrington MB, Lucatorto MA, *et al*. Validation of a medical record-based delirium risk assessment. *J Am Geriatr Soc* 2011;59 Suppl 2:S289–94.
5 McDaniel M, Brudney C. Postoperative delirium: etiology and management. *Curr Opin Crit Care* 2012;18:372–6.
6 American Psychiatric Association (APA). *Diagnostic and Statistical Manual of Mental Disorders*. 5th edn. Arlington, VA, USA: American Psychiatric Publishing, 2013.
7 Gleason LJ, Schmitt EM, Kosar CM, *et al*. Effect of Delirium and Other Major Complications on Outcomes After Elective Surgery in Older Adults. *JAMA Surg* 2015;150:1134–40.
8 Redelmeier DA, Manzoor F, Thiruchelvam D. Association Between Statin Use and Risk of Dementia After a Concussion. *JAMA Neurol* 2019;76:887–96.
9 Saczynski JS, Marcantonio ER, Quach L, *et al*. Cognitive trajectories after postoperative delirium. *N Engl J Med* 2012;367:30–9.
10 Järvelä K, Porkkala H, Karlsson S, *et al*. Postoperative Delirium in Cardiac Surgery Patients. *J Cardiothorac Vasc Anesth* 2018;32:1597–602.
11 Wang H-B, Jia Y, Zhang C-B, *et al*. A randomised controlled trial of dexmedetomidine for delirium in adults undergoing heart valve surgery. *Anaesthesia* 2023;78:571–6.
12 Sadlonova M, Duque L, Smith D, *et al*. Pharmacologic treatment of delirium symptoms: A systematic review. *Gen Hosp Psychiatry* 2022;79:60–75.
13 Neufeld KJ, Yue J, Robinson TN, *et al*. Antipsychotic Medication for Prevention and Treatment of Delirium in Hospitalized Adults: A Systematic Review and Meta-Analysis. *J Am Geriatr Soc* 2016;64:705–14.
14 van den Boogaard M, Slooter AJC, Brüggemann RJM, *et al*. Effect of Haloperidol on Survival Among Critically Ill Adults With a High Risk of Delirium: The REDUCE Randomized Clinical Trial. *JAMA* 2018;319:680–90.
15 Fukata S, Kawabata Y, Fujisiro K, *et al*. Haloperidol prophylaxis does not prevent postoperative delirium in elderly patients: a randomized, open-label prospective trial. *Surg Today* 2014;44:2305–13.
16 Schrijver EJM, de Vries OJ, van de Ven PM, *et al*. Haloperidol versus placebo for delirium prevention in acutely hospitalised older at risk patients: a multi-centre double-blind randomised controlled clinical trial. *Age Ageing* 2018;47:48–55.
17 Loewenstein DA, Acevedo A, Czaja SJ, *et al*. Cognitive rehabilitation of mildly impaired Alzheimer disease patients on cholinesterase inhibitors. *Am J Geriatr Psychiatry* 2004;12:395–402.
18 Humeidan ML, Reyes J-PC, Mavarez-Martinez A, *et al*. Effect of Cognitive Prehabilitation on the Incidence of Postoperative Delirium Among Older Adults Undergoing Major Noncardiac Surgery: The Neurobics Randomized Clinical Trial. *JAMA Surg* 2021;156:148–56.
19 O'Gara BP, Mueller A, Gasangwa DVI, *et al*. Prevention of Early Postoperative Decline: A Randomized, Controlled Feasibility Trial of Perioperative Cognitive Training. *Anesth Analg* 2020;130:586–95.
20 Neurology Physician Branch of Chinese Medical Doctor Association, China Guide Writing Group for Cognitive Training. Chinese Guidelines for Cognitive Training. *Chin J Med* 2022;102:2918–25.
21 Lee-Archer P, McBride C, Paterson R, *et al*. Does dexmedetomidine given as a premedication or intraoperatively reduce post-hospitalisation behaviour change in children? A study protocol for a randomised controlled trial in a tertiary paediatric hospital. *BMJ Open* 2018;8:e019915.
22 Shehabi Y, Riker RR, Bokesch PM, *et al*. Delirium duration and mortality in lightly sedated, mechanically ventilated intensive care patients. *Crit Care Med* 2010;38:2311–8.
23 Inouye SK, van Dyck CH, Alessi CA, *et al*. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. *Ann Intern Med* 1990;113:941–8.
24 Ely EW, Inouye SK, Bernard GR, *et al*. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). *JAMA* 2001;286:2703–10.
25 Ely EW, Truman B, Shintani A, *et al*. Monitoring sedation status over time in ICU patients: reliability and validity of the Richmond Agitation-Sedation Scale (RASS). *JAMA* 2003;289:2983–91.
26 Kang JM, Cho Y-S, Park S, *et al*. Montreal cognitive assessment reflects cognitive reserve. *BMC Geriatr* 2018;18:261.
27 Mitchell AJ. A meta-analysis of the accuracy of the mini-mental state examination in the detection of dementia and mild cognitive impairment. *J Psychiatr Res* 2009;43:411–31.
28 Evered L, Silbert B, Knopman DS, *et al*. Recommendations for the nomenclature of cognitive change associated with anaesthesia and surgery-2018. *Can J Anaesth* 2018;65:1248–57.
29 Huang M-C, Lee C-H, Lai Y-C, *et al*. Chinese version of the Delirium Rating Scale-Revised-98: reliability and validity. *Compr Psychiatry* 2009;50:81–5.
30 Yesavage JA, Brink TL, Rose TL, *et al*. Development and validation of a geriatric depression screening scale: a preliminary report. *J Psychiatr Res* 1982;17:37–49.
31 Royse CF, Newman S, Chung F, *et al*. Development and feasibility of a scale to assess postoperative recovery: the post-operative quality recovery scale. *Anesthesiology* 2010;113:892–905.
32 Farrar JT, Young JP Jr, LaMoreaux L, *et al*. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain* 2001;94:149–58.