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The effect of different duration of preoperative computerized cognitive training on postoperative delirium in elderly patients undergoing cardiac surgery: a study protocol for a prospective, randomized controlled trial

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The effect of different duration of preoperative computerized cognitive training on postoperative delirium in elderly patients undergoing cardiac surgery: a study protocol for a prospective, randomized controlled trial

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ABSTRACT

Introduction Postoperative delirium (POD) is a common neurological complication after surgery among elderly patients, characterized by acute disturbances in consciousness, attention, and cognition, usually occurring within 24 to 72 hours after surgery[1]. Postoperative delirium (POD) has a significant impact on the prognosis of elderly patients undergoing major cardiac vascular surgery, including increased length of hospital stay, hospital costs, and readmission rates, with an incidence rate as high as 26% to 52%[2]. Computerized Cognitive Training (CCT) refers to difficulty-adaptive training in cognitive domains such as attention, memory, and logical reasoning, using systematically designed tasks[3]. Existing studies have showed that CCT has reduced the risk of delirium in non-cardiac surgery patients with at least minimal compliance[4]. The purpose of this study is to investigate the effects of Computerized Cognitive Training (CCT) on postoperative delirium in elderly 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-blinded, randomized controlled trial that aims to enroll 261 elderly patients scheduled for elective cardiac surgery at the Affiliated Hospital of Xuzhou Medical University. The patients will be randomly divided into three groups: Group C will be the routine care group (no CCT prior surgery); Group L will be the low-dose time group (with a total of 5 hours of CCT prior surgery); Group H will be the high-dose time group (with a total of 10 hours of CCT prior surgery). The primary outcome is the incidence of delirium within 7 days after surgery. Secondary outcomes include the incidence of delayed neurocognitive recovery (from 7 to 30 days), the incidence of postoperative cognitive dysfunction (from 30 days to 1 year), the onset time and duration and severity of delirium, and all-cause mortality rate within 1 year after surgery. The results of this study are of significant importance for establishing effective, patient-led, and low-risk prevention strategies for postoperative delirium/postoperative cognitive dysfunction.

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Key words Computerized Cognitive Training; Cardiac surgery; Elderly; Postoperative Delirium

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 This study protocol has been developed in accordance with clinical practice guidelines and has been registered with the China Clinical Trials Center (Registration Number: ChiCTR2300072806).

- **The study investigates the effects of computerized cognitive training on postoperative delirium among elderly patients undergoing elective cardiac surgery.**
- **This study is divided into three groups for the first time to explore the effects of different duration of preoperative computerized cognitive training on postoperative delirium.**
- **Although postoperative delirium typically occurs within 72 hours after surgery, we follow up with patients until 1 year to assess their postoperative cognitive function.**
- **This study is a single-center clinical trial with elderly cardiac surgery patients as the subjects, which has inherent limitations. Further multi-center studies with larger sample sizes are needed.**
- **The study uses subjective scales to quantify the research results, lacking objective evidence such as laboratory indicators like S100β protein, neuron-specific enolase (NSE), which can reflect postoperative delirium to some extent.**

INTRODUCTION

Postoperative delirium (POD) is an acute brain dysfunction characterized 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 to 72 hours after surgery. The incidence rates range from 5% to 62%[1]. Based on clinical presentation, postoperative delirium (POD) can be categorized into three types: hyperactive, inactive, or mixed. Hyperactive delirium, which accounts for approximately 25% of cases, is characterized by noticeable clinical symptoms such as restlessness, irritability, sudden aggression, hallucinations, and incoherent speech. Inactive delirium, comprising about 50% of cases, presents with less obvious clinical features including drowsiness, silence, and reduced activity, making it easy to overlook. Mixed delirium, representing around 25% of cases, exhibits features of both hyperactive and inactive delirium. Postoperative delirium of cardiovascular surgery

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(PODOCVS) has a high incidence rate ranging from 26% to 52%, which is significantly higher compared to other surgical procedures such as spine surgery (3.3% to 19.5%), abdominal surgery (10.7% to 25%), urological surgery (8.8% to 26%), and cataract surgery (5%)[2]. The gold standard for diagnosing postoperative delirium is based on the Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (DSM-5) published by the American Psychiatric Association. The main diagnostic features include acute onset and fluctuating symptoms, decline in cognitive function, disruption of attention, and altered level of consciousness. Supportive features include abnormal sleep-wake cycle, perceptual disturbances (hallucinations or illusions), mental disturbances (inactivity or hyperactivity), and behavioral and emotional disturbances. Other potential causes of the current symptoms and severe reduction in the patient's level of consciousness (such as coma) must be ruled out. Research has shown that postoperative delirium has numerous adverse effects on patient outcomes, including increased length of hospital stay and hospital costs, higher short-term and long-term mortality rates, increased complications, decreased ability for self-care, and long-term decline in postoperative cognitive function[5-7], especially PODOCVS[8].

The prevention measures for postoperative delirium of cardiovascular surgery (PODOCVS) mainly include pharmacological and non-pharmacological approaches. Pharmacological prevention has limited effectiveness in preventing postoperative delirium, with some approaches even being ineffective. Importantly, pharmacological prevention carries potential risks such as sedation, extrapyramidal symptoms, orthostatic hypotension, and arrhythmias[9]. It is not recommended to use medication to prevent the risk of PODOCVS. Cognitive training is considered a proactive and effective non-pharmacological intervention that may reduce the risk of delirium and improve postoperative cognitive function in surgical patients. Cognitive training is a cognitive intervention method that applies various cognitive tasks to enhance cognitive function, and in recent years, it has gradually shifted from traditional paper-and-pencil, instructional training methods to computerized cognitive training that is adaptive in difficulty and focuses on skill enhancement[10]. A recent study by Humeidan et al. suggests that preoperative cognitive training can reduce the incidence of delirium in patients aged 60 and above undergoing non-cardiac and non-neurological surgeries. This randomized single-blind clinical trial used electronic tablet-based cognitive exercises targeting memory, speed, attention, flexibility, and problem-solving skills. Compared to the control group, the cognitive training group showed a significant reduction in delirium rates. Moreover, in the cognitive intervention group, incidence of delirium was twice as prevalent among those who played less than 5 hours than those completing more than 10 hours. However, there were no statistically significant differences between the two groups in terms of delirium onset time, duration, and total days with delirium positivity[11]. A study demonstrated the feasibility of perioperative cognitive training via mobile devices in elderly patients undergoing cardiac surgery. The research found that patients scheduled for elective cardiac surgery were most likely to adhere to the training program and had sufficient time for such interventions before surgery[4].

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A structured preoperative computerized cognitive training(CCT) program may have a more pronounced effect on reducing the incidence of postoperative delirium (POD). However, there are several challenges in current clinical practice. Firstly, the quality of training is difficult to ensure without supervision and guidance, as highlighted in the Cognitive Training Guidelines for China (2022), which recommend implementing cognitive training in specialized centers for optimal efficacy. Secondly, in many elective surgeries, patients cannot guarantee sufficient preoperative training time before surgery, and the dose-response relationship between training time and cognitive improvement is unknown. At last, some patients undergoing routine surgeries may not prioritize cognitive training, leading to poor compliance, as demonstrated in previous studies. Therefore, we aim to find an efficient training program that achieves optimal cognitive improvement in the shortest time possible, to facilitate its implementation in clinical practice. Based on these reasons, we have designed a randomized clinical trial where elderly patients scheduled for elective cardiac surgery will undergo varying duration of preoperative computerized cognitive training under the guidance of trained professionals, to evaluate the impact of different training time on POD in this patient population.

METHODS AND ANALYSIS

Study design

A prospective, single-center, randomized controlled trial was designed to evaluate the impact of computerized cognitive training(CCT) on the incidence of postoperative delirium (POD) in elderly patients undergoing elective cardiac surgery. It aims to clarify the dose-response relationship between different duration of preoperative CCT and POD, exploring the minimum effective time target that significantly improves POD. This trial is an innovative, patient-led, low-risk intervention and has been registered in the Chinese Clinical Trial Registry (ChiCTR2300072806). The study is scheduled to commence on July 1, 2023, and is planned to conclude on October 31, 2024. It includes three groups: the routine care group (C group), low-dose time group (L group), and high-dose time group (H group). Figure 1 shows the patients flow chart of this RCT.

Study population

The CCT trial aims to enroll patients aged 60 and above undergoing elective cardiac surgery at the Affiliated Hospital of Xuzhou Medical University. Patients meeting the inclusion criteria will be informed about the study details and required to sign a written informed consent form before randomization, respecting individual autonomy and ethical principles. Details of the inclusion and exclusion criteria are shown in Table 1.

Recruitment, randomization and blinding

Recruitment of participants

All subjects will be recruited on the first day after admission. Trained researchers will conduct baseline assessments, and recommend eligible patients who meet the

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inclusion criteria to participate in the study. Written informed consent will be obtained from patients and their families before randomization and trial inclusion. After the baseline assessment, eligible subjects (n=261) will be randomized by researchers who are unknown of preoperative assessment tests. The results will be measured at the following time points: on admission (T0), postoperative day 1 to day 5 and day 7 (T1~T6, T7), postoperative day 30 (T8), postoperative day 90 (T9), and postoperative one year (T10).

Randomization

The study employs a computer-generated random number table to randomize eligible patients(as shown in Table 1) into the routine care group (C group, no CCT before surgery), low-dose time group (L group, total CCT time of 5 hours before surgery), and high-dose time group (H group, total CCT time of 10 hours before surgery). The group allocation information is stored in sealed envelopes, sequentially numbered, ensuring strict sealing and blinding procedures to minimize selection bias. The randomization process will be conducted by an unbiased and unrelated graduate student (Student A).

Blinding

Patients cannot be blinded before surgery in this study, but they are informed that they may be assigned to either the routine care group or the computerized cognitive training group without knowledge of the specific design and training protocol of the study. Unblinding for patients in the intervention group will occur at the final follow-up (1 year), where they will be informed of the detailed research plan. Blinding for researchers is maintained by separating preoperative cognitive training and postoperative follow-up activities. Researchers who provide preoperative guidance and supervise the computerized cognitive training will withdraw from the subsequent follow-up of patients after they undergo surgery. Postoperative follow-up will be conducted by other researchers who are unaware of the group assignments. Data collection after discharge will avoid inquiring about preoperative training information from patients, and if accidental unblinding occurs, the follow-up researcher will be replaced at the next follow-up.

Sample size

Previous studies have shown that the incidence of postoperative delirium (POD) after cardiac surgery in elderly patients is approximately 50%[2]. Clinical significant reduction in POD occurrence rate is defined as reducing the overall ratio from 50% to 25%. The effect size will be calculated by determining the proportion difference between two of the three groups and pooling data from the two comparison groups. Therefore, assuming a power of 90% and α=0.05, each group will require 78 participants, considering a 10% dropout rate, which results in an actual sample size of 87 participants per group and a total sample size of 261 participants[12].

Intervention

During hospitalization, after obtaining written informed consent from the patients, baseline assessments will be conducted using questionnaire evaluations. The

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assessments will cover areas such as depression, anxiety, health-related quality of life, cognitive and social activities in daily life, and recent sleep quality. These assessments must be completed by the patients themselves. Patients who have completed the testing and meet the eligibility criteria will be randomly assigned to one of three groups. All three groups will undergo routine laboratory tests, preoperative preparations, health education promotion, and ward safety management. Upon entering the operating room, all patients will undergo routine monitoring of electrocardiography, blood pressure, pulse, oxygen saturation and BIS. After establishing intravenous access, dexmedetomidine will be administered at a rate of $0.5\mu g \cdot kg^{-1} \cdot h^{-1}$. Invasive arterial blood pressure monitoring will be performed under ultrasound-guided radial artery cannulation. General anesthesia will be induced using lidocaine 1~2mg • kg^{-1}, etomidate 0.2mg • kg^{-1}, rocuronium 0.6~0.9mg • kg^{-1}, and sufentanil $7\mu g \cdot kg^{-1}$. Manual ventilation via a mask will be conducted for 3~5 minutes until adequate muscle relaxation is achieved for intubation, followed by the insertion of a cuffed endotracheal tube with a TEE probe. Anesthesia maintenance will include propofol infusion at 2~4mg • kg^{-1} • h^{-1}, continuous infusion of cisatracurium, adjustment of tidal volume to maintain $PetCO_2$ between 35~45mmHg, and maintenance of anesthesia depth (BIS 40-60). Heparinization with 3mg • kg^{-1} of heparin will be administered after sternotomy, reduced to 1.5mg • kg^{-1} if no cardiopulmonary bypass is required, and protamine will be used to reverse heparin after major procedures. After surgery, patients will be transferred to the 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 preparations, routine vital signs monitoring, and health education. Additionally, no additional cognitive intervention will be provided.

Computerized Cognitive Training Group (Group L & H)

In addition to receiving routine care, patients in the L group will undergo 1 hour of computerized cognitive training each day for 5 days before surgery, totaling 5 hours of training. Patients in the H group will undergo 1 hour of computerized cognitive training twice a day (morning and evening) for 5 days before surgery, totaling 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, providing extensive practice on the cognitive domains include attention, memory, logic, reaction time, speed, and language. Patients in the intervention groups are required to complete at least one game in each domain, and the intervention process will be conducted under the full supervision of research personnel to ensure training effectiveness.(see in Figure 2)

Trained research personnel, who are not involved in preoperative cognitive intervention and are unaware of the grouping, will use the CAM (Confusion Assessment Method) and CAM-ICU (Confusion Assessment Method for the Intensive Care Unit) scales to assess the presence of delirium in patients both before surgery

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and during the postoperative period. Assessments will be conducted at about 24 h after surgery and then twice daily on the subsequent six postoperative days, 08:00-10:00 and 18:00-20:00. If a patient exhibits delirium (CAM/CAM-ICU positive), the severity of delirium will be recorded using the Delirium Rating Scale-Revised-98 (DRS-R-98). We calculated the duration of delirium as the cumulative number of days during which at least one assessment diagnosed delirium[13] . For patients meeting diagnostic criteria, enhanced follow-up will be conducted. From postoperative days 1 to 5 (each afternoon), the PQRS will be used to assess postoperative recovery quality, and the Numerical Rating Scale (NRS) will be used to assess pain intensity at rest. On postoperative day 7, the CAM scale will be used again for patient assessment. Cognitive function will be evaluated using the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA), while postoperative recovery quality will be assessed using the Postoperative Quality Recovery Scale (PQRS). For patients discharged earlier, follow-up will be conducted via telephone. Follow-up assessments will be conducted via telephone on postoperative days 30, 90, and 1 year, using the GDS, MMSE, MoCA, Katz Index of Independence in Activities of Daily Living, and PQRS scales to evaluate patients' status comprehensively.

Retention and adherence

To maximize the retention of enrolled patients, we have implemented multiple measures. Firstly, we provide a thorough explanation of the research objectives to potential participants who meet the criteria, addressing any questions they may have about the study before formal enrollment. Secondly, before randomization, we conduct compliance screening to ensure that enrolled participants commit to cooperating with the training. Finally, we seek support and assistance from patients' family members, caregivers, and bedside healthcare providers. Patients who cannot commit to full cooperation during the screening phase will not be randomized. After randomization, the research personnel responsible for the intervention will conduct one-on-one computerized cognitive training with patients at specified times and locations to ensure that the training duration is met. Upon enrollment, we obtain at least two contact numbers from each patient to minimize loss to follow-up during subsequent assessments. We provide encouragement and assistance to participants throughout the intervention process and actively communicate with their family members and caregivers, sharing training effects and intervention progress when appropriate, to ensure smooth cooperation with our intervention among enrolled patients.

Outcome measures

The data were collected by well-trained researchers at baseline and follow-up assessments through on-site evaluations and phone 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),

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postoperative 30 days(T8), postoperative 90 days (T9), and postoperative 1 year (T10) (see Table 2 for details).

Primary outcome measures

The incidence of postoperative delirium (POD) within 7 days: Assessed by the CAM scale[14]. The CAM assessment covers four main aspects: 1) acute change or fluctuation in consciousness state; 2) lack of concentration; 3) disorganized thinking; and 4) altered level of consciousness. A diagnosis of POD is made if the patient exhibits both 1) and 2), along with either 3) or 4). In cases where the patient is in the ICU, the CAM-ICU[15] scale is used for assessment. Prior to using the CAM-ICU, sedation depth is evaluated using the Richmond Agitation-Sedation Scale (RASS)[16]. If the RASS score is -4 or -5, indicating unconsciousness, the assessment is stopped. However, if the RASS score is⩾-3, the CAM-ICU assessment for delirium status continues.

Secondary outcome measures

The incidence of delayed neurocognitive recovery (7~30 days) and postoperative cognitive dysfunction (30 days~1 year) : Assessed by using MoCA[17] and MMSE[18] at postoperative days 7, 30, 90, and 1 year, assessing patients' cognitive reserves and early cognitive decline. Telephone follow-ups are conducted for discharged patients. MoCA and MMSE cover a wide range of cognitive domains, including memory, language, attention, calculation, abstract thinking, orientation, visuospatial skills, and executive function.

The time of onset, duration, and severity of delirium: Assessed by using the Delirium Rating Scale-Revised-98 (DRS-R-98)[19], including 13 assessment items covering aspects such as sleep-wake cycle disturbances, 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 as 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: The patients will be assessed using the Geriatric Depression Scale (GDS)[20] to confirm the absence of active depression prior surgery. On postoperative days 30, 90, and 1 year, the GDS is used to assess whether the surgical patients developed depression. The GDS score consists of 30 items that represent the core of geriatric depression, including feelings of sadness, reduced activity, irritability, thoughts of withdrawal, negative evaluations of the past, present, and future. Scores on the GDS range from 0 to 30, with 0 to 10 indicating no clinically significant depressive symptoms, 11 to 20 indicating mild symptoms, and 21 to 30 indicating moderate to severe symptoms.

Postoperative recovery quality: The Postoperative Quality Recovery Scale (PQRS) [21] is used to assess patients' recovery status at multiple time points and in various

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domains after surgery. The scale is not designed to demonstrate cognitive decline but rather to evaluate cognitive recovery compared to baseline. PQRS consists of six domains (physiological, nociceptive, emotional, activities of daily living, cognitive, and overall patient assessment).

Physiological: Includes measures like systolic blood pressure, heart rate, temperature, respiratory rate, and oxygen saturation, assessing physiological recovery.

Nociceptive: Covers pain and nausea assessment, reflecting aspects of pain management and discomfort.

Emotional: Involves evaluating depression and anxiety levels.

Activities of Daily Living (ADL): Assesses the ability to perform daily activities independently, such as standing, walking, dressing, and self-care.

Cognitive: Includes five tests evaluating orientation, language memory, executive function, attention, and concentration.

Overall Patient Assessment: Reflects patients' recovery rates in daily activities, mental clarity, work ability, and satisfaction with anesthesia care. "Recovery" is defined as returning to baseline values or better[21].

Postoperative pain scoring: The Numerical Rating Scale (NRS) is used to assess postoperative pain intensity in patients[22]. Patients are asked to indicate a number ranging from 0 to 10, where 0 represents no pain and 10 represents the most severe pain imaginable. Scores of 1 to 3 indicate mild pain, 4 to 6 indicate moderate pain, and 7 to 10 indicate severe pain.

The overall one-year postoperative mortality rate: Recording the one-year overall mortality rate of patients through on-site follow-ups, querying electronic medical record systems, and conducting telephone follow-ups.

Statistical analysis

We will assess the impact of the intervention on various outcome measures, including quantitative, qualitative, and ordinal data. Our statistical methods will be chosen based on the nature and distribution of each outcome, considering appropriate approaches.

Use the Shapiro-Wilk test to determine if continuous data follows a normal distribution. The Levene test will be used for estimating the difference (and 95% confidence interval) between the three means or medians. Normally distributed continuous data will be presented as mean $\pm$ standard deviation (SD), while non-normally distributed data will be presented as median (M) and interquartile range (IQR). Categorical variables will be expressed as the percentage. For within-group repeated measurements at different time points, use Generalized Estimating Equation analysis. For normally distributed continuous data comparisons between three groups at the same time point, use ANOVA, followed by LSD test for pairwise comparisons and *Bonferroni* correction for multiple comparisons.

For non-normally distributed continuous data comparisons between three groups, use Kruskal-Wallis H rank-sum test, and for pairwise comparisons use Mann-Whitney U test. For comparisons of unordered categorical variable data between three groups, use chi-square test, choosing between Pearson's chi-square test or Fisher's exact test

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based on sample size and minimum expected frequency. The Kaplan-Meier estimates will be applied for the time to event results.

Post hoc subgroup analysis will also be done, as well as intention-to-treat analysis and per-protocol analysis to validate the robustness of the results. When all methods yield consistent conclusions, it increases the credibility of the study results.

We will use SPSS 26.0 software (IBM Co., Armonk, NY, USA) and R software for statistical processing and GraphPad Prism 9.0 for plotting. A two-sided p value < 0.05 will be considered to be a significant difference.

Other variables

Preoperative data collection of patient basic information includes: gender, age, ASA classification, BMI, education level, smoking history, alcohol consumption history, disability status, history of delirium, history of hypertension, history of diabetes, history of stroke or intracranial hemorrhage, albumin level, hemoglobin level, and preoperative blood glucose level.

Intraoperative data includes: surgical time, type of surgery, duration of cardiopulmonary bypass (if applicable), pre-bypass time, aortic clamping time, post-bypass time, total cardiopulmonary bypass time, intraoperative blood glucose level, blood loss, fluid replacement volume, transfusion volume, use of partial anesthesia drugs, and use of vasoactive drugs.

Postoperative data collection includes: duration of ICU stay, extubation time, additional sedative and analgesic drugs administered (if any, with record of drug types and doses), and postoperative complications such as wound infection, postoperative bleeding, heart failure, pericardial effusion, arrhythmia, acute ischemic stroke, atelectasis, pulmonary edema, 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. It has little physiological or psychological impact on patients and plays a preventive role in postoperative cognitive impairment, reducing postoperative complications and improving long-term outcomes. Therefore, it poses minimal risk to participants.

If acute postoperative delirium occurs within 7 days after surgery, we will administer midazolam for sedation, closely monitor vital signs, and observe changes in cognitive and emotional aspects. For delayed neurocognitive recovery or postoperative neurocognitive disorder (NCD), if it is mild cognitive impairment, we will enhance nursing care, provide functional exercises, and closely monitor changes in the patient's condition. In cases of severe cognitive dysfunction such as dementia, we recommend seeking specialized psychiatric evaluation and treatment.

Data collection, management and monitoring

All data obtained during the study, including data from electronic medical records, are kept in a locked cabinet (hard copy) and stored on a password-protected server

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(electronic). Only members of the study team can enter and analyse data.

The clinical trial will formulate corresponding data safety monitoring plans based on the magnitude of risk. During the implementation phase of the clinical study, all adverse events will be meticulously documented, appropriately handled, and tracked until resolved or stabilized, with timely reporting to the Ethics Committee and competent authorities for serious adverse events and accidents. The principal investigator will regularly review all adverse events cumulatively, convene investigator meetings when necessary to assess the risks and benefits of the study. The trial is single-blinded, an unmasked strategy will be performed as necessary 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 statement

Clinical partners were involved in the study design; however, subjects or the public will not be involved in the development, design, or implementation of the study.

Confidentiality

Data confidentiality is of utmost importance, and data collection will adhere to the guidelines of the Ethics Committee of the Affiliated Hospital of Xuzhou Medical University. Digitized data without patient identifying information will be securely stored in password-protected files. Access to the source data/files will be restricted to authorized research team members and auditors/inspectors designated by our Ethics Committee, ensuring complete confidentiality. Informed consent forms and other participant-related documents will be securely retained throughout the study.

Ethics and dissemination

The trial is being conducted in accordance with the Helsinki Declaration, 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 voluntary, and participants have the right to withdraw from the study at any time. Any amendments to the protocol regarding changes in eligibility criteria, outcomes, or analysis procedures will be communicated promptly to the research team, Ethics Committee, and ClinicalTrials.gov via email. Updates to the protocol will also be recorded in ClinicalTrials.gov.

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

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Author Contributions XQ drafted the manuscript. YZ, XQ, LW conceived the idea for the project and contributed to the study's design. XW, QM, CL, JQ involved in the oversight of the data collection. FL, YQ and WZ revised the manuscript. All authors approved the final manuscript.

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Competing interests None declared.

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Supplemental material

Inclusion Criteria	➢ Anticipated ASA physical status I-IV;
	➢ Age≥ 60;
	➢ Receiving any type of the following surgery under general anesthesia: coronary artery bypass grafting with or without valve surgery (aortic and/or mitral valve), valve surgery;
	➢ Meeting inclusion criteria at least 5 days prior to their surgical procedure
Exclusion Criteria	➢ Self-reported diagnosis of psychiatric illness such as anxiety or depression, stroke, dementia, epilepsy, Parkinson's disease, Alzheimer disease or other forms of cognitive decline;
	➢ Addicted to alcohol and psychotropic drugs;
	➢ Presence of significant auditory or visual impairment;
	➢ Score<24 on Mini-mental Status Exam (MMSE) (20 for patients with less than high school education, 17 for illiterate patients);
	➢ Positive preoperative Confusion Assessment Method test (CAM);
	➢ Active depression (score>10 on Geriatric Depression Scale);
	➢ Participation in other research studies;
☆Elimination Criteria	➢ Death within 24 hours after surgery;
	➢ Participants ask to terminate the trial.

Table 1 Inclusion and exclusion criteria.

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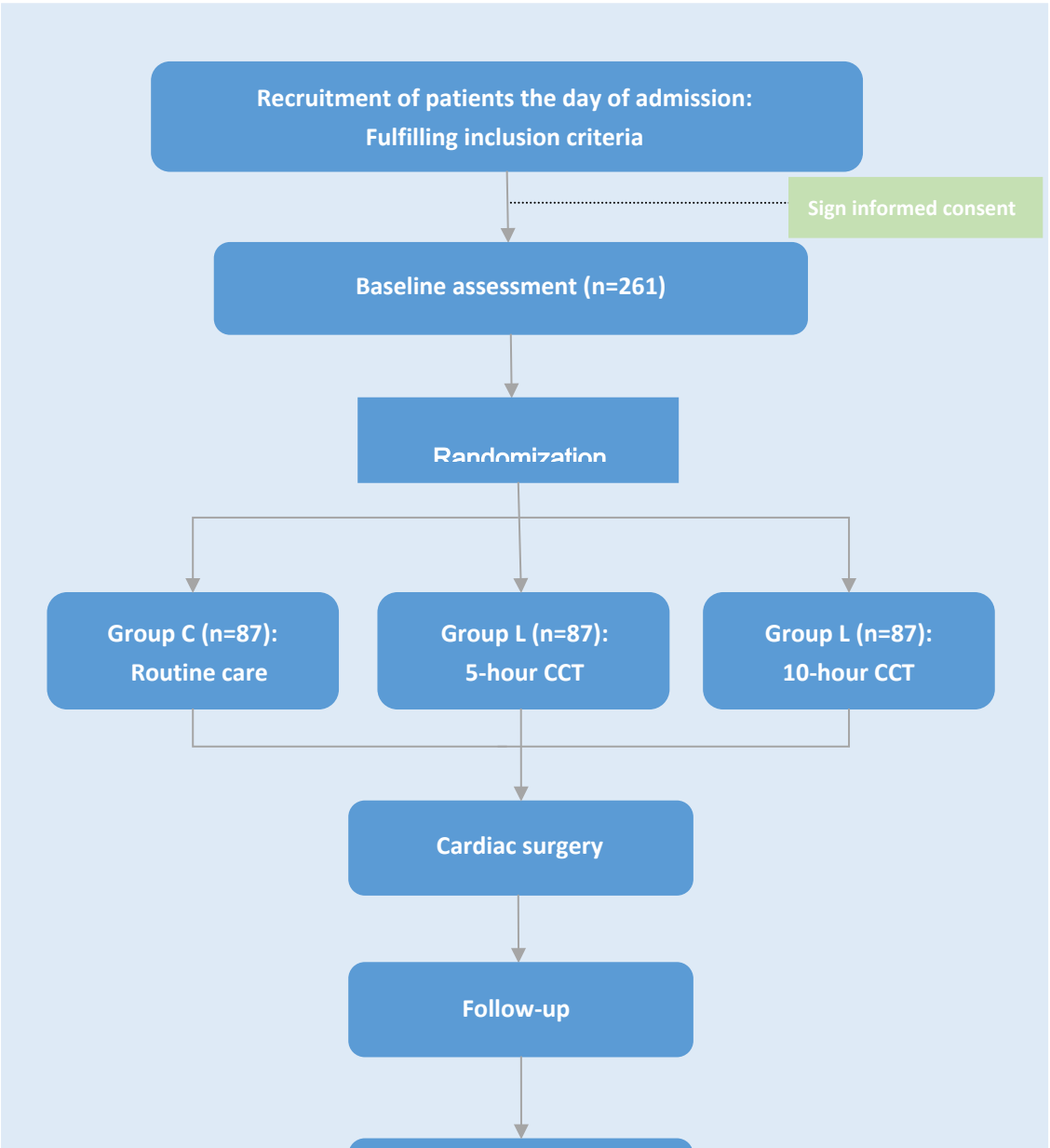

Figure 1 **Flow chart of this RCT.**

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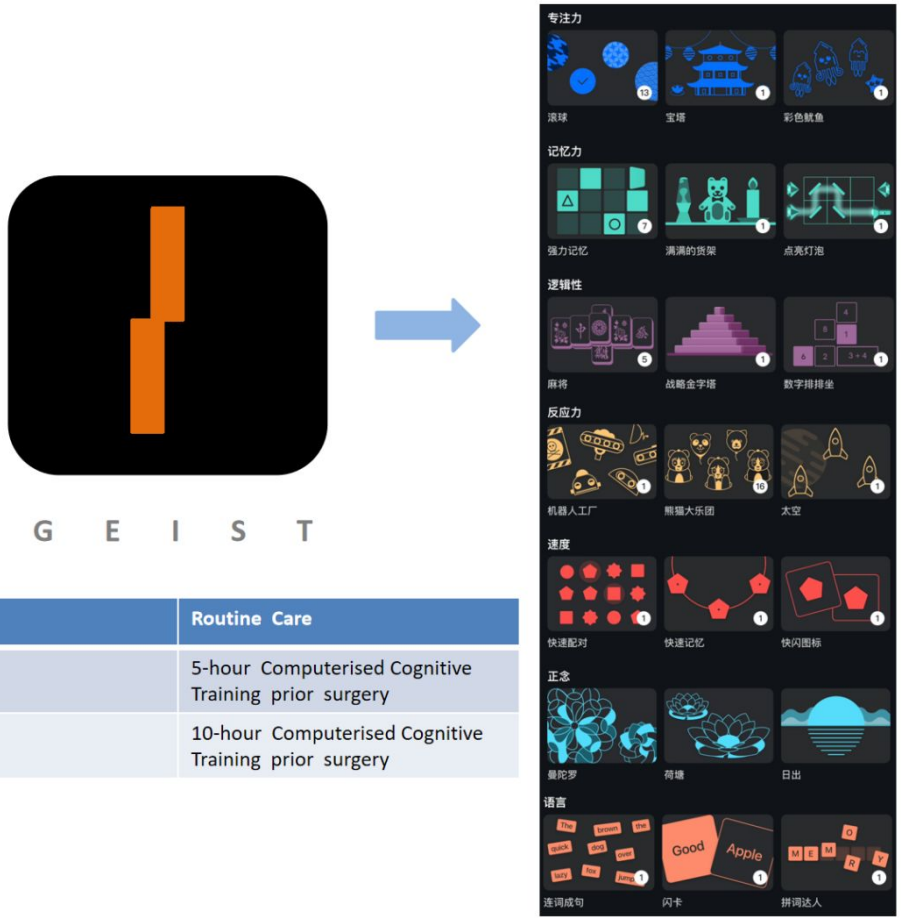

Group C	Routine Care
Group L	5-hour Computerised Cognitive Training prior surgery
Group H	10-hour Computerised Cognitive Training prior surgery

Figure 2 The app for the computerized cognitive training of elderly patients undergoing elective cardiac surgery.

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Variables	The day of admission	Follow-up				
		POD0~5	POD7	POD30	POD90	POD365
Written informed consent form	√					
MMSE	√		√	√	√	√
MoCA	√		√	√	√	√
GDS	√			√	√	√
CCI	√					
PQRS	√	√	√	√	√	√
PSQI	√					
CAM/CAM-ICU	√	√	√			
DRS-R-98 (If delirium occur)		√	√			
NRS		√				
Katz				√	√	√

MMSE, Mini-mental State Examination; MoCA, Montreal Cognitive Assessment; GDS, Geriatric Depression Scale; CCI, Charlson Comorbidity Index; PQRS, Postoperative Quality Recovery Scale; PSQI, Pittsburgh Sleep Quality Index; CAM/CAM-ICU, The Confusion Assessment Method/The confusion assessment method for the intensive care unit; DRS-R-98, Delirium Rating Scale-Revised-98; NRS, Numerical Rating Scale.

Table 2 Schedule of visits and assessments.

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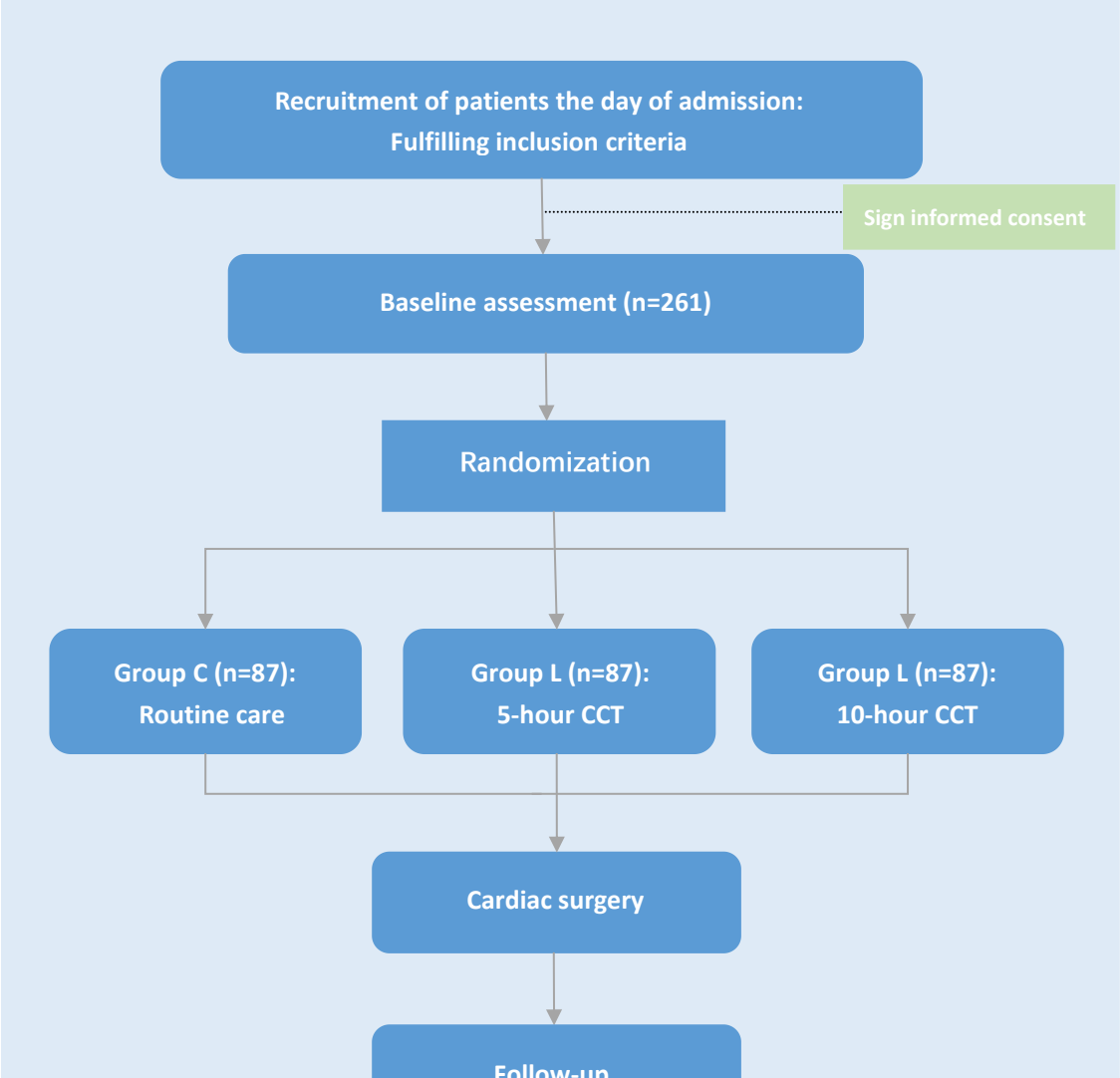

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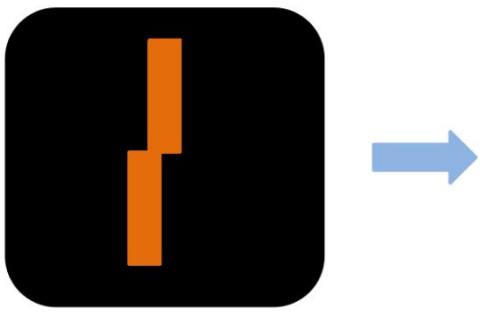

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Variables	The day of admission	Follow-up				
		POD0~5	POD7	POD30	POD90	POD365
Written informed consent form	√					
MMSE	√		√	√	√	√
MoCA	√		√	√	√	√
GDS	√			√	√	√
CCI	√					
PQRS	√	√	√	√	√	√
PSQI	√					
CAM/CAM-ICU	√	√	√			
DRS-R-98 (If delirium occur)		√	√			
NRS		√				
Katz				√	√	√

MMSE, Mini-mental State Examination; MoCA, Montreal Cognitive Assessment; GDS, Geriatric Depression Scale; CCI, Charlson Comorbidity Index; PQRS, Postoperative Quality Recovery Scale; PSQI, Pittsburgh Sleep Quality Index; CAM/CAM-ICU, The Confusion Assessment Method/The confusion assessment method for the intensive care unit; DRS-R-98, Delirium Rating Scale-Revised-98; NRS, Numerical Rating Scale.

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The effect of different durations of preoperative computerized cognitive training on postoperative delirium in older patients undergoing cardiac surgery: a study protocol for a prospective, randomized controlled trial

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The effect of different durations of preoperative computerized cognitive training on postoperative delirium in older patients undergoing cardiac surgery: a study protocol for a prospective, randomized controlled trial

Xinyuan Qiu,[1] Lili Wang,[1] Xinge Wen,[1] Qingling Meng,[1] Junwei Qi,[1] Chuang Li,[1] Hua Yin,[1] Fei Ling,[1] Yuhan Qiao,[1] Wen Zhang,[1] Yueying Zhang[1]

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XQ and LW are joint first authors.

ABSTRACT

Introduction Postoperative delirium (POD) is a common neurological complication after surgery among older patients, characterized by acute disturbances in consciousness, attention, and cognition, usually occurring within 24 to 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% to 52%. Computerized Cognitive Training (CCT) refers to difficulty-adaptive training in cognitive domains such as attention, memory, and logical reasoning, using systematically designed tasks. Existing study has 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 postoperative delirium 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, randomized controlled trial that aims to enroll 261 older patients scheduled for elective cardiac surgery at the Affiliated Hospital of Xuzhou Medical University. The patients will be randomized 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); 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-centered, and low-risk prevention strategies for postoperative delirium/postoperative neurocognitive disorder.

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

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the results of the study will be published in international peer-reviewed academic journals and presented at academic conferences.

Trial registration number This study protocol has been developed in accordance with clinical practice guidelines and has been registered with the China Clinical Trials Center (Registration Number: ChiCTR2300072806).

Key words Computerized Cognitive Training; Cardiac surgery; Older; Postoperative Delirium

- **The study investigates the effects of computerized 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 computerized 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-center clinical trial with older cardiac surgery patients as the subjects, which has inherent limitations. Further multicenter 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 (NSE), which may reflect postoperative delirium to some extent.**

INTRODUCTION

Postoperative delirium (POD) is defined as an acute brain dysfunction characterized 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 to 72 hours after surgery[1]. Postoperative delirium 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% to 19.5%), abdominal surgery (10.7% to 25%), urological surgery (8.8% to 26%), and cataract surgery (5%)[2]. Based on its clinical presentation, POD can be categorized 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

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hyperactive and inactive delirium[3-5]. The gold standard for diagnosing postoperative delirium is based on the criteria set forth in the Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (DSM-5), 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 behavioral 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 postoperative delirium 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 utilized in the management of PODOCVS. Pharmacological prevention has been demonstrated to have limited efficacy in the prevention of postoperative delirium, with some approaches even proving to be ineffective[11-12]. It is important to note that pharmacological prevention carries potential risks, including sedation, extrapyramidal symptoms, orthostatic hypotension, and arrhythmias[13].The use of pharmacotherapy for the prevention of PODOCVS is not recommended[14-17]. 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 computerized cognitive training that is adaptive in difficulty and focuses on skill enhancement[18]. 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[19]. This randomized, 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 program and had sufficient time for such interventions prior to surgery[20].

A structured preoperative CCT program may have a more pronounced effect on reducing the incidence of POD. However, there are several challenges in current

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clinical practice. First, the quality of training is difficult to ensure without supervision and guidance, emphasized by the Cognitive Training Guidelines for China (2022)[21], which recommends that cognitive training be implemented in specialized centers 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 prioritize cognitive training, leading to poor compliance, as demonstrated in previous studies. Therefore, we aim to find an efficient training program that achieves optimal cognitive improvement in the shortest possible time, to facilitate its implementation in clinical practice. For these reasons, we have designed a randomized clinical trial in which older patients scheduled for elective cardiac surgery will receive different durations of preoperative computerized cognitive training 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 significant greater improvements in the incidence of postoperative delirium compared to group C.

Secondary hypothesis: Preoperative CCT at the 5/10 hour dosage leads to statistically significant greater improvements in postoperative neurocognitive function compared to group C.

Study design

A prospective, single-center, randomized 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 program will be administrated and supervised by trained research personnel to ensure that the participants complete at least 1 game in each cognitive category and reach the goal of 1 hour of training during each session. The study is scheduled to commence on July 01, 2023, and end on October 01, 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). Supplementary Figure 1 shows the patient flow chart for this RCT.

Study population

The CCT trial aims to enroll 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 randomization, while respecting individual autonomy and ethical principles.

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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). 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, randomization 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 randomization and enrollment. Following the baseline assessment, eligible subjects (n=261) will be randomized 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 to day 5 and day 7 (T1~T6, T7), postoperative day 30 (T8), postoperative day 90 (T9), and postoperative 1 year (T10).

Randomization

The trial uses a computer-generated random number table to randomize 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 minimize selection bias. Randomization 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 computerized cognitive training 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.

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Sample size

Previous studies have shown that the incidence of postoperative delirium (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[22].

Intervention

During hospitalization, 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; the Pittsburgh Sleep Quality Index (PSQI) 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 $0.5\mu g \cdot kg^{-1} \cdot h^{-1}$. Invasive arterial blood pressure monitoring is performed under ultrasound-guided radial artery cannulation. General anesthesia is induced with lidocaine $1\sim2mg \cdot kg^{-1}$, etomidate $0.2mg \cdot kg^{-1}$, rocuronium $0.6\sim0.9mg \cdot kg^{-1}$, and sufentanil $7\mu g \cdot kg^{-1}$. Manual ventilation via a mask is performed for 3~5 minutes until adequate muscle relaxation is achieved for intubation, followed by the insertion of a cuffed endotracheal tube with a TEE probe. Maintenance of anesthesia will include propofol infusion at $2\sim4mg \cdot kg^{-1} \cdot h^{-1}$, continuous infusion of cisatracurium, adjustment of tidal volume to maintain $P_{ET}CO_2$ between 35~45mmHg, and BIS between 40 and 60. Heparinization with $3mg \cdot kg^{-1}$ of heparin is administered after sternotomy, reduced to $1.5mg \cdot kg^{-1}$ if cardiopulmonary bypass is not required, and protamine is used to reverse heparin after major procedures. After surgery, patients are transferred to the ICU while still intubated.

However, there are specific differences in non-pharmacologic 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.

Computerized Cognitive Training Group (Group L & H)

In addition to receiving routine care, patients in Group L will receive 1 hour of

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computerized cognitive training daily for 5 days prior to surgery, for a total of 5 hours of training. Patients in Group H will receive 1 hour of computerized cognitive training 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 6 categories: attention, memory, logic, reaction time, speed, and language. Patients in the intervention groups are required to complete at least 1 game under each cognitive category during each session, and more if time permits. The intervention process is be 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 in Supplementary Figure 2)

Trained research personnel, who are not involved in preoperative cognitive intervention and are unaware of the grouping, will utilize the Confusion Assessment Method (CAM) and the the Confusion Assessment Method for the Intensive Care Unit (CAM-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[23]. 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 utilized 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 Activities of Daily Living, 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 optimize the retention of enrolled patients, a series of measures have been implemented. In order to optimize the retention of enrolled patients, a series of measures have been implemented. Firstly, 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 enrollment. Secondly, prior to randomization, compliance screening is conducted to ascertain that enrolled participants are committed to cooperating with the training. Finally, we

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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 randomization process. Following randomization, the research personnel responsible for the intervention will conduct one-on-one computerized cognitive training with patients at specified times and locations to ensure that the training duration is met. At the time of enrollment, a minimum of two contact numbers are obtained from each patient in order to minimize 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 day 30 (T8), postoperative day 90 (T9), and postoperative 1 year (T10). (see Table 1 for details).

Primary outcome measures

The incidence of postoperative delirium (POD) within 7 days: Assessed by the Confusion Assessment Method (CAM)[24]. The CAM assessment covers four principal domains as follows: 1) Acute change or fluctuation in consciousness state; 2) Lack of concentration; 3) Disorganized 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 Intensive Care Unit, the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) is used for assessment[25]. Prior to utilizing 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[26].

Secondary outcome measures

Delirium subtypes: The behavioral manifestations of delirium can be classified into three main categories according to their clinical presence: hyperactive delirium, which is characterized 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(NCD) and postoperative major neurocognitive disorder (30 days up to 1 year) : Neurocognitive function is

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evaluated using the MoCA[27] and the MMSE[28] at 1 month, 3 months and 1 year postoperatively. The objective criteria are a decline of 1-2 standard deviations relative to the preoperative period for mild NCD and a decline of ≥ 2 standard deviations for major NCD[29]. 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 Delirium Rating Scale-Revised-98 (DRS-R-98)[30], 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 Geriatric Depression Scale (GDS) to ascertain the absence of active depressive symptoms[31]. 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 comprised 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 to 10 indicating no clinically significant depressive symptoms, a score of 11 to 20 indicating mild symptoms, and a score of 21 to 30 indicating moderate to severe symptoms.

Postoperative recovery quality: The Postoperative Quality Recovery Scale (PQRS) is employed for the assessment of patients' recovery status at multiple time points and across various domains following surgical procedures[32]. 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, activities of daily living, 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 activities of daily living (ADL) domain assesses the ability to perform routine activities independently, including standing, walking, dressing, and self-care.

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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 anesthesia care. The term "recovery" is defined as returning to baseline values or better.

Postoperative pain scoring: The Numerical Rating Scale (NRS) is employed to evaluate the intensity of postoperative pain in patients[33]. 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 to 3 indicate mild pain, 4 to 6 indicate moderate pain, and 7 to 10 indicate severe pain.

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

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 analyzed using the statistical software package SPSS Statistics, version 26.0 (IBM, USA). 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 interquartile range (IQR). Binomial variables are expressed as rates. The continuous data that follow a normal distribution are analyzed by one-way analysis of variance (ANOVA). The continuous data that do not follow a normal distribution among the three groups are analyzed using the Kruskal-Wallis rank-sum test. Categorical data are analyzed using the Chi-square test, with the *P* value adjusted according to the Bonferroni method and fixed at .017 for pairwise comparison. $P < .05$ 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 analyzed using a Chi-square test or Fisher exact test, with the crude odds ratio (OR) and 95% CI reported. The adjusted odds ratio (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 (cardiopulmonary bypass). When all methods yield consistent conclusions, the results of the study are more credible.

The GraphPad Prism 9.0 software will be utilized for the generation of graphical representations. A two-sided *P* value < 0.05 will be considered to be a significant

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difference.

Other variables

The preoperative data collection of patient basic information includes the following: gender, age, ASA classification, BMI, education level, smoking history, alcohol consumption history, disability status, history of delirium, history of hypertension, history of diabetes, history of stroke or intracranial hemorrhage, albumin level, hemoglobin level, and preoperative blood glucose level.

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

The postoperative data collection encompasses the following: the duration of the ICU stay, extubation time, 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 ischemic stroke, atelectasis, pulmonary edema, 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 program 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 statement

Clinical partners were engaged in the study design process; however, neither subjects

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nor the general public will be involved in the development, design, or implementation of the study.

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. Digitized 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 Helsinki Declaration, 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.

Word count 5175

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Author Contributions 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, YQ and WZ revised the manuscript. All authors approved the final manuscript.

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Competing interests None declared.

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Variables	Follow-up				
	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				√	√	√

MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; GDS, Geriatric Depression Scale; CCI, Charlson Comorbidity Index; PQRS, Postoperative Quality Recovery Scale; PSQI, Pittsburgh Sleep Quality Index; CAM/CAM-ICU, The Confusion Assessment Method/The confusion assessment method for the Intensive Care Unit; DRS-R-98, Delirium Rating Scale-Revised-98; NRS, Numerical Rating Scale; POD, postoperative day; 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 day 30(T8), postoperative day 90(T9), and postoperative 1 year (T10).

Table 1 Schedule of visits and assessments.

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Supplemental material

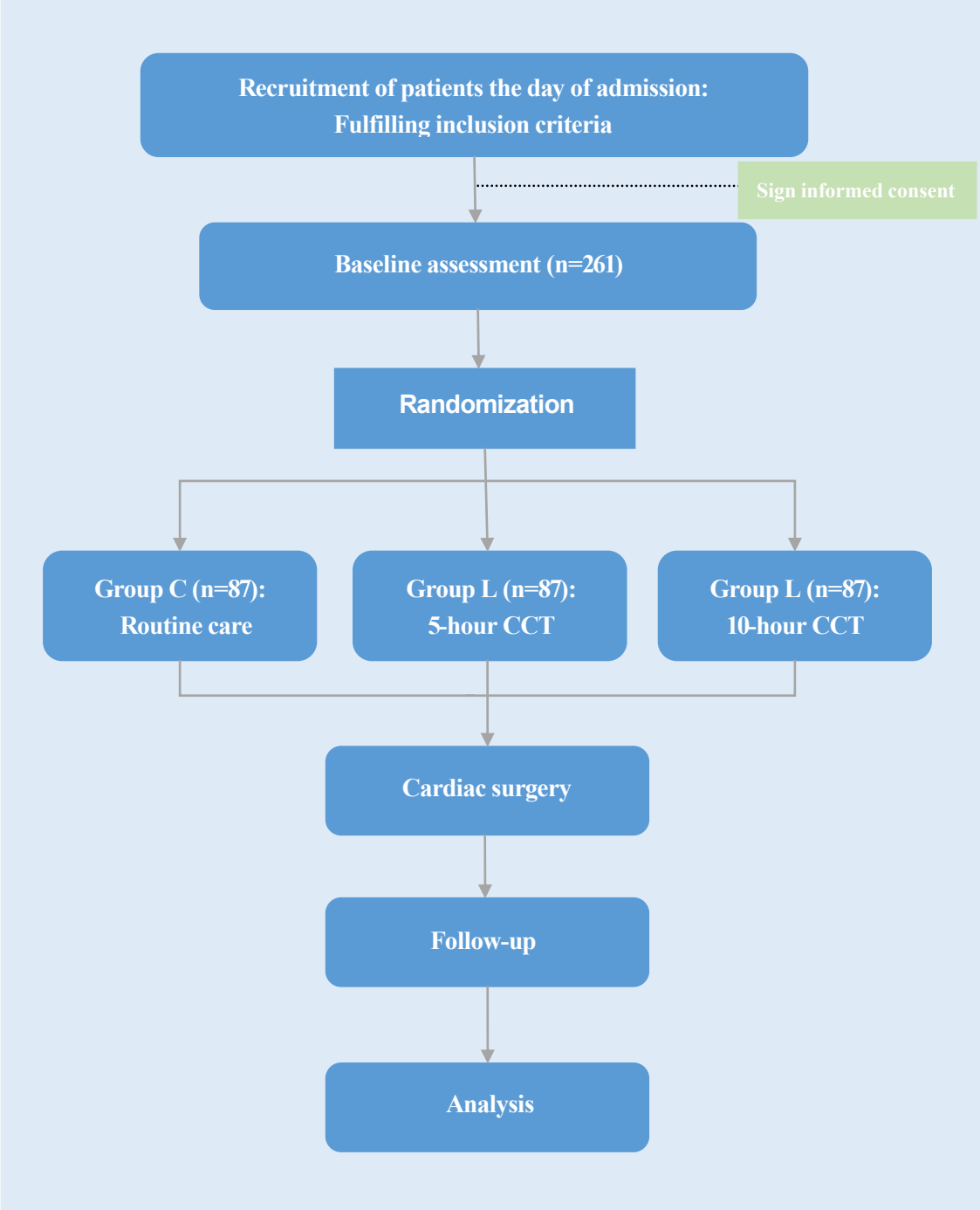

Figure 1 Flow chart of this RCT.

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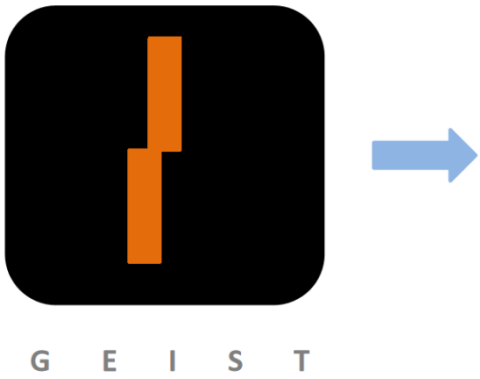

Group C	Routine Care
Group L	5-hour Computerised Cognitive Training prior surgery
Group H	10-hour Computerised Cognitive Training prior surgery

Figure 2 The app for the computerized cognitive training of older patients undergoing elective cardiac surgery.

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The effect of different durations of preoperative computerized cognitive training on postoperative delirium in older patients undergoing cardiac surgery: a study protocol for a prospective, randomized controlled trial

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ABSTRACT

Introduction Postoperative delirium (POD) is a common neurological complication after surgery among older patients, characterized by acute disturbances in consciousness, attention, and cognition, usually occurring within 24 to 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% to 52%. Computerized Cognitive Training (CCT) refers to difficulty-adaptive training in cognitive domains such as attention, memory, and logical reasoning, using systematically designed tasks. Existing study has 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 postoperative delirium 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, randomized controlled trial that aims to enroll 261 older patients scheduled for elective cardiac surgery at the Affiliated Hospital of Xuzhou Medical University. The patients will be randomized 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); 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-centered, and low-risk prevention strategies for postoperative delirium/postoperative neurocognitive disorder.

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

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the results of the study will be published in international peer-reviewed academic journals and presented at academic conferences.

Trial registration number This study protocol has been developed in accordance with clinical practice guidelines and has been registered with the China Clinical Trials Center (Registration Number: ChiCTR2300072806).

Key words Computerized Cognitive Training; Cardiac surgery; Older; Postoperative Delirium

- **The study investigates the effects of computerized 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 computerized 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-center clinical trial with older cardiac surgery patients as the subjects, which has inherent limitations. Further multicenter 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 (NSE), which may reflect postoperative delirium to some extent.**

INTRODUCTION

Postoperative delirium (POD) is defined as an acute brain dysfunction characterized 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 to 72 hours after surgery[1]. Postoperative delirium 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% to 19.5%), abdominal surgery (10.7% to 25%), urological surgery (8.8% to 26%), and cataract surgery (5%)[2]. Based on its clinical presentation, POD can be categorized 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

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hyperactive and inactive delirium[3-5]. The gold standard for diagnosing postoperative delirium is based on the criteria set forth in the Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (DSM-5), 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 behavioral 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 postoperative delirium 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 utilized in the management of PODOCVS. Pharmacological prevention has been demonstrated to have limited efficacy in the prevention of postoperative delirium, with some approaches even proving to be ineffective[11-12]. It is important to note that pharmacological prevention carries potential risks, including sedation, extrapyramidal symptoms, orthostatic hypotension, and arrhythmias[13].The use of pharmacotherapy for the prevention of PODOCVS is not recommended[14-17]. 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 computerized cognitive training that is adaptive in difficulty and focuses on skill enhancement[18]. 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[19]. This randomized, 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 program and had sufficient time for such interventions prior to surgery[20].

A structured preoperative CCT program may have a more pronounced effect on reducing the incidence of POD. However, there are several challenges in current

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clinical practice. First, the quality of training is difficult to ensure without supervision and guidance, emphasized by the Cognitive Training Guidelines for China (2022)[21], which recommends that cognitive training be implemented in specialized centers 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 prioritize cognitive training, leading to poor compliance, as demonstrated in previous studies. Therefore, we aim to find an efficient training program that achieves optimal cognitive improvement in the shortest possible time, to facilitate its implementation in clinical practice. For these reasons, we have designed a randomized clinical trial in which older patients scheduled for elective cardiac surgery will receive different durations of preoperative computerized cognitive training 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 significant greater improvements in the incidence of postoperative delirium compared to group C.

Secondary hypothesis: Preoperative CCT at the 5/10 hour dosage leads to statistically significant greater improvements in postoperative neurocognitive function compared to group C.

Study design

A prospective, single-center, randomized 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 program will be administrated and supervised by trained research personnel to ensure that the participants complete at least 1 game in each cognitive category and reach the goal of 1 hour of training during each session. The study is scheduled to commence on July 01, 2023, and end on October 01, 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). Supplementary Figure 1 shows the patient flow chart for this RCT.

Study population

The CCT trial aims to enroll 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 randomization, while respecting individual autonomy and ethical principles.

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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). 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, randomization 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 randomization and enrollment. Following the baseline assessment, eligible subjects (n=261) will be randomized 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 to day 5 and day 7 (T1~T6, T7), postoperative day 30 (T8), postoperative day 90 (T9), and postoperative 1 year (T10).

Randomization

The trial uses a computer-generated random number table to randomize 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 minimize selection bias. Randomization 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 computerized cognitive training 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.

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Sample size

Previous studies have shown that the incidence of postoperative delirium (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[22].

Intervention

During hospitalization, 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; the Pittsburgh Sleep Quality Index (PSQI) 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 $0.5\mu g \cdot kg^{-1} \cdot h^{-1}$. Invasive arterial blood pressure monitoring is performed under ultrasound-guided radial artery cannulation. General anesthesia is induced with lidocaine $1\sim2mg \cdot kg^{-1}$, etomidate $0.2mg \cdot kg^{-1}$, rocuronium $0.6\sim0.9mg \cdot kg^{-1}$, and sufentanil $7\mu g \cdot kg^{-1}$. Manual ventilation via a mask is performed for 3~5 minutes until adequate muscle relaxation is achieved for intubation, followed by the insertion of a cuffed endotracheal tube with a TEE probe. Maintenance of anesthesia will include propofol infusion at $2\sim4mg \cdot kg^{-1} \cdot h^{-1}$, continuous infusion of cisatracurium, adjustment of tidal volume to maintain $P_{ET}CO_2$ between 35~45mmHg, and BIS between 40 and 60. Heparinization with $3mg \cdot kg^{-1}$ of heparin is administered after sternotomy, reduced to $1.5mg \cdot kg^{-1}$ if cardiopulmonary bypass is not required, and protamine is used to reverse heparin after major procedures. After surgery, patients are transferred to the ICU while still intubated.

However, there are specific differences in non-pharmacologic 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.

Computerized Cognitive Training Group (Group L & H)

In addition to receiving routine care, patients in Group L will receive 1 hour of

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computerized cognitive training daily for 5 days prior to surgery, for a total of 5 hours of training. Patients in Group H will receive 1 hour of computerized cognitive training 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 6 categories: attention, memory, logic, reaction time, speed, and language. Patients in the intervention groups are required to complete at least 1 game under each cognitive category during each session, and more if time permits. The intervention process is be 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 in Supplementary Figure 2)

Trained research personnel, who are not involved in preoperative cognitive intervention and are unaware of the grouping, will utilize the Confusion Assessment Method (CAM) and the the Confusion Assessment Method for the Intensive Care Unit (CAM-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[23]. 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 utilized 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 Activities of Daily Living, 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 optimize the retention of enrolled patients, a series of measures have been implemented. In order to optimize the retention of enrolled patients, a series of measures have been implemented. Firstly, 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 enrollment. Secondly, prior to randomization, compliance screening is conducted to ascertain that enrolled participants are committed to cooperating with the training. Finally, we

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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 randomization process. Following randomization, the research personnel responsible for the intervention will conduct one-on-one computerized cognitive training with patients at specified times and locations to ensure that the training duration is met. At the time of enrollment, a minimum of two contact numbers are obtained from each patient in order to minimize 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 day 30 (T8), postoperative day 90 (T9), and postoperative 1 year (T10). (see Table 1 for details).

Primary outcome measures

The incidence of postoperative delirium (POD) within 7 days: Assessed by the Confusion Assessment Method (CAM)[24]. The CAM assessment covers four principal domains as follows: 1) Acute change or fluctuation in consciousness state; 2) Lack of concentration; 3) Disorganized 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 Intensive Care Unit, the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) is used for assessment[25]. Prior to utilizing 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[26].

Secondary outcome measures

Delirium subtypes: The behavioral manifestations of delirium can be classified into three main categories according to their clinical presence: hyperactive delirium, which is characterized 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(NCD) and postoperative major neurocognitive disorder (30 days up to 1 year) : Neurocognitive function is

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evaluated using the MoCA[27] and the MMSE[28] at 1 month, 3 months and 1 year postoperatively. The objective criteria are a decline of 1-2 standard deviations relative to the preoperative period for mild NCD and a decline of ≥ 2 standard deviations for major NCD[29]. 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 Delirium Rating Scale-Revised-98 (DRS-R-98)[30], 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 Geriatric Depression Scale (GDS) to ascertain the absence of active depressive symptoms[31]. 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 comprised 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 to 10 indicating no clinically significant depressive symptoms, a score of 11 to 20 indicating mild symptoms, and a score of 21 to 30 indicating moderate to severe symptoms.

Postoperative recovery quality: The Postoperative Quality Recovery Scale (PQRS) is employed for the assessment of patients' recovery status at multiple time points and across various domains following surgical procedures[32]. 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, activities of daily living, 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 activities of daily living (ADL) domain assesses the ability to perform routine activities independently, including standing, walking, dressing, and self-care.

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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 anesthesia care. The term "recovery" is defined as returning to baseline values or better.

Postoperative pain scoring: The Numerical Rating Scale (NRS) is employed to evaluate the intensity of postoperative pain in patients[33]. 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 to 3 indicate mild pain, 4 to 6 indicate moderate pain, and 7 to 10 indicate severe pain.

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

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 analyzed using the statistical software package SPSS Statistics, version 26.0 (IBM, USA). 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 interquartile range (IQR). Binomial variables are expressed as rates. The continuous data that follow a normal distribution are analyzed by one-way analysis of variance (ANOVA). The continuous data that do not follow a normal distribution among the three groups are analyzed using the Kruskal-Wallis rank-sum test. Categorical data are analyzed using the Chi-square test, with the *P* value adjusted according to the Bonferroni method and fixed at .017 for pairwise comparison. $P < .05$ 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 analyzed using a Chi-square test or Fisher exact test, with the crude odds ratio (OR) and 95% CI reported. The adjusted odds ratio (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 (cardiopulmonary bypass). When all methods yield consistent conclusions, the results of the study are more credible.

The GraphPad Prism 9.0 software will be utilized for the generation of graphical representations. A two-sided *P* value < 0.05 will be considered to be a significant

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difference.

Other variables

The preoperative data collection of patient basic information includes the following: gender, age, ASA classification, BMI, education level, smoking history, alcohol consumption history, disability status, history of delirium, history of hypertension, history of diabetes, history of stroke or intracranial hemorrhage, albumin level, hemoglobin level, and preoperative blood glucose level.

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

The postoperative data collection encompasses the following: the duration of the ICU stay, extubation time, 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 ischemic stroke, atelectasis, pulmonary edema, 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 program 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

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Clinical partners were engaged in the study design process; however, neither patients nor the general public will be involved in the development, design, or implementation of the study.

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. Digitized 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 Helsinki Declaration, 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.

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Variables		Follow-up				
	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				√	√	√

MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; GDS, Geriatric Depression Scale; CCI, Charlson Comorbidity Index; PQRS, Postoperative Quality Recovery Scale; PSQI, Pittsburgh Sleep Quality Index; CAM/CAM-ICU, The Confusion Assessment Method/The confusion assessment method for the Intensive Care Unit; DRS-R-98, Delirium Rating Scale-Revised-98; NRS, Numerical Rating Scale; POD, postoperative day; 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 day 30(T8), postoperative day 90(T9), and postoperative 1 year (T10).

Table 1 Schedule of visits and assessments.

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Supplemental material

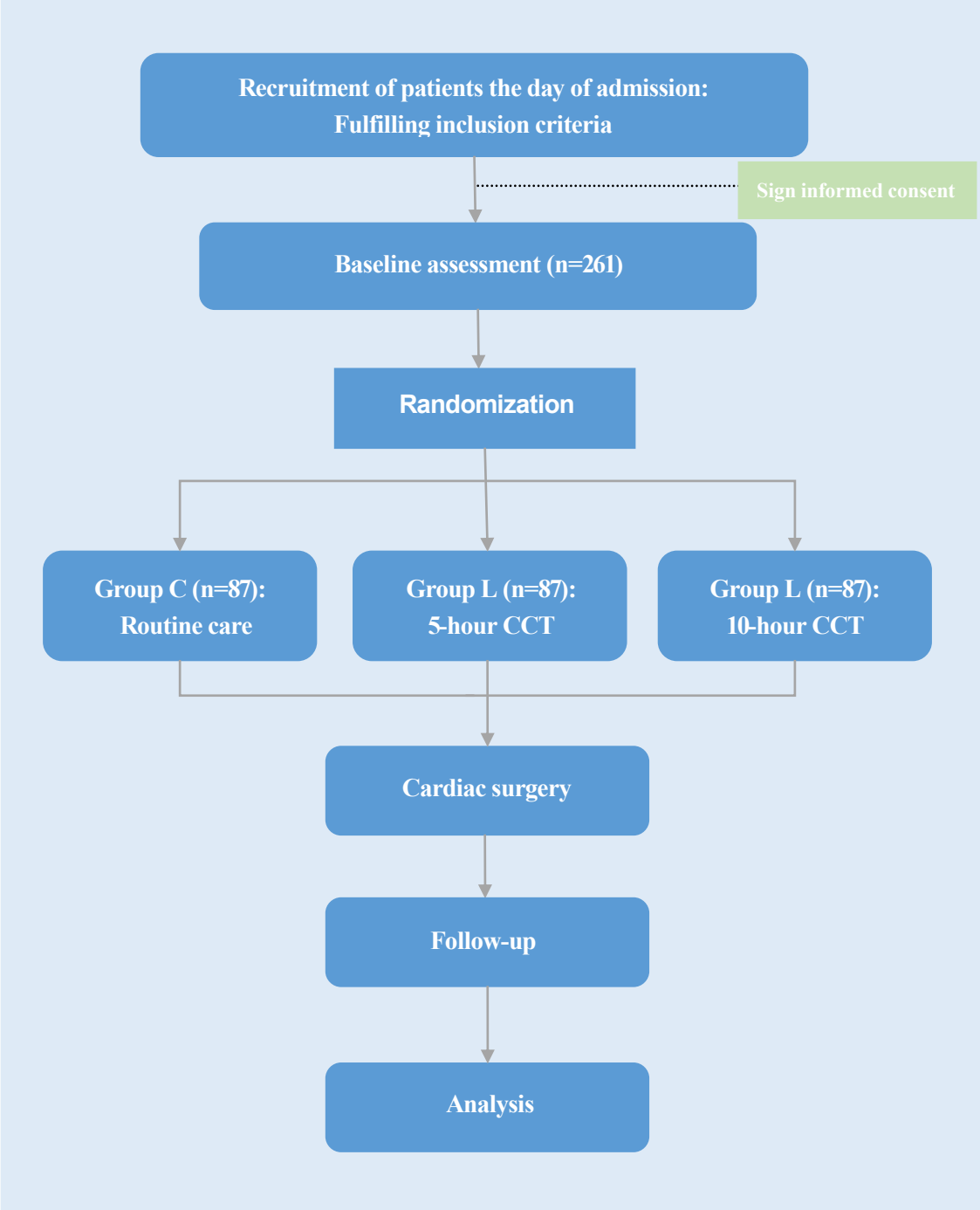

Figure 1 Flow chart of this RCT.

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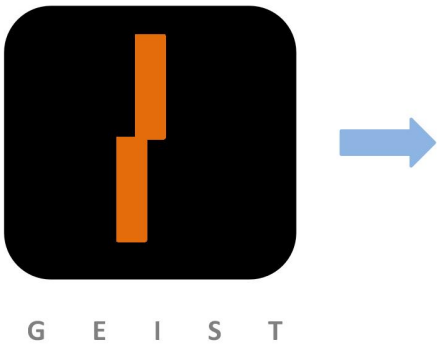

Group C	Routine Care
Group L	5-hour Computerised Cognitive Training prior surgery
Group H	10-hour Computerised Cognitive Training prior surgery

Figure 2 The app for the computerized cognitive training of older patients undergoing elective cardiac surgery.

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The effect of different durations of preoperative computerized cognitive training on postoperative delirium in older patients undergoing cardiac surgery: a study protocol for a prospective, randomized controlled trial

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The effect of different durations of preoperative computerized cognitive training on postoperative delirium in older patients undergoing cardiac surgery: a study protocol for a prospective, randomized controlled trial

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XQ and LW are joint first authors.

ABSTRACT

Introduction Postoperative delirium (POD) is a common neurological complication after surgery among older patients, characterized by acute disturbances in consciousness, attention, and cognition, usually occurring within 24 to 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% to 52%. Computerized Cognitive Training (CCT) refers to difficulty-adaptive training in cognitive domains such as attention, memory, and logical reasoning, using systematically designed tasks. Existing study has 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 postoperative delirium 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, randomized controlled trial that aims to enroll 261 older patients scheduled for elective cardiac surgery at the Affiliated Hospital of Xuzhou Medical University. The patients will be randomized 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); 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-centered, and low-risk prevention strategies for postoperative delirium/postoperative neurocognitive disorder.

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

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the results of the study will be published in international peer-reviewed academic journals and presented at academic conferences.

Trial registration number This study protocol has been developed in accordance with clinical practice guidelines and has been registered with the China Clinical Trials Center (Registration Number: ChiCTR2300072806).

Key words Computerized Cognitive Training; Cardiac surgery; Older; Postoperative Delirium

- **The study investigates the effects of computerized 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 computerized 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-center clinical trial with older cardiac surgery patients as the subjects, which has inherent limitations. Further multicenter 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 (NSE), which may reflect postoperative delirium to some extent.**

INTRODUCTION

Postoperative delirium (POD) is defined as an acute brain dysfunction characterized 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 to 72 hours after surgery[1]. Postoperative delirium 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% to 19.5%), abdominal surgery (10.7% to 25%), urological surgery (8.8% to 26%), and cataract surgery (5%)[2]. Based on its clinical presentation, POD can be categorized 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

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hyperactive and inactive delirium[3-5]. The gold standard for diagnosing postoperative delirium is based on the criteria set forth in the Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (DSM-5), 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 behavioral 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 postoperative delirium 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 utilized in the management of PODOCVS. Pharmacological prevention has been demonstrated to have limited efficacy in the prevention of postoperative delirium, with some approaches even proving to be ineffective[11-12]. It is important to note that pharmacological prevention carries potential risks, including sedation, extrapyramidal symptoms, orthostatic hypotension, and arrhythmias[13].The use of pharmacotherapy for the prevention of PODOCVS is not recommended[14-17]. 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 computerized cognitive training that is adaptive in difficulty and focuses on skill enhancement[18]. 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[19]. This randomized, 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 program and had sufficient time for such interventions prior to surgery[20].

A structured preoperative CCT program may have a more pronounced effect on reducing the incidence of POD. However, there are several challenges in current

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clinical practice. First, the quality of training is difficult to ensure without supervision and guidance, emphasized by the Cognitive Training Guidelines for China (2022)[21], which recommends that cognitive training be implemented in specialized centers 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 prioritize cognitive training, leading to poor compliance, as demonstrated in previous studies. Therefore, we aim to find an efficient training program that achieves optimal cognitive improvement in the shortest possible time, to facilitate its implementation in clinical practice. For these reasons, we have designed a randomized clinical trial in which older patients scheduled for elective cardiac surgery will receive different durations of preoperative computerized cognitive training 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 significant greater improvements in the incidence of postoperative delirium compared to group C.

Secondary hypothesis: Preoperative CCT at the 5/10 hour dosage leads to statistically significant greater improvements in postoperative neurocognitive function compared to group C.

Study design

A prospective, single-center, randomized 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 program will be administrated and supervised by trained research personnel to ensure that the participants complete at least 1 game in each cognitive category and reach the goal of 1 hour of training during each session. The study is scheduled to commence on July 01, 2023, and end on October 01, 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). Supplementary Figure 1 shows the patient flow chart for this RCT.

Study population

The CCT trial aims to enroll 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 randomization, while respecting individual autonomy and ethical principles. (the details of the informed

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consent form can be found in supplementary file)

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). 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, randomization 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 randomization and enrollment. Following the baseline assessment, eligible subjects (n=261) will be randomized 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 to day 5 and day 7 (T1~T6, T7), postoperative 1 month (T8), postoperative 3 months (T9), and postoperative 1 year (T10).

Randomization

The trial uses a computer-generated random number table to randomize 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 minimize selection bias. Randomization 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 computerized cognitive training 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.

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Sample size

Previous studies have shown that the incidence of postoperative delirium (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[22].

Intervention

During hospitalization, 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; the Pittsburgh Sleep Quality Index (PSQI) 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 0.5μg·kg^{-1}·h^{-1}. Invasive arterial blood pressure monitoring is performed under ultrasound-guided radial artery cannulation. General anesthesia is induced with lidocaine 1~2mg·kg^{-1}, etomidate 0.2mg·kg^{-1}, rocuronium 0.6~0.9mg·kg^{-1}, and sufentanil 7μg·kg^{-1}. Manual ventilation via a mask is performed for 3~5 minutes until adequate muscle relaxation is achieved for intubation, followed by the insertion of a cuffed endotracheal tube with a TEE probe. Maintenance of anesthesia will include propofol infusion at 2~4mg·kg^{-1}·h^{-1}, continuous infusion of cisatracurium, adjustment of tidal volume to maintain $P_{ET}CO_2$ between 35~45mmHg, and BIS between 40 and 60. Heparinization with 3mg·kg^{-1} of heparin is administered after sternotomy, reduced to 1.5mg·kg^{-1} if cardiopulmonary bypass is not required, and protamine is used to reverse heparin after major procedures. After surgery, patients are transferred to the ICU while still intubated.

However, there are specific differences in non-pharmacologic 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.

Computerized Cognitive Training Group (Group L&H)

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In addition to receiving routine care, patients in Group L will receive 1 hour of computerized cognitive training daily for 5 days prior to surgery, for a total of 5 hours of training. Patients in Group H will receive 1 hour of computerized cognitive training 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 6 categories: attention, memory, logic, reaction time, speed, and language. Patients in the intervention groups are required to complete at least 1 game under each cognitive category during each session, and more if time permits. The intervention process is be 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 in Supplementary Figure 2)

Trained research personnel, who are not involved in preoperative cognitive intervention and are unaware of the grouping, will utilize the Confusion Assessment Method (CAM) and the the Confusion Assessment Method for the Intensive Care Unit (CAM-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[23]. 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 utilized 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 Activities of Daily Living, 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 optimize the retention of enrolled patients, a series of measures have been implemented. In order to optimize the retention of enrolled patients, a series of measures have been implemented. Firstly, 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 enrollment. Secondly, prior to randomization, compliance screening is conducted to ascertain that

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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 randomization process. Following randomization, the research personnel responsible for the intervention will conduct one-on-one computerized cognitive training with patients at specified times and locations to ensure that the training duration is met. At the time of enrollment, a minimum of two contact numbers are obtained from each patient in order to minimize 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 postoperative delirium (POD) within 7 days: Assessed by the Confusion Assessment Method (CAM)[24]. The CAM assessment covers four principal domains as follows: 1) Acute change or fluctuation in consciousness state; 2) Lack of concentration; 3) Disorganized 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 Intensive Care Unit, the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) is used for assessment[25]. Prior to utilizing 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[26].

Secondary outcome measures

Delirium subtypes: The behavioral manifestations of delirium can be classified into three main categories according to their clinical presence: hyperactive delirium, which is characterized 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(NCD) and postoperative

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major neurocognitive disorder (30 days up to 1 year) : Neurocognitive function is evaluated using the MoCA[27] and the MMSE[28] at 1 month, 3 months and 1 year postoperatively. The objective criteria are a decline of 1-2 standard deviations relative to the preoperative period for mild NCD and a decline of ≥ 2 standard deviations for major NCD[29]. 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 Delirium Rating Scale-Revised-98 (DRS-R-98)[30], 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 Geriatric Depression Scale (GDS) to ascertain the absence of active depressive symptoms[31]. 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 comprised 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 to 10 indicating no clinically significant depressive symptoms, a score of 11 to 20 indicating mild symptoms, and a score of 21 to 30 indicating moderate to severe symptoms.

Postoperative recovery quality: The Postoperative Quality Recovery Scale (PQRS) is employed for the assessment of patients' recovery status at multiple time points and across various domains following surgical procedures[32]. 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, activities of daily living, 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 activities of daily living (ADL) domain assesses the ability to perform routine

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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 anesthesia care. The term "recovery" is defined as returning to baseline values or better.
Postoperative pain scoring: The Numerical Rating Scale (NRS) is employed to evaluate the intensity of postoperative pain in patients[33]. 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 to 3 indicate mild pain, 4 to 6 indicate moderate pain, and 7 to 10 indicate severe pain.
The one-year overall postoperative mortality rate: The one-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 analyzed using the statistical software package SPSS Statistics, version 26.0 (IBM, USA). 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 interquartile range (IQR). Binomial variables are expressed as rates. The continuous data that follow a normal distribution are analyzed by one-way analysis of variance (ANOVA). The continuous data that do not follow a normal distribution among the three groups are analyzed using the Kruskal-Wallis rank-sum test. Categorical data are analyzed using the Chi-square test, with the P value adjusted according to the Bonferroni method and fixed at .017 for pairwise comparison. $P < .05$ 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 analyzed using a Chi-square test or Fisher exact test, with the crude odds ratio (OR) and 95% CI reported. The adjusted odds ratio (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 (cardiopulmonary bypass). When all methods yield consistent conclusions, the results

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of the study are more credible.

The GraphPad Prism 9.0 software will be utilized for the generation of graphical representations. A two-sided *P* value < .05 will be considered to be a significant difference.

Other variables

The preoperative data collection of patient basic information includes the following: gender, age, ASA classification, BMI, education level, smoking history, alcohol consumption history, disability status, history of delirium, history of hypertension, history of diabetes, history of stroke or intracranial hemorrhage, albumin level, hemoglobin level, and preoperative blood glucose level.

The intraoperative data set includes the following variables: surgical time, type of surgery, duration of cardiopulmonary bypass (if applicable), aortic clamping time, total cardiopulmonary bypass time, intraoperative blood glucose level, blood loss, fluid replacement volume, transfusion volume, partial anesthesia 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 ischemic stroke, atelectasis, pulmonary edema, 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 program 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.

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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. Digitized 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 Helsinki Declaration, 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.

Word count 5255

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Author Contributions 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, YQ and WZ revised the manuscript. All authors approved the final manuscript. YZ is responsible for the overall content as guarantor.

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Competing interests None declared.

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Figure legends

Figure 1 Flow chart of this RCT.

Figure 2 The app for the computerized cognitive training of older patients undergoing elective cardiac surgery.

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Variables	Follow-up				
	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				√	√	√

MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; GDS, Geriatric Depression Scale; CCI, Charlson Comorbidity Index; PQRS, Postoperative Quality Recovery Scale; PSQI, Pittsburgh Sleep Quality Index; CAM/CAM-ICU, The Confusion Assessment Method/The confusion assessment method for the Intensive Care Unit; DRS-R-98, Delirium Rating Scale-Revised-98; NRS, Numerical Rating Scale; POD, postoperative day; 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).

Table 1 Schedule of visits and assessments.

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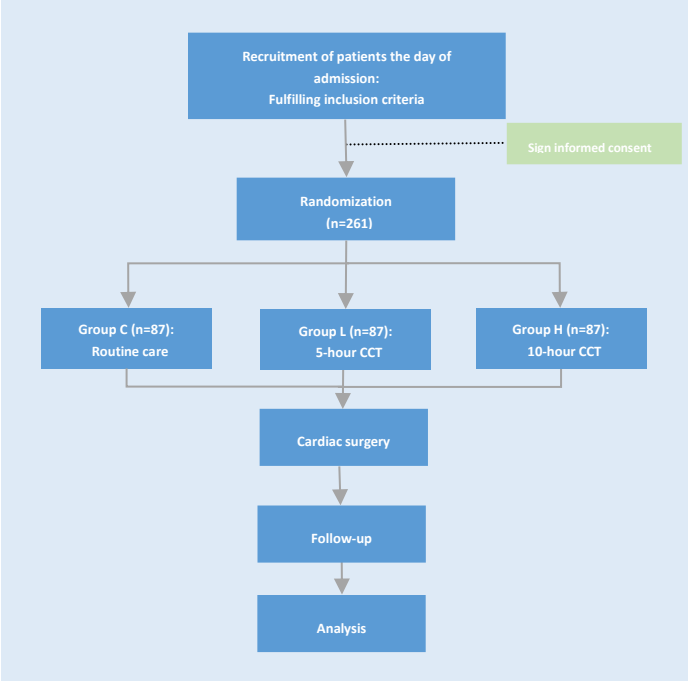

Figure 1 **Flow chart of this RCT.**

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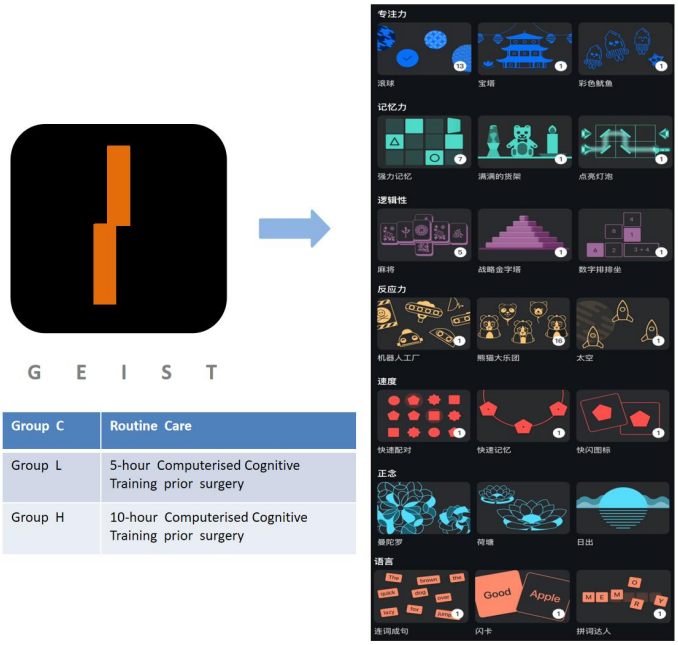

Group C	Routine Care
Group L	5-hour Computerised Cognitive Training prior surgery
Group H	10-hour Computerised Cognitive Training prior surgery

Figure 2 **The app for the computerized cognitive training of older patients undergoing elective cardiac surgery.**

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Informed Consent

Dear Subjects

We would like to invite you to participate in the study "The effect of different durations of preoperative computerized cognitive training on postoperative delirium in older patients undergoing cardiac surgery: a prospective, randomized controlled trial" approved by the Department of Anesthesiology, the Affiliated Hospital of Xuzhou Medical University. The study will be conducted at the Affiliated Hospital of Xuzhou Medical University, and it is estimated that 261 subjects will volunteer to participate. The study has been approved by the Ethics Committee of the Affiliated Hospital of Xuzhou Medical University.

You can talk to your family, friends, and your doctor about whether you want to participate in this study. You have plenty of time to think about it. Even if you have signed a consent to participate, you can change your decision to quit participating in this study at any stage of the study. You do not need any reason to leave the study.We respect your right to self-determination.

Why is this study being conducted?

Research Background

Postoperative delirium (POD) is a common neurological complication after surgery among older patients, characterized by acute disturbances in consciousness, attention, and cognition, usually occurring within 24 to 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% to 52%. Computerized Cognitive Training (CCT) refers to difficulty-adaptive training in cognitive domains such as attention, memory, and logical reasoning, using systematically designed tasks. Existing study has 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 postoperative delirium 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.

What do you need to do if you participate in the study?

If you are willing to participate in this study, you may receive one of the following 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); Group H will be the high-dose time group (with a total of 10 hours of CCT prior to surgery). Your vital signs will be closely monitored after the preoperative cognitive training and you will be followed up within 1 year after the surgery.

Who should not take part in the study?

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

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significant hearing or visual impairment and active depression (using the Geriatric Depression Scale). 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).

What are the risks of participating in the study?

If you participate in this study, all your medical procedures or examinations will be performed in current clinical practice and will not be increased by participation in this study. Your surgeon has determined prior to what you decide to participate in this study, and therefore, you will not add any additional specific treatment risk for participation in this study.

What are the benefits of participating in the research?

Participating in this study, your incidence of postoperative delirium may be reduced, thus accelerate your postoperative recovery, shorten the length of hospital stay, and reduce hospital costs. CCT may be an innovative and low-risk intervention. If preoperative cognitive training has a good impact on the postoperative delirium of cardiac surgery in older patients, it is of great significance to reduce the incidence of postoperative delirium and improve patient prognosis in future clinical work.

Do you need to pay any related fees to participate in the study?

You will not pay for participation in this study, we will pay the costs incurred from your participation in this study.

Is personal information confidential?

Your medical records will be kept in the hospital. The investigator, the study authority, and the ethics committee will be allowed to access your medical records. No public report on the results of this study will disclose your personal identity. We will make every effort to protect the privacy of your personal medical information as permitted by law.

Rights to participate in the study:

Participation in this study is completely voluntary, and you may refuse to participate in the study, or withdraw from the study at any time during the study, which will not affect the treatment of your doctor. If you believe that your rights and interests are damaged, please contact the ethics committee at 0516-85802291.

Subject statement: I have read the above introduction to this study and fully understand the possible risks and benefits of participating in this study. I have volunteered for this study.

Subject signature: _ _ _ _ _ _ _ _ _ Date: _ _ _ _ _ _ _ _ _

Contact Tel.: _ _ _ _ _ _ _ _ _

Researcher statement: I confirm that I have explained the details of the study to the patient, especially the possible risks and benefits of participating in this study.

Researcher signature: _ _ _ _ _ _ _ _ _ Date: _ _ _ _ _ _ _ _ _

Contact Tel.: _ _ _ _ _ _ _ _ _

The Clinical Trial Ethics Committee of the Affiliated Hospital of Xuzhou Medical University, Tel.: 0516-85802291

For peer review only

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