Trials

STUDY PROTOCOL

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# Intranasal administration of insulin on the incidence of postoperative delirium in middle-aged patients undergoing elective on-pump cardiac surgery (INIPOD-MOPS): a prospective double-blinded randomized control study protocol

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## Abstract

**Background** Delirium, marked by acute cognitive decline, poses a life-threatening issue among older individuals, especially after cardiac surgery, with prevalence ranging from 15 to 80%. Postoperative delirium is linked to increased morbidity and mortality. Although clinical trials suggest preventability, there is limited research on intranasal insulin (INI) for cardiac surgery-related delirium. INI has shown promise in managing cognitive disorders. It rapidly elevates brain hormone levels, enhancing memory even in non-impaired individuals. While effective in preventing delirium in gastrointestinal surgery, its impact after cardiac surgery remains understudied, especially for middle-aged patients.

**Method** This is a prospective randomized, double-blind, single-center controlled trial. A total of 76 eligible participants scheduled for elective on-pump cardiac surgery will be enrolled and randomly assigned in a 1:1 ratio to either receive Intranasally administered insulin (INI) or intranasally administered normal saline. The primary outcome of our study is the incidence of postoperative delirium (POD). Secondary outcomes include duration of ICU, postoperative hospital length of stay, all in-hospital mortality, the change in MMSE scores pre- and post-operation, and incidence of postoperative cognitive dysfunction at 1 month, 3 months, and 6 months after operation. Moreover, we will subjectively and objectively evaluate perioperative sleep quality to investigate the potential impact of nasal insulin on the development of delirium by influencing sleep regulation.

**Discussion** Our study will aim to assess the impact of intranasal administration of insulin on the incidence of postoperative delirium in middle-aged patients undergoing on-pump elective cardiac surgery. If intranasal insulin proves to be more effective, it may be considered as a viable alternative for preventing postoperative delirium.

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**Trial registration** ChiCTR ChiCTR2400081444. Registered on March 1, 2024.
**Keywords** Delirium, Intranasally administered insulin, Cardiac surgery, 4 a's Test

## Administrative information

| **Title {1}** | **Intranasal administration of insulin on the incidence of postoperative delirium in middle-aged patients undergoing elective on-pump cardiac surgery (INIPOD-MOPS): a prospective double-blinded randomized control study protocol** |
|---|---|
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| Author details {5a} | Department of Anesthesiology, Xinqiao Hospital of Chongqing, Second Affiliated Hospital of Army Medical University, PLA, Chongqing 400037, China. |
| Name and contact information for the trial sponsor {5b} | Name: Hong Li<br>Address: Department of Anesthesiology, Xinqiao Hospital of Chongqing, Second Affiliated Hospital of Army Medical University, PLA, Chongqing 400037, China.<br>Email: damingshen0930@163.com |
| Role of sponsor {5c} | The sponsor will neither take part in the process of the trial nor the decision to submit the results. |

## Introduction

### Background and rationale {6a}

Delirium, characterized by an acute deterioration in attention and cognitive function, is a prevalent, life-threatening, and potentially avoidable clinical syndrome in older persons [1]. The prevalence of postoperative delirium (POD) in older patients has been documented to range from 15 to 62% and among older persons admitted to intensive care unit, the incidence can reach 80% [2]. For patients undergoing cardiac surgery, POD has the potential to manifest in as many as one in three older patients undergoing intricate cardiac surgery [3]. Postoperative delirium is associated with increased morbidity, mortality, and complicated hospital days [4]. While some instances of delirium may be inevitable, clinical trials offer compelling evidence suggesting that a minimum of 30 to 40% of cases could be preventable [5].

Currently, a substantial body of experimental data and clinical observations supports the efficacy of intranasally administered insulin (INI) in managing Alzheimer's disease, Parkinson's disease, mild cognitive impairment, and neuropathies [6–8]. The utilization of INI enables rapid elevation of the hormone levels in the brain, thereby facilitating the stimulation of insulin signaling in neurons [9]. Recently, studies showed that INI can enhance memory in individuals without cognitive impairment, further suggesting its potential utility in restoring cognitive abilities in sleep restriction and other physiological conditions that may lead to transient, reversible cognitive decline, and mood deterioration [10, 11]. It can be employed not only for treating overt pathology but also for preventing mild cognitive impairment. They also demonstrate INI's capacity to enhance metabolic processes within the brain, such as glucose uptake and metabolism. This effect serves to mitigate hypometabolic states commonly associated with brain damage and neurodegenerative disorders. Data on the INI in the treatment of POD in elderly patients undergoing laparoscopic radical gastrointestinal surgery has proved its effectiveness in preventing the incidence of POD [12]. However, there is relatively limited research on the effects of intranasal insulin concerning delirium after cardiac surgery in middle-aged patients.

The Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) is an instrument used for monitoring delirium served by nurses and physicians in the intensive care unit [13]. They proved that CAM-ICU had excellent reliability and validity in diagnosing delirium. The 4 A's Test (4AT) serves as a screening tool designed for routine, non-specialist utilization in identifying delirium. It offers simplicity in administration, requires minimal time (< 2 min), and necessitates no formal training. The 4 AT exhibited a moderate level of sensitivity and high specificity in identifying delirium within a real-world context, specifically in the postoperative ward following cardiac surgery [14]. Both the CAM-ICU and 4 AT will be occupied in our study for assessment of POD in our study.

Our study will aim to assess the intranasal administration of insulin on the incidence of postoperative delirium in middle-aged patients undergoing elective on-pump cardiac surgery.

**Objectives {7}**

We have designed a prospective, randomized, double-blinded experiment to investigate the hypothesis that intranasal administration of insulin may decrease the incidence of postoperative delirium in patients undergoing elective cardiac surgery.

**Trial design {8}**

This is a prospective randomized, double-blind, single-center controlled trial conducted at the Second Affiliated Hospital of Army Medical University, PLA. This trial employs an exploratory framework to investigate the potential benefits of INI in this specific clinical context. The study design and participant flow are depicted in Fig. 1. Eligible participants scheduled for elective cardiac surgery will be enrolled and randomly assigned in a 1:1 ratio to either receive Intranasally administered insulin (INI) or Intranasally administered normal saline. Both intervention and control groups will follow a standardized anesthesia management protocol throughout the

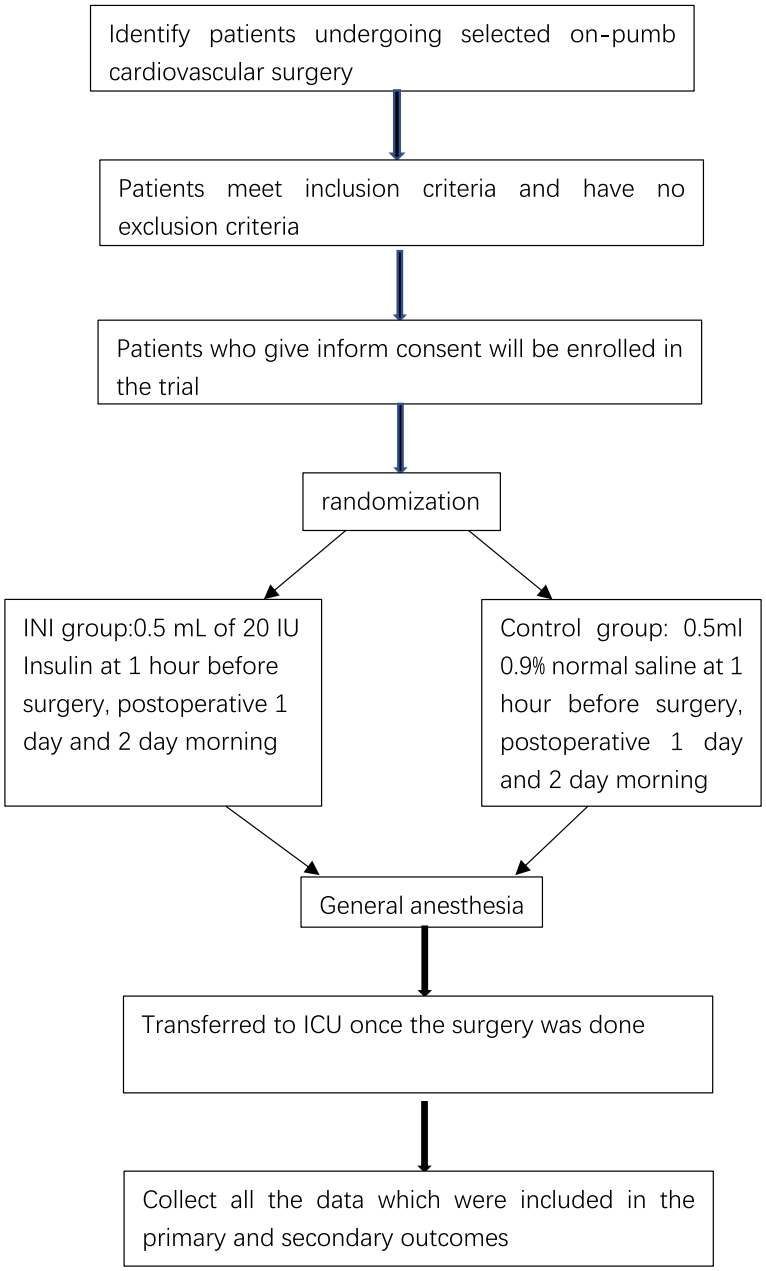


**Fig. 1** Study flow chart

perioperative period. Enrollment commenced on March 4, 2024, and is anticipated to conclude on October 30, 2024.

## Methods: participants, interventions, and outcomes

### Study setting {9}

The research protocol received approval from the Ethics Committee of the Second Affiliated Hospital of Army Medical University and was registered with the Chinese Clinical Trial Registry (Registration Number: ChiCTR2400081444 ). Each participant will provide written informed consent before enrollment.

### Eligibility criteria {10}

Individuals meeting the following criteria will be eligible for inclusion:

1. Patients aged 45–65 years scheduled for elective cardiac surgery
2. Capable of engaging in concise communication with the investigator and successfully conducting the assessment using relevant scales
3. Mini-Mental Status Examination (MMSE) score greater than 17
4. Willing to participate in this study and signed informed consent.

Patients who meet one of the following criteria will be excluded:

1. ASA I–III
2. Allergy to insulin
3. BMI > 35 kg/m$^2$
4. History of mental illness or taking psychotropic drugs
5. Combined with diabetes
6. Combined with cerebral infarction or stroke
7. Long-term use of analgesics or sedatives
8. History of drug abuse, alcohol or opioid abuse
9. Chronic pain or recent acute pain
10. Contraindicated for nasal administration
11. Participants retain the right to withdraw from the study at their discretion for any reason, or if researchers deem their inclusion in the trial inappropriate.

### Who will take informed consent? {26a}

The recruitment of eligible participants for this study will be managed by a specifically assigned member of the research team. Informed consent, in accordance with the Institutional Review Board's approval, will be secured from eligible patients or their legally authorized representatives. A comprehensive verbal explanation of the study, along with its associated benefits and risks, will precede the consent process. Participants will be explicitly informed of the voluntary nature of their participation and their right to withdraw from the trial at any point.

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

Participants will be provided with detailed information regarding the specific types of data and biological specimens to be collected, the intended analyses or investigations, and any potential sharing or storage arrangements.

## Interventions

### Explanation for the choice of comparators {6b}

INI has demonstrated neuroprotective properties and the potential to modulate metabolic processes in the brain. Given the vulnerability of the brain to perioperative insults, including ischemia-reperfusion injury and inflammation, the use of INI may contribute to neurocognitive preservation and mitigate the risk of postoperative delirium, a common complication in patients undergoing cardiac surgery. The choice of INI aligns with the goal of enhancing recovery after surgery by addressing the neurocognitive aspect, potentially improving patient outcomes, and enhancing the overall quality of care in the context of cardiac surgical procedures.

### Intervention description {11a}

Intranasal insulin (INI) administration, at a dosage of 0.5 ml containing 20 IU, was conducted 1 h prior to the induction of general anesthesia in the operating room. This intervention was implemented at 8:00 am on postoperative days 1 and 2. In parallel, for the control group, an identical procedure was carried out, with patients receiving a 0.5-ml injection of 0.9% normal saline.

### Criteria for discontinuing or modifying allocated Interventions {11b}

The withdrawal criteria are as follows:

1. Patients were found not to meet inclusion criteria after enrollment or to meet exclusion criteria after enrollment
2. Patient request to withdrawal the study
3. Life-threatening postoperative rescue or reoperation
4. the investigator may decide to end the trial due to other unforeseen reasons

**Strategies to improve adherence to interventions {11c}**
Our trial will undergo rigorous oversight by an independent investigator to verify adherence to the approved protocol throughout all procedures. Furthermore, a separate investigator will oversee the randomization process to uphold impartiality and diminish potential biases. All experiments will be executed meticulously in accordance with the study protocol, ensuring uniformity and upholding the reliability and validity of our findings.

**Relevant concomitant care permitted or prohibited during the trial {11d}**
All participants will undergo standard intraoperative anesthesia management and postoperative care after cardiac surgery.

**Provisions for post-trial care {30}**
In cases where trial participants encounter complications arising from the interventions, they will receive standard post-operative care administered by a multidisciplinary team comprising the surgical, anesthesiology, and intensive care units. Our team is committed to delivering tailored management for all participants, ensuring swift identification and proper handling of any adverse events. Moreover, we will conduct vigilant surveillance of participants throughout the post-operative phase, promptly addressing any potential complications as they arise. Our paramount objective is to guarantee that all participants receive optimal care and comprehensive support during the trial.

**Outcomes {12}**
***Primary outcome***
The primary outcome of our study is the incidence of POD (postoperative 1–4 days).

***Secondary outcomes***
The second outcomes include duration of ICU, postoperative hospital length of stay, all in-hospital mortality, the change in MMSE scores pre- and post-operation, and incidence of postoperative cognitive dysfunction at 1 month, 3 months, and 6 months after operation.

Other recorded parameters encompassed a range of indicators, including age, gender, cardiac functional classification, ASA classification, height, weight, occupation, education level, smoking history, history of alcoholism, comorbidities, postoperative pain scores (VAS at rest and during cough at 1–4 days after surgery), blood glucose and lactate levels 1 h post-administration, blood glucose and lactate values at the end of surgery, intraoperative sedative and analgesic drug dosages, intraoperative blood product infusions, intraoperative blood loss, operation time, cardiopulmonary bypass time, anesthesia time, cerebral oxygen levels at the beginning and end of surgery, preoperative and postoperative 1day neutrophil-lymphocyte ratio (NLR), preoperative Mini-Mental State Examination (MMSE) score, Pittsburgh Sleep Quality Index (PSQI), Generally Anxiety Disorder-7 (GAD-7), Patient Health Questionnaire-9 (PHQ-9) and MMSE score on the 5th day after surgery (confirmed when the patient was transferred out of the intensive care unit), Richards-Cambell Sleep Questionnaire (RSCQ) from postoperative 2 day to 5th day, Quality of sleep including Total sleep time, wake after sleep onset, sleep efficiency, times of wakening, average awakening time provided by ActiGraph wGT3X-BT (ActiGraph, USA).

**Participant timeline {13}**
The schedule of enrolment, interventions, and assessments is shown in Fig. 1.

**Sample size {14}**
The primary endpoint assessed in this study pertains to the incidence of POD. To ascertain the requisite sample size, a preliminary investigation was conducted, measuring the incidence of POD across two cohorts (INI group:12%, control group: 42%), each comprising 20 patients. Predicated on these findings, the necessary sample size was computed, considering a type I error significance level of 0.05, a type II error of 0.1, and an anticipated dropout rate of 20%. Our analysis demonstrated that enrolling 38 participants in each cohort will afford the study 90% statistical power to detect a meaningful variance in the incidence of POD between the comparative groups. By adhering to this determined sample size, our objective is to ensure the study possesses adequate statistical power to discern substantial disparities in the incidence of POD between the two cohorts.

**Recruitment {15}**
The principal investigator will be responsible for overseeing all aspects of the recruitment process and any subsequent amendments. To ensure the successful recruitment of participants and achieve the required sample size for our study, we will implement a comprehensive recruitment strategy. The recruitment process is scheduled to take place over an extended period from March 4, 2024, to October 30, 2024. We will work closely with the cardiac surgical team and the cardiology department to identify eligible patients during preoperative evaluations. Surgeons and cardiologists will be informed about the study's objectives and benefits, encouraging them to discuss participation with eligible patients. Nurses and research coordinators will follow up with identified eligible patients prior to their surgery, providing reminders and addressing any questions they may have

about participating in the study. Based on the hospital's previous data regarding elective cardiac surgeries, we anticipate an average monthly recruitment rate of approximately 20–25 eligible participants. This estimate considers historical data over the past year regarding patient flow and enrollment in similar studies.

## Assignment of interventions: allocation

### Sequence generation {16a}

In this study, participants will undergo enrollment and subsequent random allocation into either the INI group or the control group, achieved through a computerized random-number generator (using SPSS) in a 1:1 ratio. The randomization procedure will be executed by an impartial individual not directly involved in the study, ensuring an unbiased allocation devoid of potential confounding factors. Emphasizing the pivotal role of randomization in study design, it serves to mitigate selection bias, thereby attributing any observed between-group differences to the intervention under investigation.

### Concealment mechanism {16b}

To uphold the integrity of the randomization procedure, patient codes and group assignments will be enclosed in sealed, opaque envelopes, with the random sequence concealed from the researchers. Throughout the follow-up phase, randomized codes will be applied for data analysis, thereby maintaining researcher blinding to the group assignments.

### Implementation {16c}

The allocation sequence will be generated by an impartial individual who is independent of the study and not involved in any aspect of participant recruitment or management. This individual will use a secure randomization software to create a balanced allocation sequence. Participants will be enrolled by trained research coordinators who will be responsible for screening potential candidates based on the defined eligibility criteria. The research coordinators will provide detailed information about the study to eligible participants, obtain informed consent, and ensure that any questions or concerns related to participation are addressed comprehensively. Following enrollment and informed consent, participants will be assigned to interventions according to the allocation sequence generated earlier. This allocation will be managed by the same impartial individual responsible for generating the sequence, thus maintaining the integrity of the blinding process. Participants will be assigned to either the intranasally administered insulin (INI) group or the intranasally administered normal saline group based on this predetermined random sequence. Both participants and investigators involved in the clinical management of the patients will remain blinded to the treatment assignments to prevent any biases that could influence outcomes.

## Assignment of interventions: blinding

### Who will be blinded {17a}

Our study will be a double-blinded trial. All the patients included in the study, investigators, and postoperative follow-up staff will be blinded to the group allocation. Furthermore, the statisticians responsible for data analysis will be kept blinded to group allocations.

### Procedure for unblinding if needed {17b}

If participants meet the criteria necessitating experiment termination, their group allocation will be disclosed.

## Data collection and management

### Plans for assessment and collection of outcomes {18a}

The primary data source for this study will be electronic medical record systems or case report forms (CRFs). The data collection process will be conducted by independent researchers. Additionally, prior to data collection, all researchers will undergo training provided by the principal investigator, focusing on data collection, recording, and storage procedures. Subsequently, two researchers will input the collected data into the Microsoft Excel system to ensure dual verification. The principal researcher will meticulously scrutinize the raw data sheets for any missing critical data points or errors. To maintain data confidentiality, all information will be strictly confidential and used solely for research purposes. The researchers will maintain blinding to group allocation until the completion of data analysis to minimize potential biases and ensure the validity of the study results.

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

In our study, we have designed a 180-day follow-up period. A detailed explanation of the study protocol will be provided to all patients prior to the commencement of the study. Additionally, we will implement vigilant monitoring and deliver high-quality care to all participants, promptly addressing any questions or discomforts raised by patients throughout the study.

### Data management {19}

Throughout the study duration, we employed case report forms to systematically document all pertinent information. Following this, two designated investigators will undertake the responsibility of transcribing this information into a dedicated computer, with a subsequent data verification process conducted by two individuals. The resulting spreadsheet will be secured with restricted

access, and only the principal investigator holds the authorization to open it.

#### Confidentiality {27}

Patients will maintain enrollment for the entire duration of the study. To ensure confidentiality, all research data will be assigned identification numbers and securely stored in a locked cabinet throughout the trial.

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

In out study, specific plans might include the method of blood collection, we will ensure proper handling to maintain sample integrity. The laboratory evaluation process would involve blood-gas analyses. Moreover, the storage conditions and facilities, including temperature control and sample labeling, will be detailed to maintain sample quality for subsequent analyses or future use.

## Statistical methods

#### Statistical methods for primary and secondary outcomes {20a}

Statistical analysis was performed using SPSS software version 26.0 (IBM, NY, USA). All continuous variables will be expressed as mean (SD), or median (IQR [range]). Categorical variables were described with n (%). A $p < 0.05$ will be considered statistically significant. The primary outcome of POD will be compared with the chi-square test or Fisher's exact tests for differences in proportions. Odds ratios and confidence intervals for proportions will be calculated at a 95% level. For continuous data, the Mann–Whitney *U*-test and Student's *t*-test were employed based on the distribution of the data, whether it adhered to normal distribution or was nonparametric in nature. The analysis of the primary outcome will be conducted following an intention-to-treat approach.

#### Interim analyses {21b}

Interim analysis will be not performed in our study.

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

If disparities emerge in our baseline data, we will reintroduce these variables in our analysis employing logistic regression to mitigate potential bias.

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

Analysis will be performed by an intention-to-treat approach. We have taken steps to mitigate the risk of data loss. Multiple imputation techniques will be applied to accurately estimate the missing values.

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

In this study, we will rigorously and transparently conduct data analysis to ensure the accuracy and reliability of our findings. The statistical code used in our analyses will be provided upon reasonable request from the principal investigator, promoting transparency, reproducibility, and potential collaboration in the field. Additionally, we will retain all completed data for 10 years after the study's conclusion, adhering to standard data retention policies for future validation. All data will be securely stored and maintained in compliance with applicable data protection laws and regulations.

## Oversight and monitoring

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

Our study will be a single-center study. The trial steering committee for our trial is composed of major investigators, principal researchers, and experts in the relevant field. The collaborative team is responsible for overseeing the overall conduct of the trial, making critical decisions, and ensuring adherence to the study protocol. Regular meetings are held to discuss trial progress, address any challenges, and make informed decisions for the successful execution of the study.

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

The data monitoring committee include independent experts in the fields of clinical research, statistics, and neurology. The primary role of the data monitoring committee is to monitor and review the ongoing trial data to ensure participant safety, data integrity, and adherence to the study protocol. This committee will be independent from our study members. The reporting framework includes recurrent, scheduled meetings during which the committee examines interim analyses and safety reports.

#### Adverse event reporting and harms {22}

All adverse events are promptly recorded, classified, and assessed for severity and relationship to the study intervention. Our protocol outlines the procedures for reporting adverse events. The study team, including investigators and coordinators, is trained on adverse event reporting protocols to ensure consistency and accuracy. Serious adverse events are reported to the relevant ethics committee.

#### Frequency and plans for auditing trial conduct {23}

The frequency of audits will occur at predefined intervals, with thorough assessments of trial documentation, data collection procedures, and overall protocol

compliance. An independent audit team, separate from our study investigators, will be responsible for conducting these audits. Any identified deviations or concerns will be documented, addressed, and reported to the trial steering committee.

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

The study protocol received approval from the Ethics Committee of the Second Affiliated Hospital of Army Medical University and was registered with the Chinese Clinical Trial Registry. Any proposed amendments to the protocol will undergo review and approval by the principal investigator, followed by confirmation and approval from both the Ethics Committee and the Chinese Clinical Trial Registry

#### Dissemination plans {31a}

We plan to publish our data in reputable peer-reviewed journals, presenting our research in conferences and scientific meetings. In addition, we aim to engage with healthcare professionals through workshops and seminars to share insights and implications of our study. Furthermore, efforts will be made to communicate findings to the general public through press releases and social media platforms.

## Discussion

This is a prospective, randomized, double-blinded study aimed to evaluate the effectiveness of INI in middle-aged patients undergoing elective on-pump cardiac surgery. Although the pathophysiology of postoperative delirium (POD) is not fully elucidated, it is hypothesized that its primary mechanisms involve disrupted neuroendocrine regulation, neuroinflammation, dysconnectivity in neural networks, and ischemic damage resulting from a reduction in cerebral blood flow (CBF) [15].

Insulin's role in enhancing cognitive functions under conditions of oxidative stress or excitotoxicity may also stem from its neuro-modulatory impact. This effect involves altering the surface density and activity of ionotropic receptors for glutamate and γ-aminobutyric acid in neurons. Furthermore, insulin regulates the membrane transport of glutamate and γ-aminobutyric acid, optimizing their ratio in the extracellular space [16]. The use of intranasal administration insulin for the treatment of Alzheimer's disease and other diseases of the nervous system has decades of history. The primary benefit of intranasal drug administration lies in the specific targeting of substances to the central nervous system, particularly those unable to traverse the blood-brain barrier due to biological properties or other factors. In human studies, intranasal administration of insulin resulted in the circumvention of the blood-brain barrier, with detection in the cerebrospinal fluid occurring at 10 min, peaking at 30 min, and maintaining a significantly elevated level at 80 min [17]. In addition, the safety of INI has been proved by numerous studies. Vera Novak et al. have shown that 24-week treatment with 40 IU of INI in patients with type 2 diabetes mellitus had positive effects on cognition and gait [18]. Building on this evidence, our research will comprehensively assess perioperative sleep quality, investigating the potential link between intranasal insulin administration and postoperative delirium. Specifically, we will focus on how INI impacts sleep quality. Our study aims to evaluate the influence of intranasal insulin on the incidence of postoperative delirium in middle-aged patients undergoing elective on-pump cardiac surgery, seeking to identify effective strategies for preventing postoperative delirium.

## Trial status

The research protocol was officially registered on March 1, 2024, with the identified number: ChiCTR2400081444. The protocol version was version 2.0 on 15 January 2024. The initial recruitment was enrolled on March 4, 2024, with the anticipated completion of this work by October 30, 2024.

#### Abbreviations

| | |
|---|---|
| INI | Intranasal insulin |
| POD | Postoperative delirium |
| CAM-ICU | Confusion Assessment Method for the Intensive Care Unit |
| 4AT | 4 A's Test |
| MMSE | Mini-Mental Status Examination |
| VAS | Visual analog scale |
| PSQI | Pittsburgh Sleep Quality Index |
| GAD-7 | Generally Anxiety Disorder-7 |
| PHQ-9 | Patient Health Questionnaire-9 |
| RSCQ | Richards-Cambell Sleep Questionnaire |

#### Authors' contributions {31b}

MY is the Chief Investigator; she conceived the study and led the proposal and protocol development.TL conducted the data analysis and interpretation. JD and YL actively participated in the literature review, ensuring a comprehensive understanding of the existing research landscape. CX and ZD will take part in the follow-up period.MY and FC were responsible for drafting and revising the manuscript. XJ and WW contributed substantially to the acquisition of data and played a key role in ensuring the accuracy and reliability of the results.GY and HL contributed to the overall intellectual content of the work. All authors have critically reviewed and approved the final version of the manuscript.

#### Funding {4}

This work was supported by the National Natural Science Foundation of China (Project No.82171265) and the National Key Research and Development Program of China (Project No.2018YFC0117200). The funding sources played no part in the process of study.

#### Availability of data and materials {29}

The dataset used in this study are available for reasonable request from the primary investigator.

## Declarations

**Ethics approval and consent to participate {24}**
The approval for this study was granted by the Ethics Committee of the Second Affiliated Hospital of Army Medical University with registered number: 2024-yandi 038-01. All investigators conducted this study in compliance with the principles outlined in the Declaration of Helsinki. Written informed consent will be obtained from all the participants.

**Consent for publication {32}**
Not applicable - no identifying images or other personal or clinical details of participants are presented here or will be presented in reports of the trial results. The participant information materials and informed consent form are available from the corresponding author on request.

**Competing interests {28}**
The authors declare that they have no competing interests.

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## Publisher's Note