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Transcutaneous auricular vagus nerve stimulation prevents postoperative delirium in elderly patients (VNSTAR): protocol for a multicenter, randomized controlled trial

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Declarations

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Abstract

Introduction

Postoperative delirium is a common complication in elderly patients and is closely associated with delayed recovery, prolonged hospital stays, increased mortality rates, and increased medical expenses. Vagus nerve stimulation, a novel technique in the field of neuroscience, has demonstrated remarkable therapeutic potential in improving neurocognitive disorders. However, its applicability in ameliorating neurocognitive dysfunctions that arise during the perioperative period remains unclear. To date, no large prospective, randomized controlled studies have explored the effects of vagus nerve stimulation on postoperative delirium.

Method and analysis

This study is a multicenter, double-blind, parallel, randomized controlled trial. It aims to explore the preventative effects of transcutaneous auricular vagus nerve stimulation on postoperative delirium in elderly patients who are scheduled for elective surgery at several medical institutions in China from 2024--2027. The estimated sample size was 1778, with half of the patients randomly assigned to receive prophylactic standard transauricular auricular vagus nerve stimulation (taVNS) during the perioperative period (allocation ratio 1:1). The primary outcome measure was the incidence of POD within 5 days after surgery.

Ethics and Publication

This study was approved by the Ethics Committee of Beijing Tiantan Hospital, Capital Medical University, and adheres to the principles of the Declaration of Helsinki. The protocol was written in accordance with the 2013 Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines. The results of this study will be published in a peer-reviewed journal and presented at national or international conferences.

Clinical Trial Registration Number: NCT 06421077（05/10/2024）

Strengths and limitations of this study

- This study is a multicenter, prospective, randomized controlled trial to explore the effects of vagus nerve stimulation on postoperative delirium. The study features a rigorous randomizing and blinding process, clearly defined inclusion and exclusion criteria, and well-articulated outcome measures, effectively balancing intergroup variable differences.
- In accordance with the latest recommendations for POD diagnosis, this study implemented a more rigorous and frequent diagnostic approach, in which patients were assessed twice daily over a period of five days. This method is designed to more accurately capture the fluctuating and transient nature of POD, thereby minimizing the risk of underdiagnosis to the greatest extent possible.
- While anaesthesia type may influence POD incidence, the study does not mandate a standardized anaesthesia protocol to better reflect real-world clinical practice.
- The study population is specifically limited to individuals of Chinese ethnicity. Cognitive assessments do not incorporate measures to account for learning effects in this study.

BACKGROUND

Postoperative delirium (POD) is one of the most common complications in elderly patients after surgery and is associated with prolonged hospital stays, cognitive decline, the need for long-term care, and increased medical costs[1-3]. The latest report revealed that the incidence of POD in patients over 60 years of age undergoing surgery is as high as 20%-50% worldwide[4,5]. Preventing POD has become an important public health issue.

Current interventions for POD primarily focus on preoperative education, screening high-risk patients, pharmacological interventions, multimodal postoperative analgesia, and the avoidance of certain specific medications[4-6]. However, there is a lack of effective and safe measures. Although the use of dexmedetomidine has been proven effective against POD[4,6,7], it also affects the cardiovascular system, potentially causing hypotension and bradycardia. Therefore, the use of dexmedetomidine in elderly patients with comorbid cardiovascular diseases or those at high risk of perioperative stroke requires extreme caution.

The etiology of POD remains unclear, with the primary theories, including neuroinflammation and neurotransmitter imbalance, potentially induced by surgical trauma and anaesthetic agents, likely playing a significant role[8-10]. Surgical stimulation triggers the release of inflammatory mediators and cytokines, including cortisol, C-reactive protein, IL-6, S-100β, and IL-8. These factors activate the coagulation system via endothelial tissue, leading to circulatory disturbances and blood–brain barrier disruption, which exacerbate neuroinflammatory responses. This cascade results in cerebral ischemia and neuronal apoptosis, contributing to the incidence of POD. Additionally, an imbalance in neurotransmitters such as acetylcholine and dopamine is closely associated with POD. Therefore, rapidly mitigating neuroinflammatory responses and modulating neurotransmitter release in the brain during the perioperative period may prevent and reduce the incidence of POD.

Regulating autonomic function through transcutaneous auricular vagus nerve stimulation (taVNS) to improve cognitive and memory functions, particularly in Alzheimer's disease patients, has emerged as a novel therapeutic approach in the field of neurological disorders for decades[11-15]. The capacity of taVNS to modulate neuroinflammation and neurotransmitter release has been substantiated in both foundational and clinical studies[16-19]. Notably, an animal study demonstrated that taVNS can alleviate sevoflurane-induced cognitive impairments in aged rats by activating basal forebrain cholinergic neurons[20]. A subsequent small-scale clinical trial by the same team revealed

that taVNS could preemptively address postoperative cognitive delays in elderly patients and diminish the expression of inflammatory cytokines, including AChE, BChE, IL-6, HMGB1, and S100β, in postoperative blood samples, concurrently reducing acetylcholinesterase activity[21]. Given the similarity between the effects of taVNS and the primary pathogenic mechanisms implicated in POD, we hypothesize that taVNS may exert a significant preventative effect on POD. There is an imperative for rigorous, prospective, randomized controlled trials to establish the causal relationship between taVNS and POD and to offer a new therapeutic approach for improving cognitive dysfunction in elderly patients in the field of perioperative medicine.

METHODS AND ANALYSIS

Objectives and hypothesis

This study aimed to determine the efficacy of taVNS in preventing POD by observing the incidence of POD during the perioperative period in elderly patients. Additionally, this study will assess cognitive function at 90 days after surgery to explore the potential long-term effects of taVNS on cognitive dysfunction in this population. The hypothesis is that the use of taVNS during the perioperative period can reduce the incidence of POD in elderly patients undergoing elective surgery without increasing the incidence of additional complications.

Study Design

This study is a multicenter, double-blind, parallel, randomized controlled trial with an equal probability of patient enrollment. It consecutively includes elderly patients scheduled for elective surgery at Beijing Tiantan Hospital, Capital Medical University, and several other medical institutions in China from 2024--2027. The study design adheres to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines. Figure 1 depicts the flowchart for patient enrollment.

Population

This study targeted elderly patients undergoing elective surgery at designated research institutions over an anticipated period of 3 years. The inclusion criteria for the study were as follows: ① age ≥65 years; ② anticipated surgical duration ≥2 hours; ③ postoperative hospital stay ≥4 days; and ④

provision of signed informed consent. The exclusion criteria were as follows: ① neurosurgical or cardiac surgery; ② severe cognitive impairment affecting the assessment of perioperative cognitive function; ③ terminal illness with a life expectancy of less than 3 months; ④ emergency surgery within 6 hours of hospital admission; and ⑤ severe sinus bradycardia, second-degree or higher atrioventricular block, or ⑥ the presence of an implanted cardiac pacemaker.

Intervention

In the intervention group, "standard-stimulation parameters" will be employed, with a current stimulation frequency of 25 Hz and a pulse width of 250 μs. In the control group, "low-stimulation parameters" will be utilized, with a current stimulation frequency of 1 Hz and a pulse width of 250 μs. For both groups, the current intensity was set to the maximum tolerable level without inducing pain for the patients. The determination of the maximum pain-free tolerable current intensity typically begins at 10 mA; if the subject reports a sensation of tingling within 20 seconds, the stimulation current intensity is gradually reduced. Conversely, if no tingling is reported, the stimulation intensity is incrementally increased. This maximum pain-free tolerable current intensity, established during the initial stimulation session, will be used for all subsequent sessions.

taVNS therapy was conducted a total of five times. The initial stimulation occurred within 24 hours preoperatively and lasted for 30 minutes. The second session takes place intraoperatively, with a duration of 1 hour, ideally commencing as soon as the patient enters the operating room and before the surgery begins. The final three sessions were completed postoperatively on days 1 to 3, with each session lasting for 30 minutes (Figure 2).

Randomization

Once patients are enrolled and confirmed to meet the inclusion and exclusion criteria, they will undergo randomization via a website-centralized system. The method of randomization is stratified flexible block randomization, with a 1:1 allocation ratio for eligible subjects. Stratification criteria are based on the assigned various research centers.

Allocation and blinding

This study will implement blinding for the taVNS stimulation devices to ensure the conduct of a

double-blind trial. The taVNS devices used will have fixed, preset frequencies of only 1 Hz and 25 Hz, which are set internally and cannot be adjusted by the investigators or observed through the device display. Investigators can only adjust the output current intensity via the control panel, which displays the setting. Multiple devices with different stimulation frequencies for the two groups are kept by a specific research assistant not involved in this study, who randomly numbers them and correlates the numbered machine information with the central randomization system in advance. When investigators receive random sequence information, they will directly obtain the machine number required for use from the terminal rather than being informed of Groups A or B. For example, assume that machines numbered 1, 4, 5, 6, and 9 have an internal frequency of 25 Hz for the intervention group. When the central randomization system assigns a patient to the intervention group (hypothetically Group A), the investigator will obtain only the random number "1, 4, 5, 6, or 9", not the information "Group A". The random numbers corresponding to the machines for both groups will only be unblinded at the end of the study to determine group allocation information. The taVNS stimulation devices require regular quality control and calculation (every two months) to confirm whether the output current parameters are targeted and timely adjustment as needed. This process is carried out by a specific research assistant in contact with the equipment supplier. Consequently, investigators are only responsible for the implementation of the intervention and are unaware of the stimulation parameters. The subjects in both the intervention and control groups will feel the current stimulation and are equally unaware of their group assignment. Follow-up for primary outcome measures will be completed by an independent follow-up team blinded to group information. Unblinding will be considered only in the event that serious AEs are reported to the principal investigator, the ethics committee, and the data safety monitoring board.

Standardized anaesthesia management

The choice of general anaesthesia method, artificial airway selection, or opioid, muscle relaxant, or regional block technique will be determined by the responsible anesthesiologist. This study has only established a standard anaesthetic management goal, and regardless of the anaesthetic method chosen by the anesthesiologist, every effort should be made to achieve the management target values (see Appendix 1). Furthermore, this study imposes strict restrictions on participating anesthesiologists, designating specific anesthesiologists at each center to perform anaesthesia for

this study, thereby reducing the impact of variations in anaesthetic management on the research outcomes.

Postoperative pain management

Postoperative pain management is conducted in accordance with the routine management protocols of each respective center, with the autonomy of decision-making vested by the attending anesthesiologist and the attending surgeon. The objective is to maintain the patient's pain level at a visual analogue scale (VAS) score of no more than 3 points.

Data collection and follow-up

According to the data collection plan (Table 1), data will be prospectively collected via case report forms (CRFs) in accordance with specific definitions. After hospital discharge, all follow-ups were scheduled to be completed within 90 days. The need for additional follow-ups will be determined at the discretion of the attending physician. All recorded data must be sourced and submitted to the data management team. For a detailed follow-up plan and content, please refer to Table 1 and Appendix 2.

Outcomes

1. Primary outcome

The incidence of POD at discharge or within 5 days after surgery. POD assessment is conducted via the 3D-CAM or CAM-ICU scale. Assessments are performed twice daily, continuing up to the 5th postoperative day or until discharge. Delirium evaluations are scheduled between 6:00 and 10:00 AM and between 6:00 and 10:00 PM daily.

2. Secondary outcome

1) Delirium severity: Delirium severity was assessed via the 3D-CAM-S scale.

2) Incidence of delayed cognitive recovery during hospitalization, as assessed by the MMSE/MoCA.

3) Incidence of neurocognitive dysfunction at 90 days postoperatively, as assessed by AMTS.

4) Degree of decline in activities of daily living at 90 days postoperatively, as assessed by the IADL score.

5) All-cause mortality at 90 days postoperatively.

6) Proportion of patients requiring higher levels of care postdischarge, specifically long-term care.

7) Incidence of unplanned admissions to the intensive care unit (ICU) or high-dependence unit.

8) Length of hospital stay, measured from the initiation of surgery to the actual time of discharge.

3. Safety outcome measures

The incidence of adverse events (AEs) during hospitalization was utilized as a safety outcome in this study. Any AEs experienced by the subjects will be meticulously documented, irrespective of their association with this study. AEs are classified into anticipated and unanticipated categories. The anticipated AEs include but are not limited to the following: ① myocardial infarction; ② cardiac arrest; ③ pulmonary embolism; ④ pulmonary infection; ⑤ sepsis; ⑥ surgical site infection; ⑦ bradycardia; ⑧ tachycardia; ⑨ hypotension; ⑩ hypertension; ⑪ arrhythmia; ⑫ hypoxia; and ⑬ coagulation disorders. Definitions for each AE are provided in detail in Appendix 2.

Sample size calculation

Using PASS15 software (NCSS, LLC, USA) for sample size estimation, data from previous reports indicate that the incidence of POD in patients over 65 years of age undergoing noncardiac surgery ranges from 12% to 15%[22; 23]. We aim to reduce POD by at least 30% (15% vs 10%). This study plans to conduct interim analyses at the 25%, 50%, and 75% completion of patient follow-ups, adjusting the significance level via the O'Brien–Fleming method, with the overall significance level controlled at 0.05. With a power of 1-β=80%, the required sample size is 1480. Considering a 20% dropout rate, the anticipated sample size needed to validate a 30% difference is 1776 patients (888 per group). Through interim analyses, the Data Safety Monitoring Board (DSMB) will decide whether to continue the study or terminate it early. If there is a significant discrepancy between the estimated and actual primary outcomes during the study, the final sample size may be appropriately adjusted at the time of the interim analysis.

Interim analysis

Interim analyses of the trial will be conducted after 450, 900, and 1350 subjects (25%, 50%, and 75% of the sample size) have completed the 90-day postoperative follow-up. Given the use of the O'Brien–Fleming method for interim analyses, the corresponding alpha levels for the three interim

analyses are α1=0.0001, α2=0.003, and α3=0.018, and a p value less than 0.044 at the end of the trial is considered statistically significant. All the statistical analyses will be performed via R version 4.4.1. During the interim analysis, the following factors will be considered: recruitment progress of patients, comparability of baselines, sample size assumption on the basis of event rates, attrition, incidence of adverse events (AEs), and the effect of the intervention on the primary outcome. The DSMB will determine whether to continue or discontinue the study on the basis of the interim analyses. For AEs, the DSMB will assess the existing data in conjunction with the anticipated final sample size, and if the threshold is exceeded, the study will be terminated immediately. Regarding the assessment of therapeutic efficacy, if a study has met the efficacy criteria and the required significance level, the study may be concluded early; otherwise, the study will continue. If there is a significant discrepancy between the estimated and actual primary outcomes during the study, adjustments to the sample size may be made at the time of the interim analysis if necessary.

Statistical methods

On the basis of the expected variable frequencies, the incidence of POD, new-onset postoperative neurocognitive dysfunction, transfer to a higher level of care, unplanned ICU admissions, and the incidence of AEs will be compared via the chi-square test or Fisher's exact test. Continuous variables such as hospital stay duration and scale scores will be analysed via t tests if they conform to a normal distribution, and non-parametric tests will be applied if they do not. Logistic regression analysis will be employed to establish a model for independent predictors of POD, evaluating the impact of preoperative conditions, perioperative management, postoperative treatments, and complications on POD. In the case of missing data, inverse probability weighting is used, and the worst-case scenario is imputed. In the final analysis, a two-sided P value less than 0.044 was considered statistically significant for intergroup differences. Both intention-to-treat (ITT) analysis and per-protocol set (PPS) analysis principles will be applied in the statistical analysis, with the ITT dataset serving as the primary dataset for the statistical conclusions.

Adverse event monitoring and reporting

All AEs associated with this study will be meticulously documented and closely monitored until the AE is resolved, the condition stabilizes, or it can be confirmed that the AE is unrelated to the study.

Once an AE occurs, immediate reporting to the research department is needed, along with notification of the principal investigator (PI) of the study to ascertain the severity of the AE and the damage caused. A report must be submitted to the Institutional Review Board (IRB) within 24 hours as part of the annual report. The PI is responsible for all the reported AEs.

Data safety monitoring board (DSMB)

The study has established a DSMB. The DSMB comprises two anesthesiology experts and one statistical expert. As an integral part of this research, the DSMB is responsible for providing independent review and assessment of safety data to further protect the interests and safety of the subjects. The primary tasks of the DSMB are to analyse the cumulative data obtained in a phased manner and to make recommendations on the basis of the analysis results. All members are required to fulfil the following duties and obligations: understanding the research plan of this study; attending independent monitoring committee meetings; reviewing and signing the clinical trial data safety monitoring committee charter; assessing the safety of the study intervention on the basis of the analysis report from the independent statistician; and making corresponding decisions.

Data management

For this trial, an electronic data capture (EDC) system is utilized in conjunction with paper CRFs for the documentation of research data. The coordinating center will conduct onsite monitoring of source data and perform 50% source data verification for the primary outcome measures. Original data for all data points from the first two subjects enrolled at each center will be verified, and subsequent monitoring will involve the verification of source data for randomly selected subjects. Study data will be retained for a minimum of 10 years.

Protocol amendments

Any decision to amend the study protocol should be made by the PI. In the event of any modifications to the protocol during the recruitment process (such as changes to inclusion/exclusion criteria, outcome measures, and statistical methods), the PI is required to communicate with all departments involved in the study and obtain approval from the Ethics Committee of Beijing Tiantan Hospital, Capital Medical University, prior to the implementation of the amended protocol.

Research progress and schedule

This study received approval from the Ethics Committee of Beijing Tiantan Hospital, Capital Medical University (Ethics Number: KY2024-008-01， January 19, 2024) and was registered on Clinicaltrials.com (NCT 06421077， May 10, 2024). The DSMB was established on June 10, 2024, and the study was subsequently initiated. The first patient was recruited on June 20, 2024. On the basis of the actual medical service situation at our research center, assuming that 50% of the patients are eligible and consent to participate in this study, we estimate the research period to be 2--3 years. The results of this study will be published in a peer-reviewed journal and presented at domestic or international conferences.

DISCUSSION

In this study, low-frequency stimulation rather than a blank control was utilized for the control group. This decision takes into account the frequency dependency of taVNS[24,25]. Published research widely acknowledges 20–30 Hz as the safe and effective frequency range[26-28]. Studies utilizing fMRI to observe the therapeutic effects of VNS have revealed that higher stimulation frequencies result in more extensive and active brain functional area activation[24]. In contrast, activation effects on brain functional areas are limited to frequencies less than 5 Hz compared with 20 Hz[24]. Consequently, some studies have adopted 1 Hz as the control group and 25 Hz as the intervention group for taVNS, with both groups demonstrating significant differences[26,28]. Compared with sham interventions that place electrodes on nonstandard stimulation sites such as the earlobe, this approach better facilitates the blinding of researchers. Moreover, sham interventions with electrodes placed on nonstandard sites such as the earlobe may still activate the vagus nerve due to current diffusion under high-intensity electricity[29]. Therefore, this study opts for a 1 Hz stimulation frequency as the control group. Pulse width also significantly affects the efficacy of transcutaneous auricular vagus nerve stimulation (taVNS). Previous studies have indicated that a pulse width of 250 μs may be the optimal stimulation duration. Similarly, this study employed a pulse width of 250 μs[30].

POD typically occurs within one week after surgery, with some patients with hypoactive delirium often exhibiting lethargy and silence, which are frequently overlooked in clinical settings. Therefore,

this study employs a more sensitive 3D-CAM scale for the diagnosis of POD and, in accordance with the latest recommendations for POD diagnosis[5,6,10,31], extends the follow-up period to five days postoperatively, with two follow-ups per day, accurately capturing the fluctuating and transient nature of POD and increasing the successful diagnosis rate of POD.

In this multicenter randomized controlled study, the design incorporates stringent randomization, clear inclusion and exclusion criteria, unified anaesthetic management goals, and well-defined outcome measures. However, the study design has several limitations. First, the type of anaesthesia may have a certain impact on the incidence of delirium; for example, inhaled anaesthetics might increase the occurrence of POD, and strictly limiting it to total intravenous anaesthesia might be more conducive to interpreting the study results. This study designated only specialized anesthesiologists without restricting them to their preferred anaesthesia methods. However, limiting to a specific type of anaesthesia is impractical in clinical settings. No medical institution uses only one type of anaesthesia, especially in China, where many anesthesiologists prefer a combined intravenous-inhalational approach. Strict limitations could reduce the generalizability of the study's findings. Second, the study population was limited to the Chinese population. The incidence of POD varies among different ethnic groups, and the efficacy of taVNS may differ accordingly. Third, in the assessment of cognition, there is potential for a learning effect among patients, which has not been specifically addressed with professional interventions. However, cognitive evaluation serves as a secondary outcome measure intended to lay the groundwork for future research endeavors. The primary objective of this study was to elucidate the relationship between taVNS and POD. Introducing additional research procedures could complicate the study.

Patient and Public Involvement

In the design of this study, there was no direct consultation with patients or the public in the formulation of research questions or outcome measurements. Patients were not involved in the design, recruitment, or clinical implementation of this research. Following the study's conclusion, the results will be reported in written form. The final research outcomes will also be communicated to all study participants in the manner they are most accustomed to.

Authors' contributions: Ruquan Han conceived the primary idea of the study. Ruquan Han

is the principal investigator. The study was executed by Youxuan Wu, Xuan Hou, Tianyuan Wang, Xingyan Wang, Kangda Zhang, Fa Liang, Minyu Jian, Bo Wang, and Haiyang Liu. Anxin Wang performed the statistical analysis. Youxuan Wu and Xuan Hou wrote the first draft of the manuscript. All the authors revised this draft and approved the final version. Youxuan Wu and Xuan Hou contributed equally to this work.

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Figure legends

Figure 1 Consolidated Standards of Reporting Trials flow diagram for this trial

Figure 2 Scheduling of five sessions of taVNS interventions. Pre, Preoperatively. Intra, Intraoperatively. Post, Postoperatively

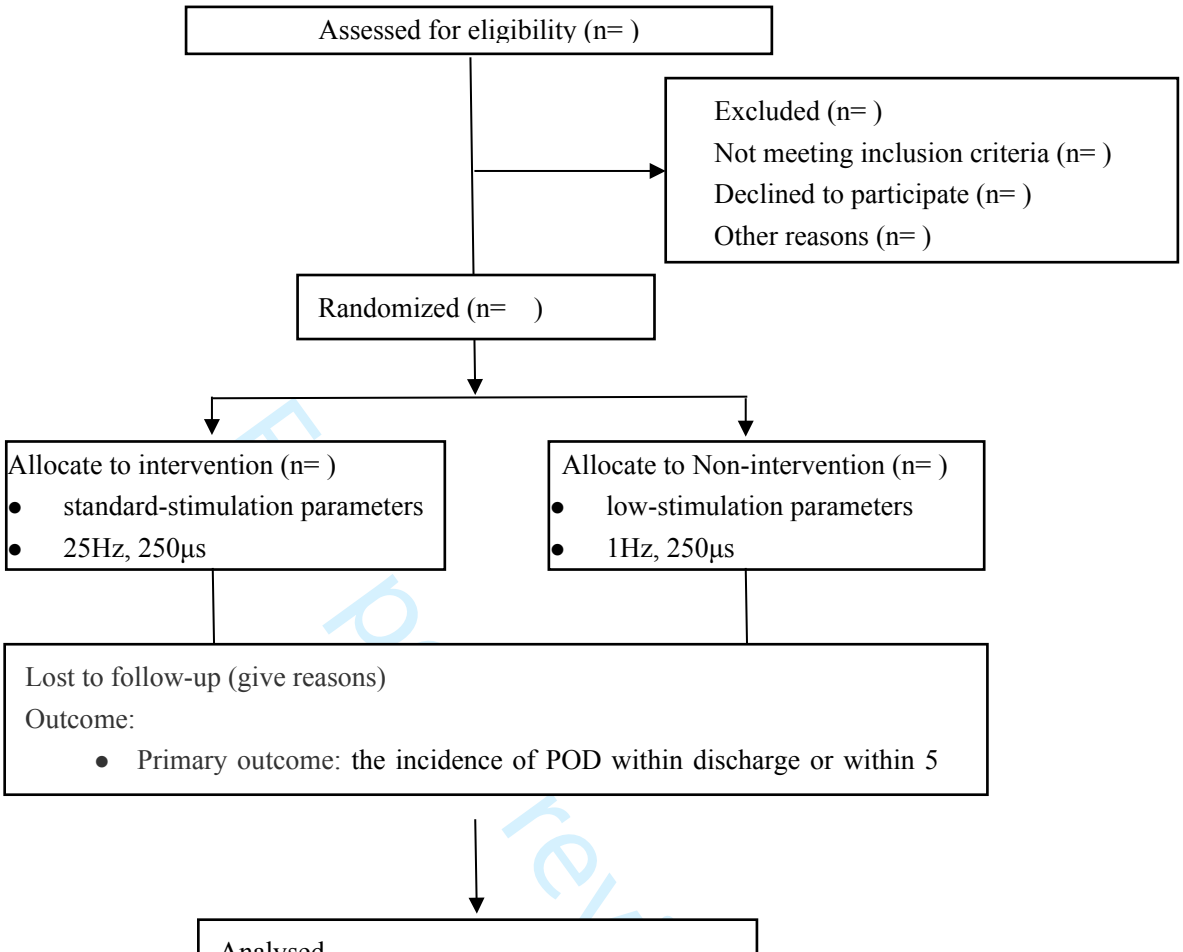

Figure 1 Consolidated Standards of Reporting Trials flow diagram for this trial.

Figure 2. Scheduling of five sessions of taVNS interventions. Pre, Preoperatively. Intra, Intraoperatively. Post, Postoperatively.

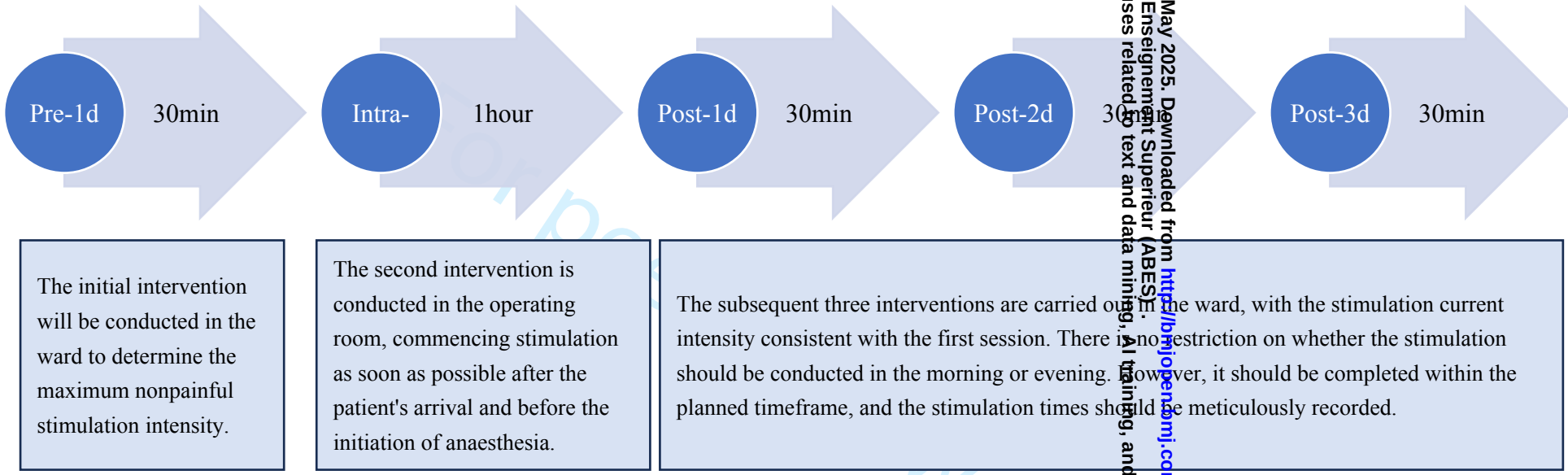

Table 1 Schedule of enrolment, intervention and assessment.

Time point Follow-up	Pre-Op	Intra-Op	Post-Op					Discharge	90d
	24h		1d	2d	3d	4d	5d		
Enrolment	×								
Eligibility screen	×								
Recruit	×								
Consent	×								
allocation	×								
Randomization	×								
Interventions									
Standard-stimulation parameters	×	×	×	×	×				
Low-stimulation parameters	×	×	×	×	×				
Assessments									
Baseline variables	×								
Clinical Frailty Scale	×								
Surgical and anesthesia conditions		×							

Emergence from Anesthesia		×						
3D-CAM/CAM-ICU	×		×	×	×	×	×	
MMSE/MoCA	×						×	
AMTS								×
IADL	×							×
All adverse events		×	×	×	×	×	×	
Length of stay							×	
Hospital expenses							×	
Unplanned HDU or ICU admissions							×	×
all-cause mortality							×	×

3D-CAM, 3-minute Diagnostic Interview for Confusion Assessment Method. CAM-ICU, Confusion Assessment Method for Intensive Care Uni. MMSE, Mini-mental State Examination. MoCA, Montreal Cognitive Assessment. AMTS, abbreviated mental test score .IADL, Instrumental Activities of Daily Living. HDU, High Dependency Unit. ICU, Intensive Care Unit.

Appendix 1. Standard anaesthetic management

a. Anaesthetic methods: total intravenous anaesthesia (TIVA) and intravenous and inhaled combined anaesthesia.

b. Induction and maintenance of anaesthesia (recommended): Induction is performed with sufentanil (0.3–0.5 μg/kg), propofol (1.5–2.5 mg/kg), and cisatracurium (0.15–0.20 mg/kg) or rocuronium (0.6–0.8 mg/kg). After endotracheal intubation, mechanical ventilation is initiated with the following parameters: tidal volume, 6–8 mL/kg; respiratory rate, 12–15/min; inspiratory/expiratory ratio, 1:2; PEEP, 5 cmH2O; inspired oxygen concentration, 60%; and fresh gas flow, 1–2 L/min, maintaining $PaCO_2$ at 35–40 mmHg. Anaesthesia is maintained with propofol (4–6 mg/kg/h) and remifentanil (0.05–0.2 μg/kg/min), with the use of inhaled anaesthetics at the discretion of the attending anaesthesiologist. Cisatracurium may be used for muscle relaxation as needed, and the BIS is maintained between 40 and 50. Anaesthetic discontinuation should occur when the surgeon has completely closed the surgical incision, and the time for emergence from anaesthesia should be recorded.

c. Hemodynamic management goals: Before randomization, the responsible anaesthesiologist must define individualized intraoperative goals for mean arterial pressure. Intraoperative blood pressure should be controlled within 20% of the target blood pressure to avoid its impact on outcomes.

d. Respiratory management goals: Both mechanical ventilation and spontaneous breathing should maintain normal carbon dioxide levels ($PaCO_2$ 35–40 mmHg), PaO_2 >60 mmHg, SpO_2 >94%, and FiO_2 0.4–0.6.

e. Temperature management goals: Maintenance between 35°C and 37°C.

f. The use of nitrous oxide and dexmedetomidine is prohibited. Benzodiazepines may be used before induction or in combination with induction. The use of low-dose continuous infusions of esketamine, which do not exceed 0.3 mg/kg/h, is permitted.

g. Postoperative pain management: Postoperative pain management is based on the routine management protocol of the center at the discretion of the attending anesthesiologist and the attending surgeon.

Other aspects of perioperative management will be decided autonomously by the responsible anesthesiologist. All complications will treated according to standard medical practice. After completion of the intraoperative interventions, the subjects received routine medical care.

Appendix 2. Data collection and definition of AEs

Data are gathered through patients, their family interviews, or physicians, and a review of hospital medical records and databases is performed. All recorded data must be sourced and submitted to the data management team.

Preoperatively: Demographic information, present illness history, past medical and medication history, admission physical examination, admission auxiliary examinations (bloodwork, imaging), ASA physical status classification, Charlson Comorbidity Index, type of surgery and urgency, cognition (MMSE/MoCA) and functional assessment (Lawton-Brody's IADL), and Clinical Frailty Scale.

Intraoperatively: Preoperative medications, vital signs, anaesthesia medications and fluid balance, surgical conditions, and anaesthesia emergence time.

Postoperative days 1--5: Delirium and its severity are screened twice daily via the 3D-CAM or CAM-ICU.

At discharge: Length of hospital stay, postdischarge outcomes, unplanned HDU or ICU admissions, and adverse events.

Postoperative 90 days: Cognition and functional evaluation (MMSE/MoCA, Lawton-Brody's IADL), and all-cause mortality.

The definitions of some AEs are as follows:

●**Myocardial infarction:** Myocardial infarction is defined as any of the following conditions: ① Typical elevation of troponin levels, a typical decrease in already elevated troponin levels, or a rapid increase and decline in CK-MB, accompanied by one of the following: symptoms of myocardial ischemia; pathological Q waves; ischemic changes on ECG; coronary artery intervention; echocardiography or imaging revealing new or suspected new wall motion abnormalities; or confirmation by autopsy.

●**Cardiac arrest:** Defined as successful resuscitation from definite or suspected ventricular fibrillation or sustained ventricular tachycardia or ventricular standstill.

●**Pulmonary embolism:** Highly suspected by radioactive nuclide lung ventilation/perfusion (V/Q) scintigraphy, confirmed by pulmonary angiography or spiral CT, or confirmed by autopsy.

Sepsis: Systemic inflammatory response syndrome (SIRS) with infection (positive blood culture or

purulent discharge from any site).

Surgical site infection: Characterized by purulent discharge and/or positive microbial culture results.

Bradycardia: Heart rate < 40 beats per minute or a decrease of 30% from the baseline level.

Tachycardia: Heart rate > 100 beats per minute or an increase of 30% from the baseline level.

Hypotension: Systolic blood pressure < 100 mmHg or a decrease of 30% from the baseline level.

Hypertension: Systolic blood pressure > 180 mmHg or an increase of 30% from the baseline level.

Arrhythmia: Including frequent atrial or ventricular premature beats, supraventricular or ventricular tachycardia, new-onset atrial fibrillation, etc., requiring antiarrhythmic treatment.

Hypoxia: SpO2 < 90%.

Coagulation abnormalities: Prothrombin time (PT) prolonged by more than 3 seconds, activated partial thromboplastin time (APTT) prolonged by more than 10 seconds, or thromboelastography (TEG) indicating coagulation mechanism abnormalities.

Other unanticipated adverse events: Any adverse event experienced by the subject was recorded truthfully, regardless of whether it was related to the study.

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Transcutaneous auricular vagus nerve stimulation prevents postoperative delirium in elderly patients (VNSTAR): protocol for a multicenter, randomized controlled trial

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Declarations

Competing interest All authors declare that they have no competing interests.

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Abstract

Introduction

Postoperative delirium is a common complication in elderly patients and is closely associated with delayed recovery, prolonged hospital stays, increased mortality rates, and increased medical expenses. Vagus nerve stimulation, a novel technique in the field of neuroscience, has demonstrated remarkable therapeutic potential in improving neurocognitive disorders. However, its applicability in ameliorating neurocognitive dysfunctions that arise during the perioperative period remains unclear. To date, no large prospective, randomized controlled studies have explored the effects of vagus nerve stimulation on postoperative delirium.

Method and analysis

This study is a multicenter, double-blind, parallel, randomized controlled trial. It aims to explore the preventative effects of transcutaneous auricular vagus nerve stimulation on postoperative delirium in elderly patients who are scheduled for elective surgery at several medical institutions in China from 2024--2027. The estimated sample size is 1776, with half of the patients randomly assign to receive prophylactic standard transauricular auricular vagus nerve stimulation (taVNS) during the perioperative period (allocation ratio 1:1). The primary outcome measure is the incidence of POD within 5 days after surgery.

Ethics and Publication

This study was approved by the Ethics Committee of Beijing Tiantan Hospital, Capital Medical University, and adheres to the principles of the Declaration of Helsinki. The protocol was written in accordance with the 2013 Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines. The results of this study will be published in a peer-reviewed journal and presented at national or international conferences.

Clinical Trial Registration Number: NCT 06421077（05/10/2024）

Strengths and limitations of this study

- This study is a multicenter, prospective, randomized controlled trial to explore the effects of vagus nerve stimulation on postoperative delirium. The study features a rigorous randomizing and blinding process, clearly defines inclusion and exclusion criteria, and well-articulated outcome measures, effectively balancing intergroup variable differences.
- In accordance with the latest recommendations for POD diagnosis, this study implements a more rigorous and frequent diagnostic approach, in which patients will be assessed twice daily over a period of five days. This method is designed to more accurately capture the fluctuating and transient nature of POD, thereby minimizing the risk of underdiagnosis to the greatest extent possible.
- While anaesthesia type may influence POD incidence, the study does not mandate a standardized anaesthesia protocol to better reflect real-world clinical practice.
- The study population is specifically limited to individuals of Chinese ethnicity. Cognitive assessments do not incorporate measures to account for learning effects in this study.

BACKGROUND

Postoperative delirium (POD) is one of the most common complications in elderly patients after surgery and is associated with prolonged hospital stays, cognitive decline, the need for long-term care, and increased medical costs[1-3]. The latest report revealed that the incidence of POD in patients over 60 years of age undergoing surgery is as high as 20%-50% worldwide[4,5]. Preventing POD has become an important public health issue.

Current interventions for POD primarily focus on preoperative education, screening high-risk patients, pharmacological interventions, multimodal postoperative analgesia, and the avoidance of certain specific medications[4-6]. However, there is a lack of effective and safe measures. Although the use of dexmedetomidine has been proven effective against POD[4,6,7], it also affects the cardiovascular system, potentially causing hypotension and bradycardia. Therefore, the use of dexmedetomidine in elderly patients with comorbid cardiovascular diseases or those at high risk of perioperative stroke requires extreme caution.

The etiology of POD remains unclear, with the primary theories, including neuroinflammation and neurotransmitter imbalance, potentially induced by surgical trauma and anaesthetic agents, likely playing a significant role[8-10]. Surgical stimulation triggers the release of inflammatory mediators and cytokines, including cortisol, C-reactive protein, IL-6, S-100β, and IL-8. These factors activate the coagulation system via endothelial tissue, leading to circulatory disturbances and blood–brain barrier disruption, which exacerbate neuroinflammatory responses. This cascade results in cerebral ischemia and neuronal apoptosis, contributing to the incidence of POD. Additionally, an imbalance in neurotransmitters such as acetylcholine and dopamine is closely associated with POD. Therefore, rapidly mitigating neuroinflammatory responses and modulating neurotransmitter release in the brain during the perioperative period may prevent and reduce the incidence of POD.

Regulating autonomic function through transcutaneous auricular vagus nerve stimulation (taVNS) to improve cognitive and memory functions, particularly in Alzheimer's disease patients, has emerged as a novel therapeutic approach in the field of neurological disorders for decades[11-15]. The capacity of taVNS to modulate neuroinflammation and neurotransmitter release has been substantiated in both foundational and clinical studies[16-19]. Notably, an animal study demonstrated that taVNS can alleviate sevoflurane-induced cognitive impairments in aged rats by activating basal

forebrain cholinergic neurons[20]. A subsequent small-scale clinical trial by the same team revealed that taVNS could preemptively address postoperative cognitive delays in elderly patients and diminish the expression of inflammatory cytokines, including AChE, BChE, IL-6, HMGB1, and S100β, in postoperative blood samples, concurrently reducing acetylcholinesterase activity[21]. Given the similarity between the effects of taVNS and the primary pathogenic mechanisms implicated in POD, we hypothesize that taVNS may exert a significant preventative effect on POD. There is an imperative for rigorous, prospective, randomized controlled trials to establish the causal relationship between taVNS and POD and to offer a new therapeutic approach for improving cognitive dysfunction in elderly patients in the field of perioperative medicine.

METHODS AND ANALYSIS

Objectives and hypothesis

This study aims to determine the efficacy of taVNS in preventing POD by observing the incidence of POD during the perioperative period in elderly patients. Additionally, this study will assess cognitive function at 90 days after surgery to explore the potential long-term effects of taVNS on cognitive dysfunction in this population. The hypothesis is that the use of taVNS during the perioperative period can reduce the incidence of POD in elderly patients undergoing elective surgery without increasing the incidence of additional complications.

Study Design

This study is a multicenter, double-blind, parallel, randomized controlled trial with an equal probability of patient enrollment. It consecutively includes elderly patients scheduled for elective surgery at Beijing Tiantan Hospital, Capital Medical University, and several other medical institutions in China from 2024--2027. The study design adheres to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines. Figure 1 depicts the flowchart for patient enrollment.

Population

This study targets elderly patients undergoing elective surgery at designated research institutions

over an anticipated period of 3 years. The inclusion criteria for the study are as follows: ① age ≥65 years; ② anticipated surgical duration ≥2 hours; ③ postoperative hospital stay ≥4 days; and ④ provision of signed informed consent（supplement1）. The exclusion criteria are as follows: ① neurosurgical or cardiac surgery; ② severe cognitive impairment affecting the assessment of perioperative cognitive function; ③ terminal illness with a life expectancy of less than 3 months; ④ emergency surgery within 6 hours of hospital admission; and ⑤ severe sinus bradycardia, second-degree or higher atrioventricular block, or ⑥ the presence of an implanted cardiac pacemaker.

Intervention

In the intervention group, "standard-stimulation parameters" will be employed, with a current stimulation frequency of 25 Hz and a pulse width of 250 μs. In the control group, "low-stimulation parameters" will be utilized, with a current stimulation frequency of 1 Hz and a pulse width of 250 μs. For both groups, the current intensity will be set to the maximum tolerable level without inducing pain for the patients. The determination of the maximum pain-free tolerable current intensity typically begins at 10 mA; if the subject reports a sensation of tingling within 20 seconds, the stimulation current intensity is gradually reduced. Conversely, if no tingling is reported, the stimulation intensity is incrementally increased. This maximum pain-free tolerable current intensity, established during the initial stimulation session, will be used for all subsequent sessions.

taVNS therapy will be conducted a total of five times. The initial stimulation occurrs within 24 hours preoperatively and lasted for 30 minutes. The second session takes place intraoperatively, with a duration of 1 hour, ideally commencing as soon as the patient enters the operating room and before the surgery begins. The final three sessions are completed postoperatively on days 1 to 3, with each session lasting for 30 minutes (Figure 2).

Randomization

Once patients are enrolled and confirmed to meet the inclusion and exclusion criteria, they will undergo randomization via a website-centralized system. The method of randomization is stratified flexible block randomization, with a 1:1 allocation ratio for eligible subjects. Stratification criteria

are based on the assigned various research centers.

Allocation and blinding

This study will implement blinding for the taVNS stimulation devices to ensure the conduct of a double-blind trial. The taVNS devices used will have fixed, preset frequencies of only 1 Hz and 25 Hz, which are set internally and cannot be adjusted by the investigators or observed through the device display. Investigators can only adjust the output current intensity via the control panel, which displays the setting. Multiple devices with different stimulation frequencies for the two groups are kept by a specific research assistant not involved in this study, who randomly numbers them and correlates the numbered machine information with the central randomization system in advance. When investigators receive random sequence information, they will directly obtain the machine number required for use from the terminal rather than being informed of Groups A or B. For example, assume that machines numbered 1, 4, 5, 6, and 9 have an internal frequency of 25 Hz for the intervention group. When the central randomization system assigns a patient to the intervention group (hypothetically Group A), the investigator will obtain only the random number "1, 4, 5, 6, or 9", not the information "Group A". The random numbers corresponding to the machines for both groups will only be unblinded at the end of the study to determine group allocation information. The taVNS stimulation devices require regular quality control and calculation (every two months) to confirm whether the output current parameters are targeted and timely adjustment as needed. This process is carried out by a specific research assistant in contact with the equipment supplier. Consequently, investigators are only responsible for the implementation of the intervention and are unaware of the stimulation parameters. The subjects in both the intervention and control groups will feel the current stimulation and are equally unaware of their group assignment. Follow-up for primary outcome measures will be completed by an independent follow-up team blinded to group information. Unblinding will be considered only in the event that serious AEs are reported to the principal investigator, the ethics committee, and the data safety monitoring board.

Standardized anaesthesia management

The choice of general anaesthesia method, artificial airway selection, or opioid, muscle relaxant, or

regional block technique will be determined by the responsible anesthesiologist. This study has only established a standard anaesthetic management goal, and regardless of the anaesthetic method chosen by the anesthesiologist, every effort should be made to achieve the management target values (see Appendix 1). Furthermore, this study imposes strict restrictions on participating anesthesiologists, designating specific anesthesiologists at each center to perform anaesthesia for this study, thereby reducing the impact of variations in anaesthetic management on the research outcomes.

Postoperative pain management

Postoperative pain management is conducted in accordance with the routine management protocols of each respective center, with the autonomy of decision-making vested by the attending anesthesiologist and the attending surgeon. The objective is to maintain the patient's pain level at a visual analogue scale (VAS) score of no more than 3 points.

Data collection and follow-up

According to the data collection plan (Table 1), data will be prospectively collected via case report forms (CRFs) in accordance with specific definitions. After hospital discharge, all follow-ups will be scheduled to be completed within 90 days. The need for additional follow-ups will be determined at the discretion of the attending physician. All recorded data must be sourced and submitted to the data management team. For a detailed follow-up plan and content, please refer to Table 1 and Appendix 2.

Outcomes

1. Primary outcome

The incidence of POD at discharge or within 5 days after surgery. POD assessment is conducted via the 3D-CAM or CAM-ICU scale. Assessments are performed twice daily, continuing up to the 5th postoperative day or until discharge. Delirium evaluations are scheduled between 6:00 and 10:00 AM and between 6:00 and 10:00 PM daily.

2. Secondary outcome

1) Delirium severity: Delirium severity is assessed via the 3D-CAM-S scale.

2) Incidence of delayed cognitive recovery during hospitalization, as assessed by the MMSE/MoCA.

3) Incidence of neurocognitive dysfunction at 90 days postoperatively, as assessed by AMTS.

4) Degree of decline in activities of daily living at 90 days postoperatively, as assessed by the IADL score.

5) All-cause mortality at 90 days postoperatively.

6) Proportion of patients requiring higher levels of care postdischarge, specifically long-term care.

7) Incidence of unplanned admissions to the intensive care unit (ICU) or high-dependence unit.

8) Length of hospital stay, measured from the initiation of surgery to the actual time of discharge.

3. Safety outcome measures

The incidence of adverse events (AEs) during hospitalization will be utilized as a safety outcome in this study. Any AEs experienced by the subjects will be meticulously documented, irrespective of their association with this study. AEs are classified into anticipated and unanticipated categories. The anticipated AEs include but are not limited to the following: ① myocardial infarction; ② cardiac arrest; ③ pulmonary embolism; ④ pulmonary infection; ⑤ sepsis; ⑥ surgical site infection; ⑦ bradycardia; ⑧ tachycardia; ⑨ hypotension; ⑩ hypertension; ⑪ arrhythmia; ⑫ hypoxia; and ⑬ coagulation disorders. Definitions for each AE are provided in detail in Appendix 2.

Sample size calculation

Using PASS15 software (NCSS, LLC, USA) for sample size estimation, data from previous reports indicated that the incidence of POD in patients over 65 years of age undergoing noncardiac surgery ranges from 12% to 15%[22; 23]. We aim to reduce POD by at least 30% (15% vs 10%). This study plans to conduct interim analyses at the 25%, 50%, and 75% completion of patient follow-ups, adjusting the significance level via the O'Brien–Fleming method, with the overall significance level controlled at 0.05. With a power of 1-β=80%, the required sample size is 1480. Considering a 20% dropout rate, the anticipated sample size needed to validate a 30% difference is 1776 patients (888 per group). Through interim analyses, the Data Safety Monitoring Board (DSMB) will decide whether to continue the study or terminate it early. If there is a significant discrepancy between the

estimated and actual primary outcomes during the study, the final sample size may be appropriately adjusted at the time of the interim analysis.

Interim analysis

Interim analyses of the trial will be conducted after 450, 900, and 1350 subjects (25%, 50%, and 75% of the sample size) have completed the 90-day postoperative follow-up. Given the use of the O'Brien–Fleming method for interim analyses, the corresponding alpha levels for the three interim analyses are $\alpha1=0.0001$, $\alpha2=0.003$, and $\alpha3=0.018$, and a p value less than 0.044 at the end of the trial is considered statistically significant. All the statistical analyses will be performed via R version 4.4.1. During the interim analysis, the following factors will be considered: recruitment progress of patients, comparability of baselines, sample size assumption on the basis of event rates, attrition, incidence of adverse events (AEs), and the effect of the intervention on the primary outcome. The DSMB will determine whether to continue or discontinue the study on the basis of the interim analyses. For AEs, the DSMB will assess the existing data in conjunction with the anticipated final sample size, and if the threshold is exceeded, the study will be terminated immediately. Regarding the assessment of therapeutic efficacy, if a study has met the efficacy criteria and the required significance level, the study may be concluded early; otherwise, the study will continue. If there is a significant discrepancy between the estimated and actual primary outcomes during the study, adjustments to the sample size may be made at the time of the interim analysis if necessary.

Statistical methods

On the basis of the expected variable frequencies, the incidence of POD, new-onset postoperative neurocognitive dysfunction, transfer to a higher level of care, unplanned ICU admissions, and the incidence of AEs will be compared via the chi-square test or Fisher's exact test. Continuous variables such as hospital stay duration and scale scores will be analysed via t tests if they conform to a normal distribution, and non-parametric tests will be applied if they do not. Logistic regression analysis will be employed to establish a model for independent predictors of POD, evaluating the impact of preoperative conditions, perioperative management, postoperative treatments, and complications on POD. In the case of missing data, inverse probability weighting is used, and the worst-case scenario

is imputed. In the final analysis, a two-sided P value less than 0.044 will be considered statistically significant for intergroup differences. Both intention-to-treat (ITT) analysis and per-protocol set (PPS) analysis principles will be applied in the statistical analysis, with the ITT dataset serving as the primary dataset for the statistical conclusions.

Adverse event monitoring and reporting

All AEs associated with this study will be meticulously documented and closely monitored until the AE is resolved, the condition stabilizes, or it can be confirmed that the AE is unrelated to the study. Once an AE occurs, immediate reporting to the research department is needed, along with notification of the principal investigator (PI) of the study to ascertain the severity of the AE and the damage caused. A report must be submitted to the Institutional Review Board (IRB) within 24 hours as part of the annual report. The PI is responsible for all the reported AEs.

Data safety monitoring board (DSMB)

The study has established a DSMB. The DSMB comprised two anesthesiology experts and one statistical expert. As an integral part of this research, the DSMB is responsible for providing independent review and assessment of safety data to further protect the interests and safety of the subjects. The primary tasks of the DSMB are to analyse the cumulative data obtained in a phased manner and to make recommendations on the basis of the analysis results. All members are required to fulfil the following duties and obligations: understanding the research plan of this study; attending independent monitoring committee meetings; reviewing and signing the clinical trial data safety monitoring committee charter; assessing the safety of the study intervention on the basis of the analysis report from the independent statistician; and making corresponding decisions.

Data management

For this trial, an electronic data capture (EDC) system will be utilized in conjunction with paper CRFs for the documentation of research data. The coordinating center will conduct onsite monitoring of source data and perform 50% source data verification for the primary outcome measures. Original data for all data points from the first two subjects enrolled at each center will be

verified, and subsequent monitoring will involve the verification of source data for randomly selected subjects. Study data will be retained for a minimum of 10 years.

Protocol amendments

Any decision to amend the study protocol should be made by the PI. In the event of any modifications to the protocol during the recruitment process (such as changes to inclusion/exclusion criteria, outcome measures, and statistical methods), the PI is required to communicate with all departments involved in the study and obtain approval from the Ethics Committee of Beijing Tiantan Hospital, Capital Medical University, prior to the implementation of the amended protocol.

Research progress and schedule

This study received approval from the Ethics Committee of Beijing Tiantan Hospital, Capital Medical University (Ethics Number: KY2024-008-02， February 18, 2024) and was registered on Clinicaltrials.com (NCT 06421077， May 10, 2024). The DSMB was established on June 10, 2024, and the study was subsequently initiated. The first patient was recruited on June 20, 2024. On the basis of the actual medical service situation at our research center, assuming that 50% of the patients are eligible and consent to participate in this study, we estimate the research period to be 2--3 years. The results of this study will be published in a peer-reviewed journal and presented at domestic or international conferences.

DISCUSSION

In this study, low-frequency stimulation rather than a blank control will be utilized for the control group. This decision takes into account the frequency dependency of taVNS[24,25]. Published research widely acknowledged 20–30 Hz as the safe and effective frequency range[26-28]. Studies utilizing fMRI to observe the therapeutic effects of VNS have revealed that higher stimulation frequencies result in more extensive and active brain functional area activation[24]. In contrast, activation effects on brain functional areas were limited to frequencies less than 5 Hz compared with 20 Hz[24]. Consequently, some studies have adopted 1 Hz as the control group and 25 Hz as the intervention group for taVNS, with both groups demonstrating significant differences[26,28].

Compared with sham interventions that place electrodes on nonstandard stimulation sites such as the earlobe, this approach better facilitates the blinding of researchers. Moreover, sham interventions with electrodes placed on nonstandard sites such as the earlobe may still activate the vagus nerve due to current diffusion under high-intensity electricity[29]. Therefore, this study opts for a 1 Hz stimulation frequency as the control group. Pulse width also significantly affects the efficacy of transcutaneous auricular vagus nerve stimulation (taVNS). Previous studies have indicated that a pulse width of 250 μs may be the optimal stimulation duration. Similarly, this study employed a pulse width of 250 μs[30].

POD typically occurs within one week after surgery, with some patients with hypoactive delirium often exhibiting lethargy and silence, which are frequently overlooked in clinical settings. Therefore, this study employs a more sensitive 3D-CAM scale for the diagnosis of POD and, in accordance with the latest recommendations for POD diagnosis[5,6,10,31], extends the follow-up period to five days postoperatively, with two follow-ups per day, accurately capturing the fluctuating and transient nature of POD and increasing the successful diagnosis rate of POD.

Compared with other similar studies, this study is a multicenter prospective randomized controlled study, with a larger sample size, stricter blinding design, and a greater variety of surgical types observed. In addition, the design incorporates stringent randomization, clear inclusion and exclusion criteria, unified anaesthetic management goals, and well-defined outcome measures. However, the study design has several limitations. First, the type of anaesthesia may have a certain impact on the incidence of delirium; for example, inhaled anaesthetics might increase the occurrence of POD, and strictly limiting it to total intravenous anaesthesia might be more conducive to interpreting the study results. This study designates only specialized anesthesiologists without restricting them to their preferred anaesthesia methods. However, limiting to a specific type of anaesthesia is impractical in clinical settings. No medical institution uses only one type of anaesthesia, especially in China, where many anesthesiologists prefer a combined intravenous-inhalational approach. Strict limitations could reduce the generalizability of the study's findings. Second, the study population is limited to the Chinese population. The incidence of POD varies among different ethnic groups, and the efficacy of taVNS may differ accordingly. Third, in the assessment of cognition, there is potential for a learning effect among patients, which has not been specifically addressed with professional

interventions. However, cognitive evaluation serves as a secondary outcome measure intended to lay the groundwork for future research endeavors. The primary objective of this study is to elucidate the relationship between taVNS and POD. Introducing additional research procedures could complicate the study.

Patient and Public Involvement

In the design of this study, there was no direct consultation with patients or the public in the formulation of research questions or outcome measurements. Patients were not involved in the design, recruitment, or clinical implementation of this research. Following the study's conclusion, the results will be reported in written form. The final research outcomes will also be communicated to all study participants in the manner they are most accustomed to.

Authors' contributions: Ruquan Han conceived the primary idea of the study. Ruquan Han was the principal investigator. The study was executed by Youxuan Wu, Xuan Hou, Tianyuan Wang, Xingyan Wang, Kangda Zhang, Fa Liang, Minyu Jian, Bo Wang, and Haiyang Liu. Anxin Wang performed the statistical analysis. Youxuan Wu and Xuan Hou wrote the first draft of the manuscript. All the authors revised this draft and approved the final version. Youxuan Wu and Xuan Hou contributed equally to this work. The guarantor is Ruquan Han.

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Figure legends

Figure 1 Consolidated Standards of Reporting Trials flow diagram for this trial

Figure 2 Scheduling of five sessions of taVNS interventions. Pre, Preoperatively. Intra, Intraoperatively. Post, Postoperatively

Table 1 Schedule of enrolment, intervention and assessment.

Time point Follow-up	Pre-Op	Intra-Op	Post-Op					Discharge	90d
	24h		1d	2d	3d	4d	5d		
Enrolment and Randomization	×								
Interventions	×	×	×	×	×				
Assessments									
Baseline variables	×								
Surgical and anesthesia conditions		×							
3D-CAM/CAM-ICU	×		×	×	×	×	×		
MMSE/MoCA	×							×	
AMTS/IADL	×								×
All adverse events and mortality		×	×	×	×	×	×	×	×

3D-CAM, 3-minute Diagnostic Interview for Confusion Assessment Method. CAM-ICU, Confusion Assessment Method for Intensive Care Uni. MMSE, Mini-mental State Examination. MoCA, Montreal Cognitive Assessment. AMTS, abbreviated mental test score .IADL, Instrumental Activities of Daily Living.

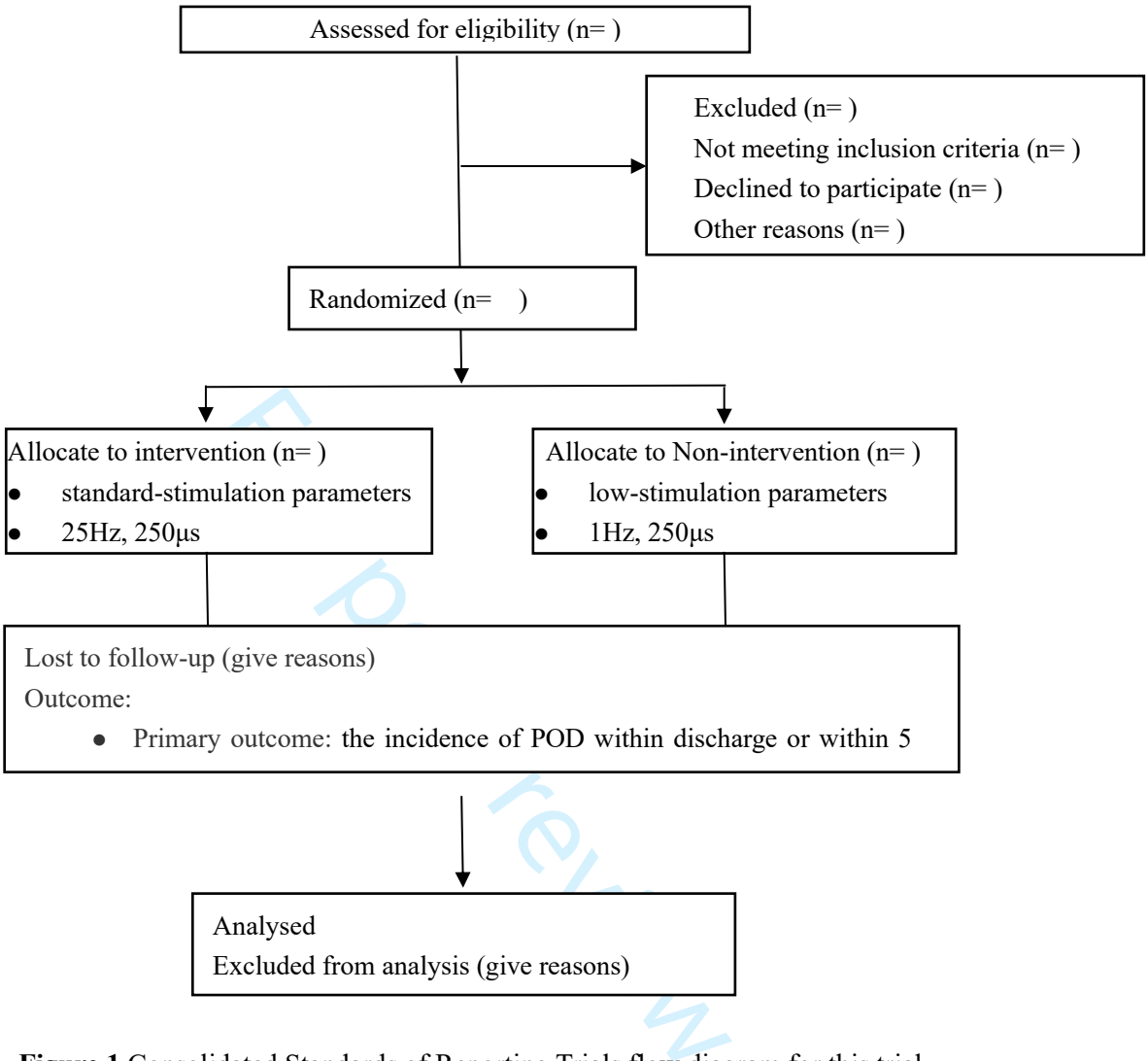
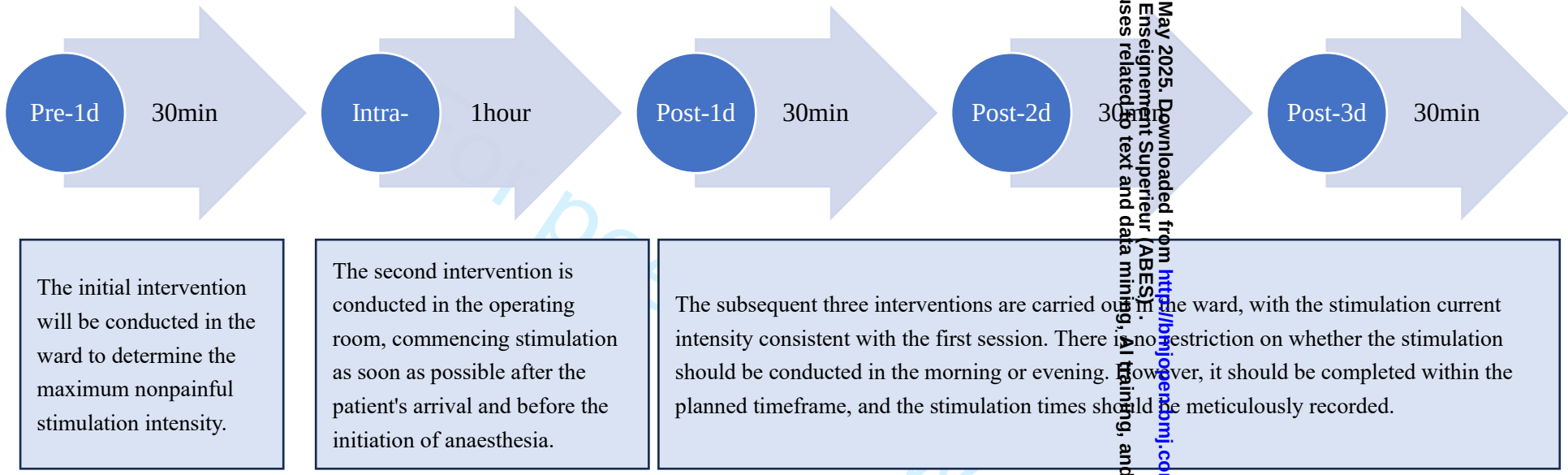


Figure 1 Consolidated Standards of Reporting Trials flow diagram for this trial.

Figure 2. Scheduling of five sessions of taVNS interventions. Pre, Preoperatively. Intra, Intraoperatively. Post, Postoperatively.



Appendix 1. Standard anaesthetic management

a. Anaesthetic methods: total intravenous anaesthesia (TIVA) and intravenous and inhaled combined anaesthesia.

b. Induction and maintenance of anaesthesia (recommended): Induction is performed with sufentanil (0.3–0.5 μg/kg), propofol (1.5–2.5 mg/kg), and cisatracurium (0.15–0.20 mg/kg) or rocuronium (0.6–0.8 mg/kg). After endotracheal intubation, mechanical ventilation is initiated with the following parameters: tidal volume, 6–8 mL/kg; respiratory rate, 12–15/min; inspiratory/expiratory ratio, 1:2; PEEP, 5 cmH2O; inspired oxygen concentration, 60%; and fresh gas flow, 1–2 L/min, maintaining $PaCO_2$ at 35–40 mmHg. Anaesthesia is maintained with propofol (4–6 mg/kg/h) and remifentanil (0.05–0.2 μg/kg/min), with the use of inhaled anaesthetics at the discretion of the attending anaesthesiologist. Cisatracurium may be used for muscle relaxation as needed, and the BIS is maintained between 40 and 50. Anaesthetic discontinuation should occur when the surgeon has completely closed the surgical incision, and the time for emergence from anaesthesia should be recorded.

c. Hemodynamic management goals: Before randomization, the responsible anaesthesiologist must define individualized intraoperative goals for mean arterial pressure. Intraoperative blood pressure should be controlled within 20% of the target blood pressure to avoid its impact on outcomes.

d. Respiratory management goals: Both mechanical ventilation and spontaneous breathing should maintain normal carbon dioxide levels ($PaCO_2$ 35–40 mmHg), PaO_2 >60 mmHg, SpO_2 >94%, and FiO_2 0.4–0.6.

e. Temperature management goals: Maintenance between 35°C and 37°C.

f. The use of nitrous oxide and dexmedetomidine is prohibited. Benzodiazepines may be used before induction or in combination with induction. The use of low-dose continuous infusions of esketamine, which do not exceed 0.3 mg/kg/h, is permitted.

g. Postoperative pain management: Postoperative pain management is based on the routine management protocol of the center at the discretion of the attending anesthesiologist and the attending surgeon.

Other aspects of perioperative management will be decided autonomously by the responsible anesthesiologist. All complications will treated according to standard medical practice. After completion of the intraoperative interventions, the subjects received routine medical care.

Appendix 2. Data collection and definition of AEs

Data are gathered through patients, their family interviews, or physicians, and a review of hospital medical records and databases is performed. All recorded data must be sourced and submitted to the data management team.

Preoperatively: Demographic information, present illness history, past medical and medication history, admission physical examination, admission auxiliary examinations (bloodwork, imaging), ASA physical status classification, Charlson Comorbidity Index, type of surgery and urgency, cognition (MMSE/MoCA) and functional assessment (Lawton-Brody's IADL), and Clinical Frailty Scale.

Intraoperatively: Preoperative medications, vital signs, anaesthesia medications and fluid balance, surgical conditions, and anaesthesia emergence time.

Postoperative days 1--5: Delirium and its severity are screened twice daily via the 3D-CAM or CAM-ICU.

At discharge: Length of hospital stay, postdischarge outcomes, unplanned HDU or ICU admissions, and adverse events.

Postoperative 90 days: Cognition and functional evaluation (MMSE/MoCA, Lawton-Brody's IADL), and all-cause mortality.

The definitions of some AEs are as follows:

●**Myocardial infarction:** Myocardial infarction is defined as any of the following conditions: ① Typical elevation of troponin levels, a typical decrease in already elevated troponin levels, or a rapid increase and decline in CK-MB, accompanied by one of the following: symptoms of myocardial ischemia; pathological Q waves; ischemic changes on ECG; coronary artery intervention; echocardiography or imaging revealing new or suspected new wall motion abnormalities; or confirmation by autopsy.

●**Cardiac arrest:** Defined as successful resuscitation from definite or suspected ventricular fibrillation or sustained ventricular tachycardia or ventricular standstill.

●**Pulmonary embolism:** Highly suspected by radioactive nuclide lung ventilation/perfusion (V/Q) scintigraphy, confirmed by pulmonary angiography or spiral CT, or confirmed by autopsy.

Sepsis: Systemic inflammatory response syndrome (SIRS) with infection (positive blood culture or

purulent discharge from any site).

Surgical site infection: Characterized by purulent discharge and/or positive microbial culture results.

Bradycardia: Heart rate < 40 beats per minute or a decrease of 30% from the baseline level.

Tachycardia: Heart rate > 100 beats per minute or an increase of 30% from the baseline level.

Hypotension: Systolic blood pressure < 100 mmHg or a decrease of 30% from the baseline level.

Hypertension: Systolic blood pressure > 180 mmHg or an increase of 30% from the baseline level.

Arrhythmia: Including frequent atrial or ventricular premature beats, supraventricular or ventricular tachycardia, new-onset atrial fibrillation, etc., requiring antiarrhythmic treatment.

Hypoxia: SpO2 < 90%.

Coagulation abnormalities: Prothrombin time (PT) prolonged by more than 3 seconds, activated partial thromboplastin time (APTT) prolonged by more than 10 seconds, or thromboelastography (TEG) indicating coagulation mechanism abnormalities.

Other unanticipated adverse events: Any adverse event experienced by the subject was recorded truthfully, regardless of whether it was related to the study.

Informed consent

Name of the research scheme:Transcutaneous auricular vagus nerve stimulation prevents postoperative delirium in elderly patients: a multicenter, randomized controlled trial (VNSTAR)

Applicant: Beijing Tiantan Hospital, Capital Medical University

CRO: None

Version number: V1.4

Version date: 2024–12-01

Informed consent

Dear patients,

We will invite you to participate in a study on the prevention of postoperative delirium in elderly patients via transcutaneous auricular vagus nerve stimulation (taVNS). This study was approved by the Ethics Committee of Beijing Tiantan Hospital, Capital Medical University, and complied with the principles of the Helsinki Declaration and medical ethics. Participation in this study was voluntary.

Please read this article as carefully as possible before you decide whether to participate in this study. Part of the content covered in this article is determined by the requirements of laws and regulations, and to protect the rights and interests of the patients who participated in the study, it was examined and approved by the Ethics Committee of Beijing Tiantan Hospital, Capital Medical University. It can help you understand the content of the study and why it is conducted, the procedure and duration of the study, and the benefits and discomfort that may be brought to you after they participate in the study. If you are inclined to participate in this study, you can also discuss it with your relatives and friends or ask your doctor for an explanation to help you make a decision.

1. Why does it conduct this research?

Postoperative delirium (POD) is the most common and potentially preventable serious complication after surgery. The latest reports indicate that the incidence of POD in patients aged 65 years and above who undergo noncardiac surgery is as high as 25%-50%. POD is associated with prolonged hospitalization, long-term care after discharge, cognitive decline, death, and increased medical expenses in elderly patients. A prospective cohort study in the United States revealed that among patients aged 70 years and above who developed POD after elective surgery, the cost attributed to POD was $44291 per person per year, and this number increased with increasing severity of POD. The main reason for the increase in costs is hospitalization, readmission, and prolonged postoperative recovery. In addition, POD is also associated with dementia in 10% of elderly individuals, and the ongoing medical expenses for dementia patients can double the cost of delirium treatment. Therefore, perioperative prevention of POD has become an important

public health issue. The purpose of this study was to prevent and treat POD to improve patient prognosis.

2. How many people will participate in the study?

Approximately 1776 people will participate in this study.

3. Who was selected for the study?

Individuals can participate in this study if they meet the following conditions: (i) age ≥65 years; (ii) anticipated surgical duration ≥2 hours; (iii) postoperative hospital stay ≥4 days; and (iv) provision of signed informed consent. Whether you can participate in the study needs to be examined by your doctor and finally decided.

4. Who is not suitable to participate in the study?

It is not appropriate for you to participate in this study if you meet any of the following criteria: (i) neurosurgical or cardiac surgery; (ii) severe preoperative cognitive impairment affecting the assessment of perioperative cognitive function; (iii) terminal illness with a life expectancy of less than 3 months; (iv) emergency surgery within 6 hours of hospital admission; or (v) severe sinus bradycardia, second-degree or higher atrioventricular block, or the presence of an implanted cardiac pacemaker. If you have the above situation, the doctor will also let you know.

5. How long will this study last?

This study will last for 3 years. During follow-up, information about the patient's clinical prognosis after treatment was collected. The follow-up period was 3 months after discharge. You can opt out of the study at any time without losing any of the benefits you should have earned, but it is not recommended. If you decide to quit during the study, we suggest that you consult with your doctor first. In view of your security issues, it is possible to conduct a check after exiting.

6. How was the study conducted?

If you would like to participate in this study, your doctor will review your medical history, ask about past and current treatments and medications, and undergo the following tests to further confirm your suitability for participation in this study:

·Physical examination and medical history inquiry

·Important signs (such as breathing, temperature, heartbeat, etc.)

·Cognitive function, delirium, quality of life, physical function, etc.

· Laboratory examination and imaging examination (CT/CTA/MR/MRA)

·Electrocardiogram for recording electrophysiological activity of the heart

After the relevant examinations are completed, it is necessary for clinical doctors and anesthesiologists to conduct a comprehensive safety assessment of the patient's individual situation and agree that the patient can be enrolled before the study can continue. In addition to the evaluation of relevant scales, this study did not include any additional examinations. Preoperative blood tests, imaging examinations, electrocardiograms, etc., are all required for normal medical procedures. The computer randomly groups all patients, and you have a 50% chance of being assigned to the treatment group or the control group. If you enter the treatment group, we treat you with a transauricular vagus nerve stimulator (TVNS-100) with the research parameters. If you enter another group, we will provide you with sham stimulation treatment. Other treatments will follow the standard clinical treatment protocol. Throughout the research process, we will collect your health status through a series of monitoring methods and inspection steps to ensure your safety. However, this approach will also not affect or delay surgical treatment. This study aimed to determine the effect of transauricular vagus nerve stimulation on delirium by comparing the incidence of postoperative delirium between patients who received prophylactic transauricular vagus nerve stimulation and those who did not, providing a theoretical basis for subsequent clinical treatment.

7. What are my obligations to participate in research?

During the study period, you need to do the following things:

1) Have the obligation to truthfully provide medical history and "previous participation in clinical trials";

2) Research requires a mental scale assessment and patience;

3) Communicate truthfully with your doctor about changes in your condition;

4) During the study period, patients did not participate in other relevant clinical studies.

8. What are the costs involved in participating in the research?

The costs of anaesthesia drugs and anaesthesia during surgery are not included in the free range. If you combine the treatment and examination required for other diseases at the same time and switch to other treatments because the treatment is ineffective, those costs are not included in the free range. However, you do not need to pay for the related procedures, consumables, or additional monitoring fees for transauricular vagus nerve stimulation therapy.

9. What are the benefits of participating in the research for my disease treatment?

This study may or may not improve your condition, but the information from this study will help determine whether transauricular vagus nerve stimulation can be safer and more effective in treating other patients with similar conditions.

10. Do I have other treatment options?

In the past 20 to 30 years, through continuous optimization of perioperative anaesthesia management strategies for elderly patients, including preoperative screening for high-risk factors, preoperative education, multimodal analgesia, intraoperative use of dexmedetomidine, and control of anaesthesia depth, the incidence of postoperative delirium in elderly patients has decreased; however, currently, no definite and effective treatment plan has been developed. If you do not participate in this study, we will provide you with appropriate treatment according to the standard perioperative management plan of our medical institution. If you participate in this study, in addition to receiving standard treatment, you will also receive additional transauricular vagus nerve stimulation.

11. What are the possible risks of participating in research?

Invasive vagus nerve stimulation may cause symptoms such as hoarseness and discomfort in the throat, affecting the recurrent laryngeal nerve. A very small number of patients may experience difficulty breathing or suffocation and may also experience bradycardia. The transauricular vagus nerve stimulation device (TVNS-100) used in this study is safer, less expensive, and noninvasive than traditional invasive vagus nerve stimulation. Compared with traditional invasive stimulation, it may also cause the same adverse reactions mentioned above, but with a lower incidence rate. When the stimulation parameters are reduced or the stimulation is stopped, concurrent adverse reactions immediately disappear. Long-term use by a very small number of people may affect heart rhythm, such as slowing the basal heart rate. During treatment, excessive electrical stimulation of the ear may cause pain and tingling related to electrical currents. In this study, we individually tested the maximum tolerable current of the subjects, i.e., the maximum amplitude of painless current, before administering intervention therapy to avoid increasing discomfort related to stimulation therapy. During the research period, you need to receive timely doctor inquiries, undergo some physical and chemical examinations, and conduct questionnaire surveys, which may cause trouble or inconvenience.

If your health has indeed suffered research-related harm due to participation in this study, please notify the study doctor immediately, and they will be responsible

for taking appropriate treatment measures for you. The applicant, Beijing Tiantan Hospital, Capital Medical University, will bear the treatment costs and provide you with corresponding economic compensation in accordance with relevant national regulations.

Even if you have signed this informed consent form, you still retain all your legal rights.

12. Can I voluntarily choose to participate in and withdraw from the study?

Participation in this study was entirely voluntary. You may refuse to participate in this study or withdraw from it at any time during the study. This decision will not affect the doctor's treatment, medical treatment or rights.

Your doctor or investigator may discontinue your continued participation in this study during the course of the study in your best interest.

If you withdraw from this study for any reason, you may also be ordered to undergo laboratory tests and physical examinations, which are beneficial to your health, if they are deemed clinically necessary by your doctor.

13. What happens if there is new information related to the research content?

Occasionally, new information about the research content is available. If there is any new relevant information that may affect your willingness to continue participating in this study, we will promptly notify you and discuss with you whether it is appropriate to continue participating in this study.

14. How will participating in this study affect my life?

One may find follow-up and review visits inconvenient and require special arrangements. Additionally, some tests can make you feel uncomfortable. You can ask your study doctor if you have any questions about the tests and procedures in the study.

You cannot participate in any other clinical studies of drugs or medical devices during the entire study period.

15. Is my personal information confidential?

Your medical records will be kept in the hospital. Investigators, research authority personnel, ethics committees, monitors, and drug regulatory authority inspectors can consult the subjects' original medical records to verify the clinical trial process and data. The abovementioned personnel are responsible for keeping their personal information confidential, and violations are punished for disclosure. Any confidential matters relating to your identification records will not be used publicly. If clinical trial results are released, identifying information will remain

confidential. We will make every effort to protect the privacy of your personal medical information to the extent permitted by law. Your name will not be reflected in any reports.

16. Related consultation

If you have any questions related to this study, please contact Youxuan Wu on landline **010--59976536** or mobile **15596400136**.

If you have any questions related to your own rights or if you would like to report your dissatisfaction and concerns during your participation in this research, please contact the Office of the National Clinical Trials Institute of Beijing Tiantan Hospital, Tel: **010--59975178**, or the Ethics Committee Office of Tiantan Hospital, contact Tel: **010--59975692**. Email: **ttyyirb@163.com.**

Subject Consent Statement

I agree to participate in a clinical study of transauricular vagus nerve stimulation to prevent postoperative delirium in elderly patients: a multicenter, randomized controlled trial (VNSTAR).

Signing here means:

1. I have read this informed consent form and the researcher has explained the study to me.
2. I have discussed and asked relevant questions about this study, and they have been answered to my satisfaction.
3. I understand that I will be able to obtain compensation from the sponsor in the event of research-related damages.
4. I have plenty of time to make a decision.
5. I voluntarily agree to participate in the clinical research presented in this article.
6. I have been informed of the researcher I should consult during the study.

As described in this informed consent form, I consent to hospital supervision, researchers and other relevant personnel having access to my medical and personal information.

Subject's signature：_____ Date：_____

Name in block letters：_____ Contact number：_

Signature of legal representative (if any)：_____Date：_____

The name of the legal representative in block letters：_____

Contact number：_____

Legal representative and patient relationship：_____

Fair Witness Statement：

I was present throughout the informed process, and the contents of the informed consent form and other written materials were accurately explained to the subjects or legal representatives. The subjects or legal representatives fully understood the meaning of the content, and they agreed to participate in the test.

Signature of an impartial witness (if any)：_____Date：_____

The name of the impartial witness in block letters：_____

Contact number：_____

Signature of researcher：_____ Date：_____

Name of researcher in block letters：_____

Contact number：_