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'Transauricular vagus nerve stimulation' for prevention of postoperative delirium in elderly patients undergoing major surgery: a study protocol for a multicentre, participant-blinded and assessor-blinded, randomised, controlled trial

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ABSTRACT

Introduction Postoperative delirium (POD) is a frequent complication in elderly patients undergoing major surgery. Research has shown that neuroinflammation, postoperative pain and autonomic nervous system dysfunction play significant roles in its onset. Vagus nerve stimulation (VNS) has the potential to reduce inflammation, ease postoperative pain and aid in recovery by enhancing acetylcholine release and activating the cholinergic anti-inflammatory pathway. This study aims to assess the effectiveness and safety of transauricular VNS (ta-VNS) in preventing POD in elderly patients undergoing major surgery.

Methods and analysis This multicentre, participant-blinded and assessor-blinded, randomised, parallel-group controlled trial will compare the incidence of POD in elderly patients undergoing major surgery who receive ta-VNS versus sham stimulation. A total of 300 eligible patients will be randomly assigned in a 1:1 ratio to either the active or sham stimulation group. The active stimulation group will receive electrical stimulation to the left cymba conchae at a frequency of 30 Hz and a pulse width of 250 µs, with a 30 s on/30 s off cycle. The intensity will start at 0.4V and be increased in 0.4V increments until a tingling sensation is felt, then adjusted to the highest tolerable level without pain. After obtaining informed consent and randomisation, the initial intervention will begin in the preoperative area and continue throughout the surgery. For the four postoperative days, the intervention will be administered twice daily in 2-hour sessions each morning and afternoon. The sham group will follow the same procedure, with electrodes placed on the left cymba conchae. After adjusting the stimulation intensity, the device will be switched off. The primary outcome is the incidence of POD from postoperative day 0 to day 7 or discharge. Secondary outcomes include the severity of POD, quality of recovery, sleep quality and adverse events.

Ethics and dissemination The protocol was approved by Sir Run Run Shaw Hospital Affiliated to Zhejiang University School of Medicine on 9 January 2024 (Approval number: 20240014), and the trial was registered on the Chinese Clinical Trial Registry on 21 February 2024, prior to recruitment. The study will be performed according to the guidelines of the Declaration of Helsinki. Written informed consent will be obtained from all participants. The results will be submitted for publication in a refereed journal.

Trial registration number ChiCTR2400081078.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The study will offer a low-risk, accessible, non-pharmacologic and titratable autonomic neuromodulation intervention, transauricular vagus nerve stimulation (ta-VNS), to prevent the common complication of postoperative delirium.
⇒ Employing a multicentre, participant-blinded and assessor-blinded, randomised, sham-controlled design minimises bias and improves the reliability and validity of the study results.
⇒ The effectiveness of ta-VNS may be influenced by patient compliance, particularly in elderly patients, where reduced compliance could impact the precision of the study results.

INTRODUCTION

Postoperative delirium (POD) is a prevalent neurological complication in adult patients during the perioperative period, characterised by impaired cognition or altered level of consciousness occurring within 1 week following surgery.[1] In high-risk surgeries like trauma and cardiac procedures, around 40% of patients may develop POD.[2] For those undergoing non-cardiac and non-neurosurgical operations, the incidence

of POD ranges from 5% to 28%.[3–5] Elderly patients are particularly vulnerable to POD due to physiological decline, poor nutritional status, the impact of multiple medications, the stress response and surgical trauma.[5 6] POD is linked to long-term cognitive decline, resulting in significant economic burdens for families and society.[7] Currently, preventive measures and interventions for POD are only moderately effective.[8 9] Therefore, researching safe and effective strategies to reduce the incidence of POD in elderly patients has become a major focus in the medical community, aiming to improve postoperative outcomes.

Previous studies on the mechanisms of POD have shown that neuroinflammation, postoperative pain, sleep disturbances, acute stress responses and autonomic nervous system dysfunction are significant contributors to its development.[10–16] Among these factors, autonomic nervous system dysfunction is often overlooked and is primarily characterised by decreased vagal nerve tone and increased sympathetic activity.[17–20] Importantly, vagal nerve activity is essential for motor function, reducing complications and accelerating recovery.[17–19 21–23] Vagus nerve stimulation (VNS) is a commonly used method for regulating the autonomic nervous system. VNS enhances acetylcholine (ACh) release and activates the cholinergic anti-inflammatory pathway, thereby limiting inflammation.[24–26] Peripherally, VNS has been shown to prompt T lymphocytes in the spleen and enteric cholinergic neurons to release ACh, modulating the inflammatory response.[27–29] Centrally, ACh has been found to mitigate neuroinflammation by binding to α7-nicotinic ACh receptors (α7-nAChR) on microglia and astrocytes.[30–32] The European Union and the US Food and Drug Administration have approved VNS for adjunctive treatment of multiple diseases, including epilepsy,[33 34] depression,[35–38] poststroke limb motor impairments,[39–42] cardiovascular disease,[43 44] cluster headaches and migraines.[39]

Among VNS methods, invasive VNS (i-VNS) is the most used. It involves surgically implanting a stimulator and electrode connected to the vagus nerve. However, i-VNS can lead to various postoperative complications, including hoarseness, cough, pain, deep wound infections, arrhythmias and device malfunction or rupture.[45 46] Anatomical studies have shown that the only accessible branch of the vagus nerve at the body surface is the auricular branch of the vagus nerve (ABVN), which innervates the external ear, including the cymba conchae, tragus and external auditory meatus, with the cymba conchae being fully innervated by the ABVN.[47] Transauricular VNS (ta-VNS) is a newly developed method that addresses the limitations of i-VNS.[48] Previous studies have shown that stimulation of the cymba conchae, which is innervated by the vagus nerve,[49] can achieve effects similar to those of i-VNS.[50] Recent findings have suggested VNS may also be effective for postoperative pain relief,[51–53] sleeplessness,[54] autonomic nervous system dysfunction, [55]cognitive enhancement[18 32 56] and reducing inflammation.[57] However, these conclusions are based on some studies with limited sample sizes. To accurately determine the effectiveness of ta-VNS, especially in preventing POD in elderly patients undergoing major surgery, further large-scale, high-quality clinical trials are required.

Thus, we designed a multicentre, participant-blinded and assessor-blinded, randomised, controlled trial to assess the efficacy and safety of ta-VNS in preventing POD in elderly patients undergoing major surgery. This study hypothesises that ta-VNS treatment will reduce the incidence of POD in elderly patients undergoing major surgery compared with the sham stimulation group.

RESEARCH DESIGN AND METHODS

Participants

This study plans to enrol elderly patients scheduled for major surgery at Sir Run Run Shaw Hospital, affiliated with Zhejiang University School of Medicine (the lead centre) and other participating centres. Each centre will adhere to a standardised protocol to ensure data consistency and reliable results. Recruitment commenced on 29 July 2024 and will continue until 31 December 2025. Figure 1 shows the participant enrolment, randomisation and flow diagram.

Inclusion criteria

1. Age ≥65 years.
2. Scheduled for major surgery under general anaesthesia (eg, radical surgery for upper abdominal malignancies like liver, pancreatic or gastric cancer; hip replacement; oesophageal, cardiac or major vascular surgery).
3. American Society of Anesthesiologists classification of 1–3.
4. Expected surgery duration of more than 2 hours and anticipated hospital stay of more than 3 days.
5. Ability to understand the study procedures and assessment scales and to communicate effectively with the research staff.
6. Willingness to participate in the study and provide informed consent.

Exclusion criteria

1. Presence of visual or auditory impairments.
2. History of substance abuse, including opioids.
3. Inability to cooperate with various assessments.
4. Undergoing a second surgery within 5 days.
5. Vulnerable populations, including individuals with mental illnesses, critically ill patients, minors and pregnant women.

Randomisation and blinding

After obtaining written informed consent, patients will be randomly assigned (1:1) to receive either active or sham stimulation. Randomisation will take place 1 hour before the first intervention and prior to surgery, using a random block size of 4. Participant details, including IDs and relevant documents, will be entered into a centralised randomisation system developed by DAP Software (Beijing),

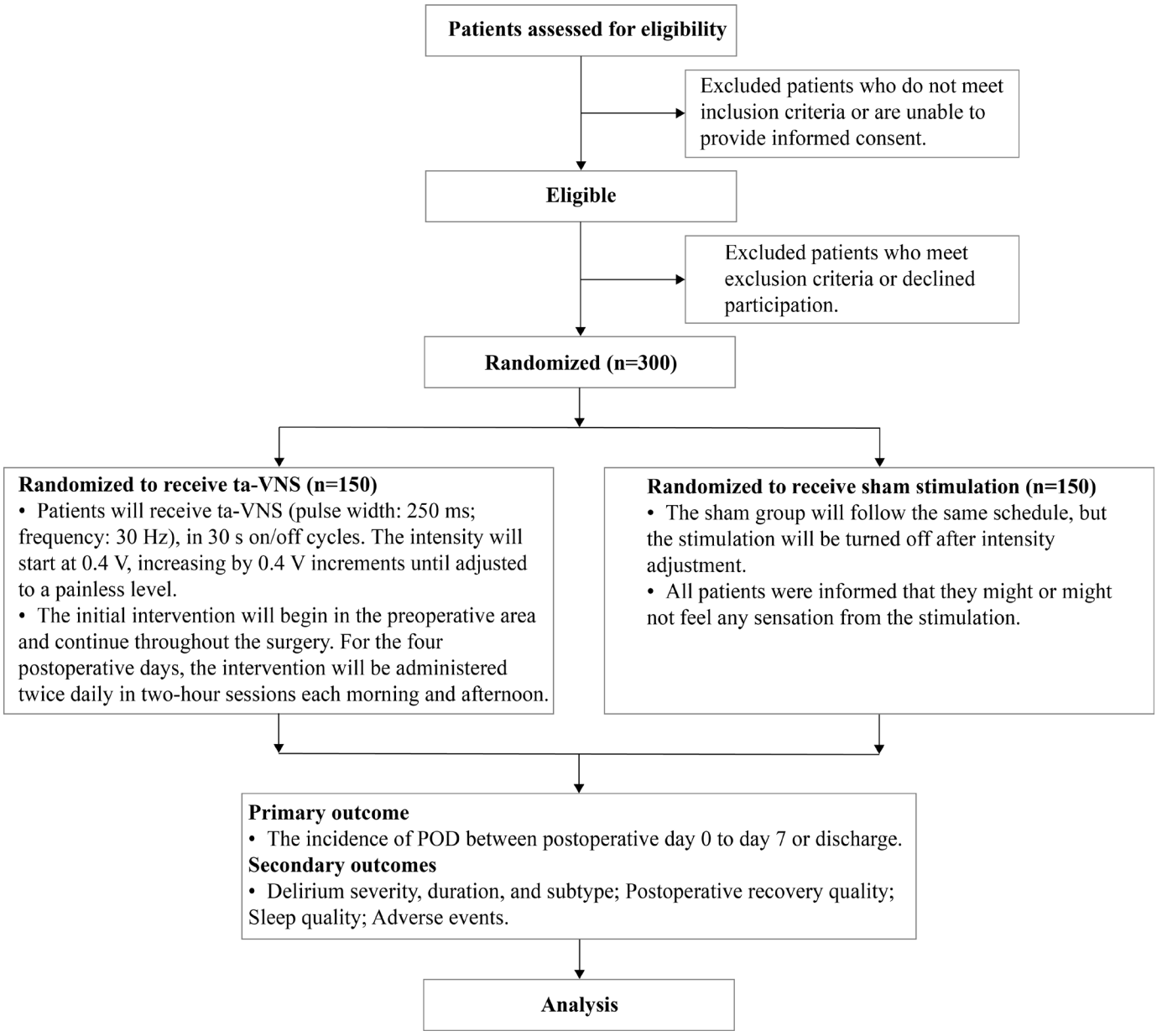

Figure 1 Participant enrolment, randomisation and flow diagram. POD, postoperative delirium; ta-VNS, transauricular vagus nerve stimulation.

which will assign participants to groups based on a predetermined randomisation method. Each participant will receive a random number corresponding to their assigned intervention.

This study will employ a participant-blinded and assessor-blinded design. Only the persons overseeing random assignment and the intervention provider will know the treatment allocations. Throughout data collection and analysis, participants, follow-up staff and data analysts will remain unaware of the treatment assignments. The success of participant blinding was evaluated using the Bang Blinding Index, with values between −0.2 and 0.2 indicating adequate blinding integrity.[58]

Intervention

The stimulation group will receive transcutaneous electrical stimulation on the left cymba conchae (pulse width: 250 ms; frequency: 30 Hz) in 30 s on/off cycles. The intensity will start at 0.4 V and be increased in 0.4 V increments until the patient feels a sensation of pain, then adjusted to a tolerable, painless level. The first intervention will begin when the patient arrives in the preoperative area on the day of surgery and will continue until the surgery is completed. Following surgery, the intervention will be administered twice daily for 2 hours each session, in the morning and afternoon, for an additional 4 days. The sham group will follow the same schedule, but the stimulation will be turned off after the intensity adjustment.[44 50 59] All patients will be informed that they might or might not feel any sensation from the stimulation.

The auricular vagus nerve stimulator (tVNS501) is used as an adjunctive therapy for sleep disorders, fatigue, reduced appetite and anxiety symptoms, and to

support diabetes treatment. In this study, tVNS501 will be employed to prevent POD in elderly patients undergoing elective major surgery.

All patients will follow a standardised anaesthesia protocol. Preoxygenation will be administered at 6 L/min for 3 min before induction, which includes propofol 1–2 mg/kg, sufentanil 0.5 µg/kg and rocuronium 0.6–0.8 mg/kg. Endotracheal intubation will be performed after 3–5 min of mask-assisted ventilation using a visual laryngoscope. Mechanical ventilation will be set with a tidal volume of 6–8 mL/kg, a respiratory rate of 12–16 breaths per minute, an inspiratory-to-expiratory ratio of 1:1.5–2, FiO2 of 50%, a flow rate of 2 L/min and PEEP of 5 cmH_2O. Maintenance anaesthesia will include sevoflurane 1%–2%, propofol 2–4 µg/kg/hour, remifentanil 0.5–1 µg/kg/min and intermittent rocuronium 0.2–0.3 mg/kg. Blood pressure and heart rate will be maintained within 20% of baseline values, with phenylephrine 6 mg and urapidil 5–15 mg administered as needed. Ventilation parameters will aim to maintain $PetCO_2$ at 35–45 mm Hg, and entropy values will be kept between 40 and 60. After surgery, patients will be transferred to the PACU or intensive care unit (ICU) for further monitoring.

Primary outcome

Incidence of pod

The primary outcome is the incidence of POD from postoperative day 0 to day 7 or discharge. Delirium assessments will follow the evaluation of the patient's agitation or sedation level using the Richmond Agitation-Sedation Scale. Delirium will then be assessed using the Confusion Assessment Method (CAM) or the CAM for ICU patients (CAM-ICU).[5 60] Follow-up assessments will be conducted twice daily for seven postoperative days, from 8:00 to 9:00 and 16:00 to 17:00, continuing until discharge or death.

Secondary outcomes

Delirium severity, duration and subtype

Patients with delirium will be assessed using the Delirium Rating Scale-Revised-98 to evaluate the severity, duration and subtype of the condition.[60]

Preoperative cognitive function

The Mini-Mental State Examination was used to assess preoperative cognitive function, with a total score of 30 points. The score ranges are as follows: 0–10 points indicate severe cognitive impairment, 11–20 points indicate moderate cognitive impairment, 21–25 points indicate mild cognitive impairment and 26–30 points indicate normal cognition.

Postoperative recovery quality

The Quality of Recovery-15 (QOR-15) scale will assess postoperative recovery over seven consecutive days.[61] It consists of 15 items evaluating comfort, emotional state, self-care ability, psychological support and pain. Scores are categorised as follows: 0–30 (very poor recovery), 31–45 (poor recovery), 46–60 (fair recovery), 61–75 (good recovery) and 76–90 (excellent recovery).

Sleep quality

The Richards-Campbell Sleep Questionnaire will be used to assess nighttime sleep at preoperative and postoperative time points during the seven consecutive days after surgery.[62] It evaluates sleep depth, difficulty falling asleep, number of awakenings, trouble returning to sleep and overall sleep quality. Scores are classified as follows: 0–25 (very poor sleep), 26–50 (poor sleep), 51–75 (good sleep) and 76–99 (very good sleep).

Serum creatinine

Serum creatinine levels will be assessed at four predefined time intervals: preoperatively (baseline), followed by daily measurements on postoperative days 1, 2 and 3.

Inflammatory markers

Routine inflammatory markers, including white cell count and CRP, will be measured presurgery and on postsurgery days 1 and 3 in both groups to identify mechanisms through which ta-VNS may exert its effects.

Adverse events

The occurrence of adverse events related to ta-VNS will be recorded. Ta-VNS is a non-invasive, low-risk VNS technique. Common adverse events may include nausea, vomiting, discomfort in the auricular region, influenza-like symptoms and skin irritation.

Data management

Participants' demographic data, clinical laboratory results, disease history, surgical characteristics, primary and secondary outcomes, and event data will be collected and stored in an electronic case report form using a secure electronic data capture (EDC) system developed by DAP Software (Beijing). Training for all users, including data entry personnel, investigators and monitors, will ensure accurate and consistent data entry. The EDC system incorporates security measures such as encryption, secure login, and audit trails to protect data integrity and confidentiality. Access to the system is restricted to authorised users. Data management computers are password-protected, and physical documents are stored securely. Participant identity information will remain confidential and will only be disclosed in accordance with applicable laws and regulations.

The original data are scheduled for release in December 2028 on the ResMan data-sharing platform (IPD-sharing platform) of the China Clinical Trial Registry, which can be accessed via the following website: http://www.medresman.org.cn.

Sample size estimation

The sample size calculation is based on a published study that reports a 20% incidence of POD. We deemed a 10% absolute reduction (corresponding to a number needed to treat of ten patients) due to ta-VNS to be a realistic

estimate.[63] A significance level of α=0.05 and a power of (1–β) = 0.8 for a two-sided test were used, with calculations performed using G*Power software (V.3.1.9.7). To account for an estimated dropout rate of around 10%, the study will include a total of 300 patients, with 150 patients assigned to each group.

Patient and public involvement

None.

Ethics and dissemination

The protocol was approved by Sir Run Run Shaw Hospital Affiliated to Zhejiang University School of Medicine on 9 January 2024 (Approval number: 20240014). The study will be performed according to the guidelines of the Declaration of Helsinki. Written informed consent will be obtained from all participants. The results will be submitted for publication in a refereed journal. This trial was registered at the China Clinical Trial Registration Centre (Registration number: ChiCTR2400081078) on 21 February 2024.

Statistical analysis

All statistical analyses will be performed with IBM SPSS Statistics V.22. Continuous variables will first be assessed for normality. For normally distributed data, results will be presented as mean (SD) and analysed using the t-test. Data that do not follow a normal distribution will be summarised as median (25th–75th percentile) and compared using the Mann-Whitney U test. Categorical variables will be reported as frequencies (n) and percentages (%) and examined with the χ^2 test or Fisher's exact test. A p value of less than 0.05 will be deemed statistically significant.

In this study, we will first conduct a per-protocol (PP) analysis, which will include only those patients who have completed the full 5-day stimulation according to the protocol. This analysis will help us assess the efficacy of the intervention under ideal conditions of full adherence. Given the need for a continuous 5-day intervention and the potential for non-adherence, we will also conduct an intention-to-treat (ITT) analysis, including all randomised patients, regardless of their adherence to the intervention. The ITT analysis will provide a more comprehensive and generalisable estimate of the intervention's effectiveness, reflecting real-world scenarios of non-adherence.

DISCUSSION

The study is a multicentre, large-scale, participant-blinded and assessor-blinded, randomised, sham-controlled trial to evaluate the efficacy and safety of ta-VNS in preventing POD in elderly patients undergoing major surgery.

In our study, the primary outcome is the incidence of POD from postoperative day 0 to day 7 or until discharge, as well as the effects of ta-VNS on the severity, duration and subtype of delirium.[64] By assessing these factors, we aim to gain a comprehensive understanding of how ta-VNS affects different aspects of POD, revealing its overall effectiveness and impact on various dimensions of the condition.

Multiple studies have shown that high autonomic vagal tone can improve exercise capacity, prevent myocardial injury, reduce postoperative complications, alleviate postoperative pain and accelerate recovery.[17–19 21–23] Therefore, to further investigate whether ta-VNS can enhance postoperative recovery, we will also evaluate the QOR, sleep quality and postoperative complications in patients.

This trial has potential limitations. Research on ta-VNS for perioperative conditions is limited, and the optimal stimulation parameters for preventing POD remain unclear. We considered factors such as postoperative inflammation, pain peaks, POD onset time, treatment efficacy, patient adherence and safety to determine the stimulation protocol described earlier. Another limitation of this study is that the extended stimulation duration may affect patient adherence, potentially leading to incomplete treatment sessions. To address this issue, we will use both ITT and PP analyses.

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Competing interests None declared.

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