BMJ Open

Effects of transcutaneous auricular vagus nerve stimulation on postoperative delirium in older patients with hip fracture: protocol for a randomised controlled trial

Hongyan Zhou , Ailin Song , Hui Zhang , Liang Zhang

To cite: Zhou H, Song A, Zhang H, *et al*. Effects of transcutaneous auricular vagus nerve stimulation on postoperative delirium in older patients with hip fracture: protocol for a randomised controlled trial. *BMJ Open* 2025;**15**:e092413. doi:10.1136/bmjopen-2024-092413

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2024-092413).

HZ and AS contributed equally.

Received 13 August 2024
Accepted 30 January 2025

Department of Anesthesiology, Chongqing Traditional Chinese Medicine Hospital, Chongqing, China

Correspondence to
Dr Liang Zhang;
seamanzl@126.com

ABSTRACT

Background Postoperative delirium (POD) is an acute neurocognitive impairment and is commonly observed in older patients with hip fractures. POD is associated with poor outcomes, including increased postoperative complications, prolonged hospitalisation, high costs and increased perioperative mortality. Therefore, reducing the occurrence of POD and improving cognitive abilities in older patients are critical and urgent. Transcutaneous auricular vagus nerve stimulation (TAVNS) is a simple, safe, non-invasive treatment and has great potential to improve cognitive function. This clinical study will evaluate the effectiveness of TAVNS in reducing the incidence of POD in older patients and further elucidate the possible underlying mechanisms.

Methods and analysis This randomised, double-blind, single-centre controlled trial will enroll 154 older patients undergoing hip fracture surgery, who will be randomly assigned to the TAVNS group (n=77), receiving TAVNS from 1 hour before anaesthetic induction to the end of the surgery, or the sham stimulation group (n=77), receiving sham stimulation in the same manner. The primary outcome measure will be the incidence of POD during the first 7 days post-surgery, as assessed by the confusion assessment method for the intensive care unit. The secondary outcomes include the incidence of delayed neurocognitive recovery; serum acetylcholinesterase and butyrylcholinesterase levels; the concentrations of tumour necrosis factor-α, interleukin-1β, interleukin-6 and S100β; unplanned intensive care unit admission rates; the length and cost of hospital stay; the incidence of postoperative complications during hospitalisation; and mortality at 1 month, 6 months and 1 year after surgery.

Ethics and dissemination This study was approved by the Ethics Committee of the Chongqing Traditional Chinese Medicine Hospital on 15 May 2024 (2024-KY-HY-13). The findings will be published in the international peer-reviewed academic journals and presented orally at academic conferences.

Trial registration number ChiCTR2400085508.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is a randomised controlled study to observe the effect of perioperative transcutaneous auricular vagus nerve stimulation (TAVNS) on postoperative delirium (POD).
⇒ Our team members have been engaged in postoperative cognitive impairment research for a long time and have received professional training to make accurate judgments of POD.
⇒ Diverse outcomes have been integrated to explore the effects and possible mechanisms of TAVNS on POD.
⇒ This is a single-centre study, which limits the generalisability of the results.
⇒ Due to the patient's delirium possibly appearing outside the follow-up period, the observation of POD may have missed diagnoses.

INTRODUCTION

Postoperative delirium (POD) is an acute brain dysfunction characterised by fluctuating changes in attention, consciousness and cognitive function after surgery.[1 2] POD is a type of perioperative neurocognitive disorder (PND) that usually occurs 2 to 5 days after surgery and is strongly associated with poor outcomes, including increased postoperative complications, prolonged hospitalisation, high costs and increased perioperative mortality.[3 4] POD is commonly observed in older patients following surgery, with an incidence rate of up to 65%.[5 6] As surgical advances and population ageing continue, POD is expected to become a public health concern, with its incidence increasing, leading to greater morbidity and mortality. Given the limited effectiveness of treatments for delirium, preventive strategies are critically important.

At present, the pathophysiology of POD is not fully understood and is thought to involve neuroinflammation, oxidative stress, mitochondrial dysfunction, autophagy disorders, impaired synaptic function and damage to the

blood–brain barrier (BBB).[7] Recent scientific evidence has highlighted the crucial role of neuroinflammation in the development of POD, which has become a mainstream hypothesis in recent years.[8] Surgical injury triggers toll-like receptors via damage-associated molecular patterns, initiating intracellular inflammatory responses. Pro-inflammatory factors, such as tumour necrosis factor-α (TNF-α), interleukin-1β (IL-1β) and interleukin-6 (IL-6), increase, leading to the loss of structural and functional integrity of the BBB. These factors then cross the BBB, causing neurotoxicity and neuronal apoptosis, ultimately leading to brain dysfunction.[9] Therefore, inhibiting neuroinflammatory pathways may be an effective strategy for preventing POD.[10]

Transcutaneous auricular vagus nerve stimulation (TAVNS), an emerging neuromodulation therapy, can effectively promote the coordination of various physiological functions by stimulating the auricular branches of the vagus nerve (ABVN) in a non-invasive manner.[11–15] The neurophysiological mechanism is similar to that of invasive stimulation: afferent fibres from the ABVN pass through the jugular ganglion, enter the vagus trunk and project to the nucleus of the solitary tract, where central integration of autonomic neurons occurs. This integration activates the ventral lateral medulla and dorsal motor nucleus, regulating central autonomic nervous activity.[16] TAVNS has been successfully used on patients with epilepsy and depression, effectively reducing the frequency of seizures and decreasing the severity of depression.[17 18] It has also been used in patients with consciousness disorders, facilitating consciousness recovery in severely brain-injured individuals, which suggests its great potential for improving cognitive impairment.[19 20] Recent studies have shown that TAVNS not only decreases cholinesterase activity and inflammatory responses induced by surgery but also prevents postoperative cognitive impairment in aged rats by inhibiting neuroinflammation.[9 21 22] Zhou *et al* demonstrated that TAVNS can decrease the occurrence of delayed neurocognitive recovery (dNCR) in older patients following total joint arthroplasty, potentially through the inhibition of inflammatory cytokine production.[23] As dNCR and POD are part of the PND spectrum and share similar neuroinflammatory mechanisms, TAVNS may also reduce the occurrence of POD in older patients by inhibiting neuroinflammation, thereby reducing postoperative complications and mortality. This study aims to confirm these findings.

METHODS

Design

This prospective, randomised controlled trial will be conducted at Chongqing Traditional Chinese Medicine Hospital. The Ethics Committee of Chongqing Traditional Chinese Medicine Hospital has approved the protocol on 15 May 2024 (2024-KY-HY-13). This study has been registered in the Chinese Clinical Trial Registry on 12 June 2024 (identification number: ChiCTR2400085508). 154 recruited patients will be randomly assigned to the experimental group (TAVNS) or the control group (sham stimulation) at a 1:1 ratio. Table 1 summarises the timeline of the study, and figure 1 shows the study flow chart. This protocol follows the recommendations of interventional trial guidelines.[24] The Standard Protocol Items: Recommendations for Interventional Trials Checklist is provided in online supplemental file 1.

Patient and public involvement

There will be no patient or public involvement in designing, conducting, reporting or disseminating plans for the research.

Participants

We will consecutively recruit older patients with brittle hip fractures (femoral neck, femoral head, intertrochanteric or subtrochanteric) who are scheduled for elective surgery. The main inclusion criteria are 65 years of age or older and an American Society of Anesthesiologists Physical Status (ASA PS) of I to IV.

Patients who meet any of the following criteria will be excluded: (1) patients with chronic fractures, multiple trauma or fractures; (2) patients with serious primary or secondary diseases, such as severe diseases of the liver, kidneys or haematopoietic system, severe cardiopulmonary insufficiency or infectious diseases (refers to conditions with considerable surgical risks that lead to the delay or even suspension of surgery, such as Child–Pugh Grade C, end-stage renal disease with electrolyte abnormalities, severe coagulation abnormalities and severe respiratory failure requiring supportive treatment); (3) patients who have a clear history of neurological or psychiatric disorders or the use of corresponding medications; (4) patients addicted to drugs, alcohol or other substances; (5) recent use of cholinergic drugs, anticholinergic drugs or hormones; (6) patients suffering from inflammation and taking anti-inflammatory drugs; (7) the presence of local skin rash, infection, skin lesions, ulcers or scars in the ear concha region; (8) bradycardia (heart rate of <60 beats/min, based on the results of the preoperative ECG); (9) patients with a history of implantable stimulators (such as pacemakers, implantable vagus nerve stimulators, deep brain stimulators and spinal cord electrical stimulators), cochlear implants or metal implants in the body (except dental work); (10) communication issues, such as severe hearing or visual impairment; and (11) patients who refuse to participate or are involved in another randomised clinical trial.

The withdrawal criteria are as follows: (1) the patient requests withdrawal, (2) loss to follow-up and (3) the investigator orders the patient to withdraw (poor compliance, serious complications or adverse events).

Patient recruitment and baseline data collection

Patients will be enrolled from 15 June 2024 to 14 May 2026, and eligible patients will be screened by the investigators before surgery. The objectives, methodology and

Table 1 Summary of enrolment, intervention and assessment timelines

	Study period						
	Screening	Allocation	Intervention			Follow-up	
TIMEPOINT	1 day before surgery	Day of surgery	T1	T2	T3	T4	T5
ENROLMENT							
Eligibility screen	×						
Informed consent	×						
Randomisation		×					
INTERVENTIONS							
TAVNS			⟷	⟷	⟷		
Sham			⟷	⟷	⟷		
ASSESSMENTS							
Baseline variables	×	×					
Blood samples	×					×	
MMSE	×						×
CAM-ICU	×					⟷	⟷
Haemodynamic parameters			⟷	⟷	⟷	⟷	⟷
Adverse events			⟷	⟷	⟷	⟷	⟷

Table 1. Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) figure. T1: 1 hour before anesthetic induction; T2: anesthetic induction; T3: surgery end; T4: 1 day after surgery; T5: 7 day after surgery
CAM-ICU, confusion assessment method for the intensive care unit; MMSE, mini-mental state examination; TAVNS, transcutaneous auricular vagus nerve stimulation.

potential risks and benefits of the study will be explained to the patients and their families. Informed consent will be obtained from all participants (online supplemental file 2), and they will be informed of their right to withdraw from the study at any time.

After obtaining written informed consent from the patients, we will collect the following baseline data: demographic data, previous history and comorbidities, medication use, ASA PS, cardiac function classification, main results of physical and laboratory examinations, anaesthesia and surgical information, vital signs and vasoactive drug use.

Randomisation, grouping and blinding

Using SAS v9.4 software, a statistical staff member will generate random numbers (block size of four, intergroup ratio 1:1), which will be sealed in an opaque envelope. The envelope will be opened by an assistant who is not involved in patient recruitment, anaesthesia management or delirium assessment according to the order of the random numbers and then provide the intervention accordingly 1 hour before anaesthetic induction. The surgeons, anaesthesiologists, follow-up staff, statisticians and patients will be blinded to group allocation during the study period.

TAVNS and sham stimulation will be administered to the left ear using a commercial transcutaneous electrical nerve stimulation unit (tVNS501, RISHENA) (figure 2A), and the ear electrode will be placed on the left cymba conchae (where the vagus nerve projection density is highest at 100%) (figure 2B). The stimulation parameters will be set with a frequency of 10 Hz, a pulse width of 300 µs and the electrical stimulation amplitude will be gradually increased from zero until the participant experiences a 'tingling' sensation, at which point the current will either be reduced to a level slightly below this threshold (TAVNS) or the stimulation will be stopped (sham stimulation). The stimulus settings will be adjusted by an independent researcher, and after adjusting the stimulus parameters, the screen will be turned off, and these parameters will be hidden. Stimulation will begin 1 hour before anaesthesia induction, continue during the operation and end at the end of the operation. The participants and intraoperative researchers will not be able to view the device settings. For blinding purposes, all patients will be informed that they might or might not feel anything from the stimulus.

Anaesthesia and perioperative management

Anticholinesterase drugs (such as penehyclidine or scopolamine), hormones and nonsteroidal anti-inflammatory drugs are prohibited before the operation. Intraoperative monitoring includes blood pressure, pulse oxygen saturation, electrocardiography, bispectral index (BIS), nasopharyngeal temperature and end-tidal CO_2. All patients will undergo a block of the affected iliac fascia

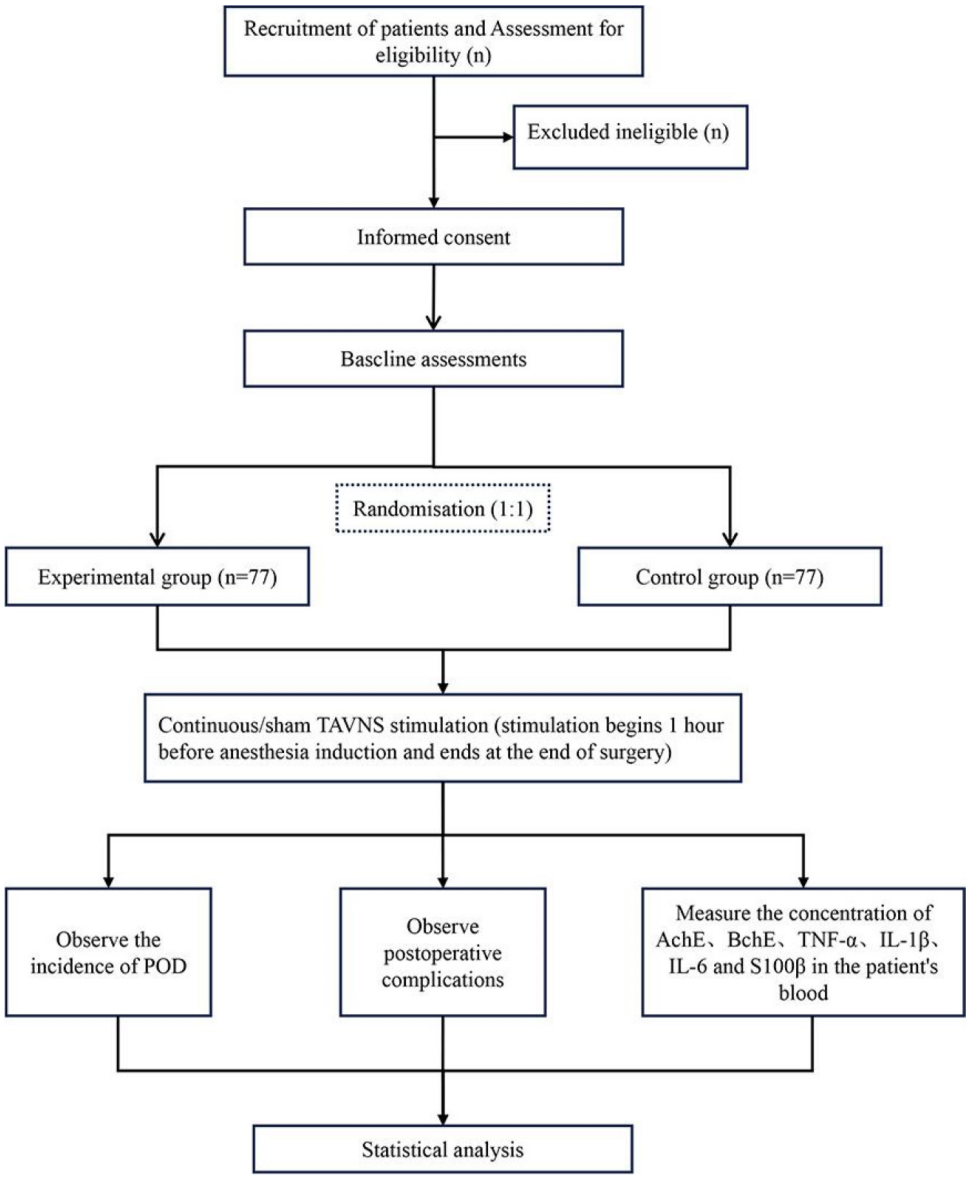

Figure 1 The flowchart of this study. TAVNS, transcutaneous auricular vagus nerve stimulation; POD, postoperative delirium; AchE, acetylcholinesterase; BchE, butyrylcholinesterase; TNF-α, tumour necrosis factor-α; IL-1β, interleukin-1β; IL-6, interleukin-6.

A B

Figure 2 (A) Stimulation device (tVNS501, RISHENA). (B) Stimulation location of transcutaneous auricular vagus nerve stimulation.

before anaesthesia induction using 0.375% ropivacaine (30 mL). Anaesthesia will be induced intravenously using sufentanil, etomidate and cisatracurium, followed by tracheal intubation. Anaesthesia will be maintained with an intravenous infusion of propofol and remifentanil and by inhalation of sevoflurane. The depth of anaesthesia will be controlled by maintaining the BIS between 40 and 60. Intraoperative nasopharyngeal temperature will be maintained at 36–37°C.

Mechanical ventilation parameters will be set as a tidal volume of 8 to 10 mL/kg, a respiratory rate of 12 to 14/min and end-tidal carbon dioxide pressure maintained between 35 and 45 mmHg. An air and oxygen mixture will be inhaled, with an initial concentration (FiO_2) of 50%, and blood oxygen saturation (SpO_2) will be maintained at ≥95%. In principle, FiO_2 should not exceed 50%. However, if SpO_2 remains continuously low and

does not respond to positive end-expiratory pressure treatment, FiO_2 can be increased. During the operation, Ringer's sodium lactate fluid will be routinely transfused, and artificial colloids, concentrated red blood cells and blood products will be transfused when necessary.

At the end of the operation, all participants will receive a patient-controlled intravenous analgesia pump, which contains 100 µg of sufentanil in 100 mL of isotonic sodium chloride solution. The background infusion rate will be 2 mL/h, with an additional 2 mL bolus administered with a lockout interval of 10 min. The actual analgesic drug dose will be adjusted according to the patient's analgesic needs.

Follow-up

After surgery, all participants will be followed until discharge, mainly to observe the incidence of perioperative complications. After discharge, all participants can return to their original lifestyle. We will follow-up 30 days, half a year and 1 year after surgery by telephone. All outcome evaluations and postoperative follow-ups will be conducted by an investigator who is unaware of the study protocol and subgroups and who has received relevant training before the study.

Outcome assessment

All outcomes will be measured at baseline (1 day before surgery) and subsequent assessment points through on-site evaluations or telephone follow-ups.

Primary outcome

The primary outcome will be the incidence of delirium during the first 7 days after hip fracture surgery. Delirium will be assessed using the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU), whether the patients are in the ICU or the general ward, which is a standardised tool for assessing delirium, based on the Richmond Agitation-Sedation Scale to assess the sedation of the patient, and has four features: (1) acute onset of changes or fluctuations during mental status, (2) inattention, (3) disorganised thinking and (4) altered level of consciousness. If the patient exhibits features one and two, plus either feature three or four, they will be diagnosed with delirium.[25]

Delirium assessment will be performed twice daily (8:00–10:00 AM and 18:00–20:00 PM) for 7 days after surgery, recording the subtype, duration and medication of delirium in detail. The occurrence of delirium during hospitalisation will be considered for patients discharged or deceased within 7 days of surgery.

Secondary outcomes

The secondary outcomes will include the incidence of dNCR, serum acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) levels, concentrations of TNF-α, IL-1β, IL-6 and S100β, unplanned ICU admission rate, length and cost of hospital stay, incidence of postoperative complications during hospitalisation and mortality at 1 month, 6 months and 1 year after surgery. The Mini-Mental State Examination will be used to measure dNCR. A baseline assessment will be performed 1 day before surgery, and a follow-up assessment will be performed on the seventh day after surgery.

Venous blood samples will be collected before surgery and on the first day after surgery to measure inflammatory indicators and their rates of change in both groups. The whole blood sample will be centrifuged for 15 min at 3000 g, after which the supernatant serum will be transferred to individual, clean tubes and stored frozen at −80°C. AChE and BChE activities will be assayed using commercial enzyme immunoassay kits. The concentrations of TNF-α, IL-1β, IL-6 and S100β will be quantified using ELISA kits.

Safety management

Any unexpected adverse medical event associated with the medical measures used in this study will be considered an adverse event. All adverse events must be reported separately, with detailed records of occurrence, treatment and outcome, and patients will be followed up until complete resolution or the end of treatment. Serious adverse events will be reported immediately to the Ethics Committee directly. Clinical studies have confirmed that TAVNS is well tolerated and compliant, and most patients complete the intervention without significant adverse events.[26–28] The main adverse events associated with TAVNS are generally mild and transient, including transient dizziness, headache and skin irritation and itching; serious adverse events related to TAVNS are rare.[26–28] The other adverse events are as follows:

(1) POD

Discontinue drugs that may cause delirium and correct the internal environment, including water and electrolyte balance. Pharmacological interventions will mainly involve the administration of dexmedetomidine and/or haloperidol to control the condition. If the patient experiences recurrent delirium, we will consult a psychiatrist for treatment.

(2) Tachycardia or bradycardia

A heart rate of >100 beats/min indicates tachycardia, and <45 beats/min indicates bradycardia. In this case, especially with bradycardia, the management includes suspending the surgical operation and adjusting the dose of vasoactive drugs or the rate of infusion.

(3) Hypotension or hypertension

Hypotension is defined as a systolic blood pressure of <80 mmHg or a decrease of >30% from the preoperative value. Hypertension is defined as systolic blood pressure of >160 mmHg or an increase of >30% from the baseline value. Management will include adjusting the depth of anaesthesia, infusion speed and intravenous infusion of vasoactive agents.

(4) Arrhythmia

This includes new-onset atrial fibrillation, frequent premature ventricular beats and ventricular or supraventricular tachycardia. Management will include suspension of the operation, administration of antiarrhythmic drugs and electrocardioversion.

Data management and monitoring

Data will be collected and entered in a case report form by two investigators who are not involved in the study assignment, treatment or evaluation. Another two investigators will be responsible for checking the data. All participants' data will be encoded and protected.

Statistical analysis

Sample size calculation

According to a previous study, the incidence of delirium in patients after hip fracture surgery is approximately 35%.[29] We hypothesised that the incidence of POD would decrease by 15% after TAVNS. PASS v2021 software will be used for a bilateral test, with a significance level of 0.05 and a power of 0.9. The minimum sample size required will be 70 individuals per group. Considering a 10% loss rate, a total of 154 cases are required.

Outcomes analysis

SPSS software (version 23.0) will be used to analyse the data. Normally distributed continuous variables will be presented as the mean±SD and analysed using one-way analysis of variance, with the least significant difference method used for multiple comparisons between groups. Non-normally distributed data will be presented as the median and IQR and compared using the Mann–Whitney U test. Categorical variables will be presented as percentages and compared using Pearson's X2 test. Two-sided tests with $p<0.05$ will be considered significant.

DISCUSSION

This is the first single-centre, prospective, double-blind, randomised controlled trial to investigate the effectiveness of reducing the incidence of POD in older patients undergoing hip fracture surgery. In addition, serum AChE and BChE levels, along with inflammatory indicators TNF-α, IL-1β, IL-6 and S100β, will be measured to help explain the underlying mechanisms by which TAVNS reduces POD. The results of this study may advance novel, safe and effective POD prevention strategies with few adverse effects.

Numerous risk factors are closely associated with POD, including age, health status, long operative time, perioperative pain and infection. Among these, advanced age is an independent risk factor.[30 31] This may be because the risk of cerebral embolism gradually increases with age, while cholinergic reserves decrease.[32–34] The risk of POD after hip fracture surgery ranges from 4.7% to 70%, and the risk increases with age.[32–35] Therefore, we selected older patients (≥65 years old) who underwent hip fracture surgery as the participants of the current study. In addition, our hospital specialises in treating older patients with orthopaedic issues, and the surgeons and anaesthetists have extensive experience in the perioperative management of patients undergoing hip fracture surgery.

The sample size is an approximate value that varies depending on the results of references and calculation methods. Because preoperative dementia and delirium were not used as exclusion criteria in this study, we chose the closest study for reference, reported by Mosk *et al*, where the incidence of POD was approximately 35% in older patients with hip fractures.[29] The incidence of POD after TAVNS can only be estimated because there are no previous reports of TAVNS intervention for POD. Given the close relation between dNCR and POD, we referred to the literature on the treatment of dNCR using TAVNS. According to the literature, after TAVNS treatment, the incidence of dNCR in the experimental group was reduced by 63% ((27.1–10%)/27.1%) compared with that in the control group.[23] Therefore, we expect that after TAVNS intervention, the incidence of POD will be reduced to 13% (35%× (1–63%)). Considering that the ratio of the incidence of dNCR and POD in the same study was approximately 14:12,[36] this study has set the incidence of POD after TAVNS intervention to 15%, allowing for a more accurate sample size calculation.

TAVNS is an emerging, non-invasive adjuvant therapy that modulates brain physiology through electrical stimulation of the ABVN.[11–15] Since it is traditionally believed that the vagus nerve efferent fibres leading to the heart are usually located on the right side,[37] our study placed the ear electrode on the left ear. The intensity and timing of TAVNS stimulation vary from study to study, and different pulse widths activate different types of nerve fibres. The stimulation parameters will be set with a frequency of 10 Hz, a pulse width of 300 µs and stimulation started 1 hour before anaesthetic induction and continued until the end of surgery. These settings were based on a published study showing that TAVNS can decrease the incidence of dNCR in older patients.[23] Although no optimal parameters have been identified, current research has shown that it is relatively safe when the stimulation frequency is within the range of 0.5 to 120 Hz and the pulse width is within 0.02–1 ms.[38]

The effects of TAVNS on POD and its related mechanisms have not yet been fully explored. Studies have shown that TAVNS can treat patients with mild cognitive impairment or consciousness disorders by stimulating the ABVN and activating the cholinergic anti-inflammatory pathway.[21] Recent data have also demonstrated that TAVNS can reduce cholinesterase activity and acute inflammatory responses induced by surgery.[22] Animal studies have shown that TAVNS can inhibit neuroinflammation and relieve postoperative memory impairment in aged rats.[9] Therefore, this study measured inflammatory factors in the blood of patients 1 day before and 1 day after surgery. Zhou *et al* pointed out that the mechanism of TAVNS reducing the incidence of dNCR in patients is

not only to reduce inflammatory factors, such as TNF-α, IL-1β and IL-6, in the blood of patients but also to lower levels of AChE and BChE.[23] Since dNCR and POD belong to the PND group and may share the same central inflammatory mechanism, TAVNS is highly likely to reduce the occurrence of POD in older patients by inhibiting inflammatory factors. Therefore, while exploring the inflammatory mechanism, we also examined cholinesterase levels to further investigate the mechanism of TAVNS.

Currently, the most used assessment scales for delirium are the CAM-ICU and the CAM. For patients in the ICU, CAM-ICU is preferred. For patients in the general ward, CAM is generally chosen, but CAM-ICU may also be chosen in studies focusing on the occurrence of POD and not the severity of delirium because the criteria for defining the occurrence of POD are consistent between the CAM-ICU and CAM.[25 39 40] As the primary outcome of this study will be the occurrence of POD rather than the severity of delirium, and the patients may go to the general ward or to the ICU after surgery, we uniformly use the CAM-ICU to assess delirium, which is also consistent with our previous studies.[41]

In conclusion, this study explores whether intraoperative TAVNS can reduce the incidence of POD and postoperative complications in patients while elucidating the possible mechanisms involved. We hope to identify a new method for POD prevention and treatment, thereby promoting perioperative rehabilitation in patients.

Limitations

This study has several limitations. First, this is a single-centre study, which limits the generalisability of the results. Second, the observation of POD can be misdiagnosed for two reasons: the patient's delirium may have appeared outside the period of our follow-up or the patient was discharged early, resulting in the evaluation of delirium lasting less than 7 days. Third, the incidence of delirium is used as the primary outcome in this study, and the CAM-ICU is used as the assessment scale; however, it may not evaluate the severity of delirium or facilitate further comparisons.

Trial status

This trial has been registered since 12 June 2024 and was approved by the Ethics Committee of the Chongqing Traditional Chinese Medicine Hospital on 15 May 2024. The trial began on 15 June 2024, and its completion is expected by the end of 14 May 2026.

Contributors Contributors: HZ designed and wrote the study protocol. AS contributed to drafting the study protocol and participated in study implementation. HZ participated in study coordination and implementation. LZ designed and revised the study protocol. All authors contributed to writing the protocol description and have read and approved the final version for submission. LZ is the guarantor.

Funding This work is supported by the Chongqing medical scientific research project (Joint project of Chongqing Health Commission and Science and Technology Bureau) (No. 2024MSXM134)

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs

Hongyan Zhou http://orcid.org/0009-0006-2929-5609
Ailin Song http://orcid.org/0000-0001-7378-5281
Hui Zhang http://orcid.org/0000-0001-5238-7743
Liang Zhang http://orcid.org/0009-0005-7213-589X

REFERENCES

1 Swarbrick CJ, Partridge JSL. Evidence-based strategies to reduce the incidence of postoperative delirium: a narrative review. *J Anaesthesia* 2022;77 Suppl 1:92–101.
2 International Advisory Group for the Revision of ICD-10 Mental and Behavioural Disorders. A conceptual framework for the revision of the ICD-10 classification of mental and behavioural disorders. *World Psychiatry* 2011;10:86–92.
3 Jin Z, Hu J, Ma D. Postoperative delirium: perioperative assessment, risk reduction, and management. *Br J Anaesth* 2020;125:492–504.
4 Yan E, Veitch M, Saripella A, *et al*. Association between postoperative delirium and adverse outcomes in older surgical patients: A systematic review and meta-analysis. *J Clin Anesth* 2023;90:111221.
5 Thedim M, Vacas S. Postoperative Delirium and the Older Adult: Untangling the Confusion. *J Neurosurg Anesthesiol* 2024;36:184–9.
6 Vacas S, Cole DJ, Cannesson M. Cognitive Decline Associated With Anesthesia and Surgery in Older Patients. *JAMA* 2021;326:863.
7 Lin X, Chen Y, Zhang P, *et al*. The potential mechanism of postoperative cognitive dysfunction in older people. *Exp Gerontol* 2020;130:110791.
8 Nešković N, Budrovac D, Kristek G, *et al*. Postoperative cognitive dysfunction: Review of pathophysiology, diagnostics and preventive strategies. *J Perioper Pract* 2025;35:47–56.
9 Cai L, Lu K, Chen X, *et al*. Auricular vagus nerve stimulation protects against postoperative cognitive dysfunction by attenuating neuroinflammation and neurodegeneration in aged rats. *Neurosci Lett* 2019;703:104–10.
10 Yamanashi T, Sullivan EJ, Comp KR, *et al*. Anti-inflammatory medication use associated with reduced delirium risk and all-cause mortality: A retrospective cohort study. *J Psychosom Res* 2023;168:111212.
11 Zou N, Zhou Q, Zhang Y, *et al*. Transcutaneous auricular vagus nerve stimulation as a novel therapy connecting the central and peripheral systems: a review. *Int J Surg* 2024;110:4993–5006.
12 Clancy JA, Mary DA, Witte KK, *et al*. Non-invasive vagus nerve stimulation in healthy humans reduces sympathetic nerve activity. *Brain Stimul* 2014;7:871–7.
13 Li H, Zhang J-B, Xu C, *et al*. Effects and mechanisms of auricular vagus nerve stimulation on high-fat-diet--induced obese rats. *Nutrition* 2015;31:1416–22.
14 Yin J, Ji F, Gharibani P, *et al*. Vagal Nerve Stimulation for Glycemic Control in a Rodent Model of Type 2 Diabetes. *Obes Surg* 2019;29:2869–77.
15 Zhu Y, Xu F, Lu D, *et al*. Transcutaneous auricular vagal nerve stimulation improves functional dyspepsia by enhancing vagal efferent activity. *Am J Physiol Gastrointest Liver Physiol* 2021;320:G700–11.

16 Yang Y, Du F, Ye W, *et al*. Inpatient cost of treating osteoporotic fractures in mainland China: a descriptive analysis. *Clinicoecon Outcomes Res* 2015;7:205–12.
17 Yang H, Shi W, Fan J, *et al*. Transcutaneous Auricular Vagus Nerve Stimulation (ta-VNS) for Treatment of Drug-Resistant Epilepsy: A Randomized, Double-Blind Clinical Trial. *Neurotherapeutics* 2023;20:870–80.
18 Rong P, Liu J, Wang L, *et al*. Effect of transcutaneous auricular vagus nerve stimulation on major depressive disorder: A nonrandomized controlled pilot study. *J Affect Disord* 2016;195:172–9.
19 Noé E, Ferri J, Colomer C, *et al*. Feasibility, safety and efficacy of transauricular vagus nerve stimulation in a cohort of patients with disorders of consciousness. *Brain Stimul* 2020;13:427–9.
20 Yu Y-T, Yang Y, Wang L-B, *et al*. Transcutaneous auricular vagus nerve stimulation in disorders of consciousness monitored by fMRI: The first case report. *Brain Stimul* 2017;10:328–30.
21 Yuan H, Silberstein SD. Vagus Nerve and Vagus Nerve Stimulation, a Comprehensive Review: Part III. *Headache* 2016;56:479–90.
22 Salama M, Akan A, Mueller MR. Transcutaneous Stimulation of Auricular Branch of the Vagus Nerve Attenuates the Acute Inflammatory Response After Lung Lobectomy. *World J Surg* 2020;44:3167–74.
23 Zhou Q, Yu L, Yin C, *et al*. Effect of transcutaneous auricular vagus nerve stimulation on delayed neurocognitive recovery in elderly patients. *Aging Clin Exp Res* 2022;34:2421–9.
24 Chan A-W, Tetzlaff JM, Gøtzsche PC, *et al*. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;346:e7586.
25 Ely EW, Inouye SK, Bernard GR, *et al*. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). *JAMA* 2001;286:2703–10.
26 Zhou Y-F, Kang J-W, Xiong Q, *et al*. Transauricular vagus nerve stimulation for patients with disorders of consciousness: A randomized controlled clinical trial. *Front Neurol* 2023;14:1133893.
27 Wang L, Zhang J, Guo C, *et al*. The efficacy and safety of transcutaneous auricular vagus nerve stimulation in patients with mild cognitive impairment: A double blinded randomized clinical trial. *Brain Stimul* 2022;15:1405–14.
28 Wang Y, Li S-Y, Wang D, *et al*. Transcutaneous Auricular Vagus Nerve Stimulation: From Concept to Application. *Neurosci Bull* 2021;37:853–62.
29 Mosk CA, Mus M, Vroemen JP, *et al*. Dementia and delirium, the outcomes in elderly hip fracture patients. *Clin Interv Aging* 2017;12:421–30.
30 Zhu C, Wang B, Yin J, *et al*. Risk factors for postoperative delirium after spinal surgery: a systematic review and meta-analysis. *Aging Clin Exp Res* 2020;32:1417–34.
31 Ormseth CH, LaHue SC, Oldham MA, *et al*. Predisposing and Precipitating Factors Associated With Delirium. *JAMA Netw Open* 2023;6:e2249950.
32 Flikweert ER, Wendt KW, Diercks RL, *et al*. Complications after hip fracture surgery: are they preventable? *Eur J Trauma Emerg Surg* 2018;44:573–80.
33 Connolly KP, Kleinman RS, Stevenson KL, *et al*. Delirium Reduced With Intravenous Acetaminophen in Geriatric Hip Fracture Patients. *J Am Acad Orthop Surg* 2020;28:325–31.
34 Xing H, Xiang D, Li Y, *et al*. Preoperative prognostic nutritional index predicts postoperative delirium in elderly patients after hip fracture surgery. *Psychogeriatrics* 2020;20:487–94.
35 Maldonado JR. Acute Brain Failure: Pathophysiology, Diagnosis, Management, and Sequelae of Delirium. *Crit Care Clin* 2017;33:461–519.
36 Viderman D, Nabidollayeva F, Aubakirova M, *et al*. Postoperative Delirium and Cognitive Dysfunction after General and Regional Anesthesia: A Systematic Review and Meta-Analysis. *J Clin Med* 2023;12:3549.
37 Chen M, Yu L, Ouyang F, *et al*. The right side or left side of noninvasive transcutaneous vagus nerve stimulation: Based on conventional wisdom or scientific evidence? *Int J Cardiol* 2015;187:44–5.
38 Wang L, Gao F, Wang Z, *et al*. Transcutaneous auricular vagus nerve stimulation in the treatment of disorders of consciousness: mechanisms and applications. *Front Neurosci* 2023;17:1286267.
39 Li X, Yang J, Nie X-L, *et al*. Impact of dexmedetomidine on the incidence of delirium in elderly patients after cardiac surgery: A randomized controlled trial. *PLoS ONE* 2017;12:e0170757.
40 Cheng H, Li Z, Young N, *et al*. The Effect of Dexmedetomidine on Outcomes of Cardiac Surgery in Elderly Patients. *J Cardiothorac Vasc Anesth* 2016;30:1502–8.
41 Wang H -B., Jia Y, Zhang C -B., *et al*. A randomised controlled trial of dexmedetomidine for delirium in adults undergoing heart valve surgery. *Anaesthesia* 2023;78:571–6.