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ORIGINAL RESEARCH

Auricular Vagus Nerve Stimulation Reduces Postoperative Delirium After Major Non-Cardiac Surgery in Elderly Patients

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Background: Postoperative delirium (POD) is a prevalent and devastating complication in elderly patients undergoing major surgery, marked by substantial increases in morbidity, mortality, and long-term cognitive decline. However, treatment and prevention methods are limited. Accumulating evidence suggests that vagus nerve stimulation effectively enhances cognitive function.

Objective: To evaluate the efficacy of transcutaneous auricular vagus nerve stimulation (taVNS) on POD in elderly patients undergoing major non-cardiac surgery.

Methods: Patients aged ≥65 years scheduled for major non-cardiac surgery were randomly assigned to either the active taVNS group or the sham taVNS group, with stimulation targeting the cymba conchae or earlobe, respectively. In both groups, stimulation was initiated 5 minutes prior to anesthesia induction and continued until the end of surgery. The only difference between the two groups was the stimulation site. The primary outcome was the incidence of POD during the first 3 postoperative days.

Results: A total of 150 patients (median age, 73 years; 96 women [64%]) completed this trial. The incident POD risk was 12% (n = 9) vs 25.3% (n = 19) in active-taVNS and sham-taVNS groups, respectively (relative risk, 0.47; 95% CI, 0.23–0.98; $P = 0.036$). The mediation analysis revealed that postoperative sleep quality played a significant mediating role in the effect of taVNS on POD ($z = -2.30$, $P = 0.02$).

Conclusion: In this study, taVNS reduces the incidence of POD in elderly patients undergoing major non-cardiac surgery, possibly by improving postoperative sleep quality. We suggest that this non-invasive neuromodulation technique could be considered as a potential preventive strategy for POD. Further validation in future large-scale randomized controlled trials is warranted.

Keywords: taVNS, postoperative delirium, sleep quality, mediation effects

Introduction

Postoperative delirium (POD) is a prevalent and devastating complication that commonly occurs in elderly patients after surgery. The incidence of POD varies with the patient population, surgical procedure, and frequency of assessment,[1] ranging from 10% to 50%,[2] even exceeds 50% in cardiac surgical patients and those needing postoperative ICU care.[3,4] Characterized by inattention, disorganized thinking, altered level of consciousness, and fluctuating symptoms, POD heralds a cascade of adverse outcomes: protracted hospital stays, heightened mortality, accelerated long-term cognitive decline, and enduring erosion of quality of life.[5–7] However, there is currently no specific treatment strategy for POD. The primary approach to POD management is prevention through controlling or eliminating modifiable risk factors. In the updated guideline by the European Society of Anesthesiology and Intensive Care Medicine on POD in adult patients, multicomponent nonpharmacological interventions are strongly recommended for all patients at risk of POD.[8] These

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interventions include perioperative cognitive training and sleep optimization, which have shown potential in reducing POD.[9,10] Yet, despite the urgent need for targeted, evidence-based prophylaxis in high-risk patients, truly effective interventions for POD remain elusive.

The vagus nerve, a major component of the parasympathetic nervous system, serves as an important bridge between the brain and peripheral organs. Vagus nerve stimulation (VNS) has emerged as a powerful neuromodulatory tool, demonstrating remarkable clinical efficacy in a variety of neurological and psychiatric disorders, including epilepsy, depression, and cognitive impairment.[11] Of note, diminished vagal tone is associated with aging, impaired cognition, poor resolution of inflammation.[12,13] Recent studies suggest that transcutaneous auricular vagus nerve stimulation (taVNS) can improve sleep quality,[14] while Sleep disturbance is a risk factor for POD.[15] As a noninvasive alternative to traditional VNS, taVNS has also garnered attention for its potential in treating a range of clinical conditions related to cognitive impairments.[16,17] However, clinical research specifically investigating the efficacy of taVNS in preventing POD is limited.

Therefore, we utilized taVNS, a safe and efficient non-invasive method for stimulating the auricular branch of the vagus nerve, to test its effectiveness and safety in preventing POD. The primary objective of this randomized, double-blind, sham-controlled trial was to determine the efficacy of taVNS on the incidence of POD in elderly patients undergoing non-cardiac major surgery.

Methods

Study Design

This prospective, multicenter, randomized, double-blind, controlled clinical trial was conducted in the Second Affiliated Hospital of Nanjing Medical University, Jinling Hospital, Nanjing University School of Medicine, and Affiliated Hospital of Integrated Traditional Chinese and Western Medicine, Nanjing University of Chinese Medicine from October 2024 to February 2025. The study protocol was approved by the Ethics Committee of the Second Affiliated Hospital of Nanjing Medical University (Ethics approval number: 2024-KY-216-02). The trial was registered at the China Clinical Trial Center (http://www.chictr.org.cn/) with the registration identifier ChiCTR2400090660.

Study Population

Screening for eligibility was completed during the preoperative visit by the anesthesiologist one day before surgery. Patients aged 65–85 years scheduled for elective major non-cardiac surgery, with American Society of Anesthesiologists (ASA) physical status I–III, expected surgery duration over 1 hour, and anticipated hospital stay longer than 3 days were eligible. All patients who participated in the trial received detailed information about the study protocol before enrolling. These patients were all clear-headed, able to communicate fluently, and willing to participate in this research. Exclusion criteria were as follows: 1. Preoperative diagnosis of delirium or a documented history of neurological or psychiatric disorders; 2. Severe hepatic, renal, cardiac, or pulmonary dysfunction; 3. History of severe trauma or major surgery within the past year; 4. History of substance dependence or alcohol abuse, or recent use of cholinergic, anticholinergic drugs, or corticosteroids; 5. Localized skin rash, infection, lesion, ulceration, or scarring at the stimulation site; 6. History of implanted stimulators, cochlear implants, or internal metallic implants (excluding dental implants); 7. History of unilateral or bilateral vagus nerve injury; 8. Resting heart rate <60 beats per minute; 9. Participation in other clinical trials. In addition, participants were eliminated for the following reasons: voluntary withdrawal or poor compliance, violation of the protocol, use of other drugs or methods that affected the trial's outcome indicators, or failure of the subject's follow-up.

Randomization and Blinding

Based on a computer-generated random number table, participants were centrally randomized 1:1 to either the active-taVNS group or sham-taVNS group by an investigator. The allocation information was concealed in opaque envelopes and revealed by the investigators upon the patients' arrival at the operating room, who were responsible for administering the taVNS stimulation. The researchers who assessed the outcomes and collected data, as well as processed the data,

were blinded to the treatment allocation. The surgeons, anesthesiologists, and nurses were also blinded to the intervention protocol.

Intervention

Two 4.5 mm Ag/AgCl electrodes from the taVNS stimulator (tVNS501, Rishena, Changzhou, China) were placed at the cymba conchae of the left ear to stimulate the auricular branch of the vagus nerve. For sham-taVNS, electrodes were placed on the left earlobe. The parts of the left ear that were to be stimulated were cleaned using an alcohol pad, and skin impedance was reduced by applying a gel before the stimulation phase. Stimulation parameters were pulse width of 500 μs at 40 Hz and a biphasic pulse interval of 50s ON and 10s OFF.[18,19] Stimulation was initiated 5 minutes prior to anesthesia induction and continued until the end of the surgery. The stimulus intensity of the taVNS varied between individuals, starting at the minimum level and gradually increasing until a prickling sensation was perceived. The stimulation intensity was then adjusted to a tolerable level for the subjects without causing pain. The two groups differed only in the stimulation sites, while the stimulation parameters and duration remained identical. Because the right auricular vagal nerve projects to the heart, the stimulation was always applied to the left ear to avoid potential side effects to the heart.

Anesthesia Procedures

Anesthesia was induced with propofol (1–2 mg/kg) or etomidate (0.2–0.3 mg/kg), sufentanil (0.2–0.4 μg/kg), and rocuronium (0.6–1 mg/kg), followed by endotracheal intubation. Standard monitoring included ECG, invasive BP, SpO_2, and $ETCO_2$ (maintained at 35–45 mmHg). Anesthesia was maintained with propofol and remifentanil, with optional sevoflurane and vasoactive drugs to keep BIS at 40–60 and BP within ±20% of baseline. Postoperative analgesia used PCIA (2 μg/kg sufentanil, 100 mg dolasetron in 100 mL saline), with a basal infusion rate of 3 mL/h, a 2 mL bolus dose, and a 15-minute lockout interval.

Clinical Outcomes and Assessments

The primary outcome was the incidence of POD during the first 3 postoperative days. POD was assessed with the Confusion Assessment Method (CAM) or CAM for the intensive care unit (CAM-ICU) for intubated patients by trained investigators who were masked to the group assignment.[20] The CAM was used for communicative patients, while the CAM-ICU was applied to intubated ICU patients unable to communicate. The CAM is a standardized approach with high sensitivity (94%–100%) and specificity (90%–95%) in one prior study.[21] POD was assessed during the anesthesia visit on the day before surgery (T0) and twice daily from postoperative day 1 to day 3, with at least a 6-hour interval between assessments. The assessment time points included the morning of the first postoperative day (T1), the afternoon of the first postoperative day (T2), the morning of the second postoperative day (T3), the afternoon of the second postoperative day (T4), the morning of the third postoperative day (T5), and the afternoon of the third postoperative day (T6). If the patient developed POD, assessment was performed daily until the symptoms disappeared.

Secondary outcomes included delirium subtypes (hyperactive delirium; hypoactive delirium and mixed delirium), delirium severity (assessed by Delirium Rating Scale Revised 98)[22] and delirium duration; post-operative pain scores (assessed by the Numeric Rating Scale (NRS)[23] both at rest and motion within the first three postoperative days); sleep quality represented by the total Richards–Campbell Sleep Questionnaire (RCSQ) score;[24] C-reactive protein (CRP); neutrophil-lymphocyte ratio (NLR); length of hospitalization. Pain and sleep quality were assessed at T1, T3 and T5. Preoperative CRP and NLR were obtained from the preoperative tests conducted within one week prior to surgery, while postoperative CRP and NLR were derived from the morning blood samples on postoperative day 1. Preoperative anxiety and depression were measured using the Hospital Anxiety and Depression Scale (HADS), a standardized 14 items self-report instrument commonly employed to evaluate psychological distress in non-psychiatric patients, with demonstrated good sensitivity and specificity.[25] Preoperative sleep quality was evaluated using the Pittsburgh Sleep Quality Index (PSQI), a widely used tool for assessing subjective sleep patterns and disturbances.[26] POD was classified using the Richmond Agitation Sedation Scale (RASS).[27] The subtypes of POD were the hypoactive type with a RASS of −3 to 0, the hyperactive type with a RASS of +1 to +4, and the mixed type with alternative positive and negative. Outcome

assessments were performed by the investigators in the ward. To account for the fluctuating nature of POD, investigators also consulted family members and caregivers regarding the patient's symptoms.

Sample Size Calculation

We conducted a pilot study involving 67 patients in total. Of these, 37 were allocated to the sham-taVNS group, with 7 cases of POD, while 30 to the active-taVNS group, with 3 cases of POD. The incidence of POD decreased from 18.9% in the control group to 10% in the intervention group. The sample size was determined a priori using PASS 15.0. We chose a study power of 0.90 and a significance level of 0.05, and used a two-sided significance level to show a significant difference in the incidence of POD; we then derived that 60 patients per group were required. Considering a 20% loss of follow-up, the sample size was increased to 75 per group.

Statistical Analysis

Since there were no missing data for the primary outcome, and missing data for all secondary outcomes were less than 5%. We did not perform an imputation of missing data. All analyses were conducted with the intention-to-treat principle. Categorical variables are presented as frequencies or proportions and analyzed using the chi-squared test or Fisher exact test. Continuous variables are presented as mean (standard deviation [SD]) or median (interquartile range [IQR]) depending on distribution (the Shapiro–Wilk test was used to assess normality) and analyzed with independent samples *t*-test or Mann–Whitney *U*-test. Data collected at multiple points were analyzed using repeated-measures analysis of variance. The primary endpoint was analyzed using the chi-squared test. Adverse events were recorded via participant self-reports, medical record reviews and investigator observations. Exploratory analyses were conducted to evaluate the treatment effect and its heterogeneity in the primary outcome across predefined subgroups, with interaction *P* values reported. All statistical analyses were performed using and R version 4.4.2. Two-tailed tests were applied, and P value < 0.05 was considered statistically significant. A mediation analysis was conducted to assess whether postoperative sleep quality mediated the effect of taVNS on POD, based on the hypothesis that taVNS reduces POD partly by improving sleep. The total effect reflects the overall impact of taVNS on POD; the indirect effect captures the portion mediated by sleep quality; the direct effect is the remaining impact after accounting for the mediator. Ordinary least squares regression was used to model the mediator and outcome, and 95% confidence intervals (CIs) were calculated using 10,000 bootstrap samples.

Results

Flowchart

A total of 217 patients were screened for inclusion between October 12, 2024, and February 28, 2025. Of these, 9 patients were excluded due to the following reasons: suspected unilateral vagus nerve injury (n = 1), a history of implanted stimulators (n = 3), depression (n = 3), anxiety (n = 2), or insufficient ear size to enable effective stimulation by the device (n = 1). Additionally, 58 patients declined participation in the trial. Ultimately, 150 patients were enrolled and randomly assigned to either the active-taVNS group (n = 75) or the sham-taVNS group (n = 75). All participants completed the trial. The participant flow was illustrated in Figure 1.

Baseline Demographics and Clinical Characteristics

Baseline and clinical characteristics were evenly randomized between the two groups (Table 1). At baseline, no significant differences were observed between the groups for any variable except ASA classification ($P = 0.022$). The median (IQR) MMSE scores were 26 (28.0–29.0) in the sham-taVNS group and 26 (29.0–30.0) in the active-taVNS group. Baseline comorbidities, HADS scores and PSQI scores showed no significant differences between groups ($P > 0.05$, Table 1). Intraoperative variables (duration of surgery and estimated blood loss) were also comparable ($P > 0.05$; Table 2).

Primary Outcome

The primary outcome was the incidence of POD, as evaluated by the CAM and CAM-ICU, within the 3 days after surgery. Before the beginning of the study, research personnels were trained to performed CAM and CAM-ICU with the

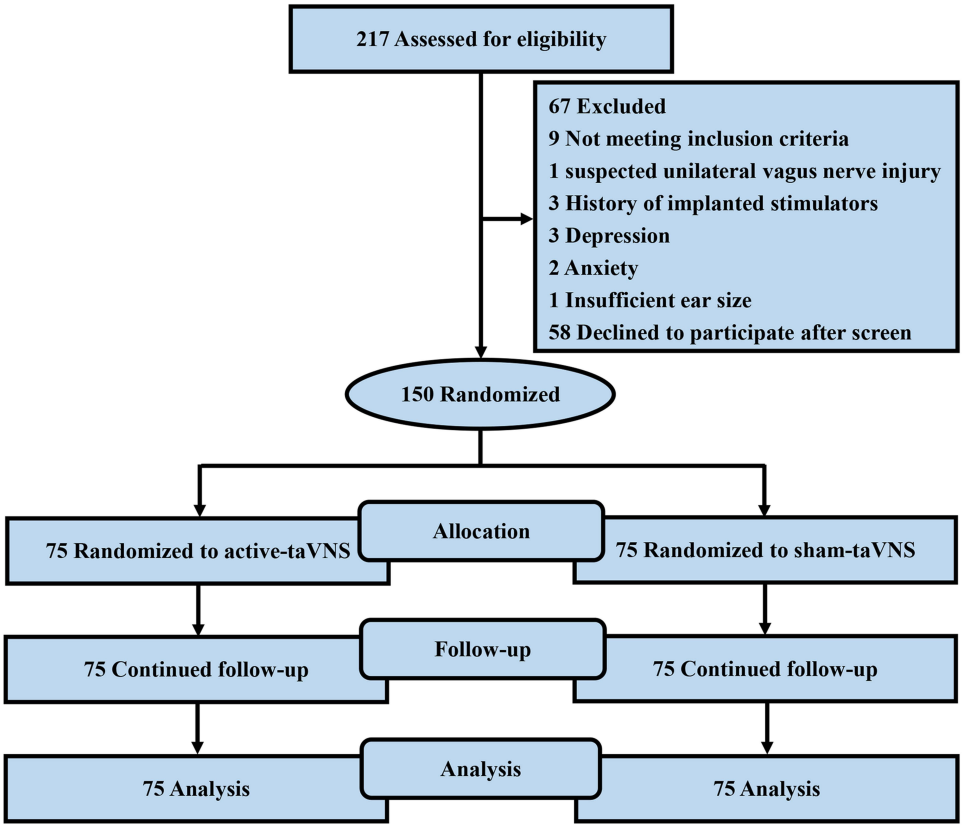

Figure 1 Consolidated Standards of Reporting Trials flow diagram for this trial.
Abbreviation: taVNS, transcutaneous auricular vagus nerve stimulation.

Chinese version of the CAM-ICU Training Manual. The incidence of POD at any time during the first postoperative 3 days was significantly lower in the active-taVNS group (9 [12%] of 75 patients) than that in the sham- taVNS group (19 [25.3%] of 75 patients; relative risk, 0.47; 95% CI, 0.23–0.98; $P = 0.036$; Figure 2). The overall incidence of POD was 19.1% (28 of 150 patients). Detailed information on the onset and duration of POD is provided in Supplementary Figure S1.

Secondary Outcomes

An ITT analysis showed no significant differences between the active-taVNS and sham-taVNS groups in POD duration (overall: median, 2 days, IQR: 1–3; $P = 0.595$), worst delirium severity scores (overall: median, 19, IQR: 17–23; $P = 0.154$), or motoric subtypes of delirium ($P = 0.513$, Table 2). During the three postoperative days, the incidence of non-POD complications and pain scores at rest and during motion were also comparable between the two groups. There were no significant differences in the duration of hospital stay (11 [IQR, 7.0–16.8] days vs 10 [IQR, 7.0–17.0] days; $P = 0.814$, Table 2) between the active-taVNS group and sham-taVNS group. However, on postoperative days 1, 2 and 3, the taVNS group had significantly higher RCSQ scores (Postoperative day 1: 60 [50, 60] vs 50 [40, 60], $P = 0.027$; day 2: 60 (60, 70) vs 60 (50, 60), $P < 0.001$; day 3: 70 (60, 70) vs 60 (50, 70), $P = 0.002$; Table 2). Additionally, no significant between-group differences were observed in NLR or CRP levels on the morning of the first postoperative day (NLR: 21.0 [IQR, 11.7–48.0] vs 21.7 [IQR, 11.3–48.9], $P = 0.942$; CRP: 12.5 [IQR, 8.9–20.0] vs 11.1 [IQR, 8.2–15.6], $P = 0.107$; Table 2).

Single factor logistic regression analysis showed that the P values of taVNS, age, ASA, education, ICU admission, duration of surgery and preoperative MMSE score are less than 0.1 (Supplementary Table S1). Incorporating these factors into the multivariate logistic regression analysis, we found that active-taVNS intervention showed significant

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Table 1 Baseline Characteristics of Study Participants by Treatment Group

Characteristic	Sham-taVNS (n = 75)	Active-taVNS (n = 75)	*P* Value
Age, years, median (IQR)	72 (70, 74)	73 (70, 77)	0.234
Sex, n (%)			0.307
Male	45 (60.0)	51 (71.8)	
Female	30 (40.0)	24 (33.8)	
BMI, kg/m^2, mean (SD)	23.3 (3.3)	23.4 (3.1)	0.766
Education level, n (%)			0.974
Less than elementary school	12 (16.0)	12 (16.0)	
Elementary school	26 (34.7)	26 (34.7)	
Middle school	22 (29.3)	19 (25.3)	
High school	10 (13.3)	12 (16.0)	
College graduate	5 (6.7)	6 (8.0)	
ASA classification, n (%)			**0.022**
II	43 (57.3)	29 (38.7)	
III	32 (42.7)	46 (61.3)	
Type of operation, n (%)			0.151
Thoracic surgery	24 (32.0)	34 (45.3)	
General surgery	24 (32.0)	15 (20.0)	
Urology surgery	8 (10.7)	10 (13.3)	
Orthopedic surgery	14 (18.7)	15 (20.0)	
Gynecologic surgery	5 (6.7)	1 (1.3)	
Comorbidities, n (%)			
Diabetes	14 (18.7)	15 (20.0)	0.836
Hypertension	37 (49.3)	43 (57.3)	0.326
Cerebral infarction	9 (12.0)	12 (16.0)	0.480
Coronary artery disease	5 (6.7)	3 (4.0)	0.719
MMSE score, median (IQR)	26 (23, 28)	26 (23, 29)	0.935
PSQI score, median (IQR)	4 (3, 6)	4 (3,5)	0.988
HADS-A score, median (IQR)	2 (1,4)	2 (2,4)	0.571
HADS-D score, median (IQR)	3 (1,4)	2 (2,4)	0.709
ICU admission after surgery, n (%)	33 (44.0)	29 (38.7)	0.507
CRP, mg/L, median (IQR)	0.65 (0.5, 2.35)	0.65 (0.5, 2.23)	0.738
NLR, median (IQR)	2.31 (1.58, 3.64)	2.37 (1.65, 3.19)	0.89

Note: Bold font represented *P* value < 0.05.
Abbreviations: IQR, interquartile range; SD, standard deviation; BMI, body mass index; ASA, American Society of Anesthesiologists; MMSE, Mini-Mental State Examination; PSQI, Pittsburgh Sleep Quality Index; HADS, Hospital Anxiety and Depression Scale; ICU, intensive care unit; CRP, C-reactive protein; NLR, neutrophil-lymphocyte ratio.

statistical differences (odds ratio, 0.178; 95% CI, 0.056–0.559; $P = 0.003$) (Supplementary Table S2). The subgroup analyses of the primary outcome were shown in Figure 3.

To further investigate whether taVNS indirectly influences POD by improving postoperative sleep quality, we conducted a mediation analysis. The mediation analysis was performed using one independent variable (taVNS), one dependent variable (POD), and one potential mediator (postoperative sleep quality). The sleep quality scores for the first three days post-operation were averaged, and then treated as a mediator variable and incorporated into the mediational model for calculation. The mediation analysis revealed that the average RCSQ scores over the three days postoperatively played a significant mediating role in the effect of taVNS on POD (z = −2.30, $P = 0.02$, Figure 4). The indirect effect of taVNS on POD mediated through average RCSQ scores was −5.30% (95% CI, −11.51% – −1.02%, Supplementary Table S3).

Table 2 Intraoperative and Postoperative Data by Treatment Group

Characteristic	Sham-taVNS (n = 75)	Active-taVNS (n = 75)	*P* Value
Intraoperative			
Duration of surgery, min, median (IQR)	160 (120, 220)	160 (120, 250)	0.537
Estimated blood loss, mL, median (IQR)	150 (100, 300)	200 (100, 300)	0.462
Primary outcome			
Overall incidence of delirium, n (%)	19 (25.3)	9 (12.0)	**0.036**
Secondary outcomes			
Days with delirium, median (IQR)	2 (1, 3)	2 (1.5, 3.5)	0.595
Worst delirium severity, median	19 (17, 22)	21 (18, 29.5)	0.154
Motoric subtype of delirium, n (%)			0.513
Hypoactive	10 (13.3)	3 (4)	
Hyperactive	5 (6.7)	2 (2.7)	
Mixed	4 (5.3)	4 (5.3)	
Delirium on postoperative day 1, n (%)	12 (16.9)	6 (8.0)	0.102
Delirium on postoperative day 2, n (%)	5 (7.0)	2 (2.7)	0.266
Delirium on postoperative day 3, n (%)	2 (2.8)	1 (1.3)	0.612
Delirium without surgical complications, n (%)	12 (16.9)	3 (4)	**0.010**
Delirium with surgical complications, n (%)	7 (9.9)	6 (8.0)	0.693
Richards-Campbell Sleep Questionnaire			
Postoperative day 1	50 (40, 60)	60 (50, 60)	**0.027**
Postoperative day 2	60 (50, 60)	60 (60, 70)	**<0.001**
Postoperative day 3	60 (50,70)	70 (60,70)	**0.002**
Pain score at rest, median (IQR)			
Postoperative day 1	2 (1, 2)	2 (1, 2)	0.942
Postoperative day 2	1 (1, 2)	1 (1, 2)	0.997
Postoperative day 3	1 (0,1)	1 (0, 1)	0.594
Pain score with movement, median (IQR)			
Postoperative day 1	3 (3, 4)	3 (3, 4)	0.327
Postoperative day 2	3 (2, 3)	3 (3, 3)	0.130
Postoperative day 3	2 (2, 3)	2 (2, 3)	0.487
Length of hospitalization, days, median (IQR)	11 (7, 16.8)	10 (7,17)	0.814
Incidence of non-delirium complications, n (%)	7 (9.3)	10 (13.3)	0.440
Postoperative CRP, mg/L, median (IQR)	21.0 (11.7, 48.0)	21.70 (11.3, 48.9)	0.942
Postoperative NLR, median (IQR)	12.5 (8.9, 20.0)	11.11 (8.2, 15.6)	0.107

Note: Bold font represented *P* value < 0.05.
Abbreviations: IQR, interquartile range; CRP, C-reactive protein; NLR, neutrophil-lymphocyte ratio.

Discussion

This prospective randomized double-blind controlled trial indicates one session of taVNS reduced the incidence of POD and improved postoperative sleep quality in elderly patients undergoing non-cardiac major surgery. To our knowledge, this is the first sham-controlled study evaluating the prophylactic efficacy in the incidence of POD using taVNS in elderly patients undergoing non-cardiac major surgery. POD developed in 25.3% of patients in sham-taVNS group, which is consistent with previously reported rates for non-cardiac surgery.[28] POD is caused primarily by the acute postoperative changes in brain function, and acute neurobiological changes associated with postoperative psychosis may occur in the short-term critical period after surgery. Despite the substantial body of research on POD, it remains a resource-consuming adverse event but is often preventable POD is widely recognized as preventable through enhanced perioperative management, with anesthesiologists playing a pivotal intraoperative role. Maintaining adequate anesthetic depth, hemodynamic stability, and multimodal analgesia effectively reduces POD risk, while perioperative modulation of inflammatory responses, preservation of sleep–wake rhythms, and cognitive reserve training further contribute to its

Variable	Active-taVNS	Sham-taVNS	OR (95% CI)	*P* value for interaction
ASA				0.596
II	43 (57)	29 (39)	0.18 (0.02−1.58)	
III	32 (43)	46 (61)	0.35 (0.12−1.00)	
ICU admission				0.143
No	42 (56)	46 (61)	0.11 (0.01−0.95)	
Yes	33 (44)	29 (39)	0.67 (0.23−1.96)	
Age				0.134
≤75	62 (83)	46 (61)	0.14 (0.03−0.66)	
>75	13 (17)	29 (39)	0.72 (0.17−3.06)	
Surgery duration				0.754
≤180	48 (64)	44 (59)	0.43 (0.12−1.52)	
>180	27 (36)	31 (41)	0.33 (0.1−1.120)	
Education				0.564
≤9	60 (80)	57 (76)	0.46 (0.17−1.24)	
>9	15 (20)	18 (24)	0.25 (0.04−1.54)	
MMSE score				0.420
≤28	57 (76)	54 (72)	0.49 (0.19−1.26)	
>28	18 (24)	21 (28)	0.18 (0.02−1.74)	

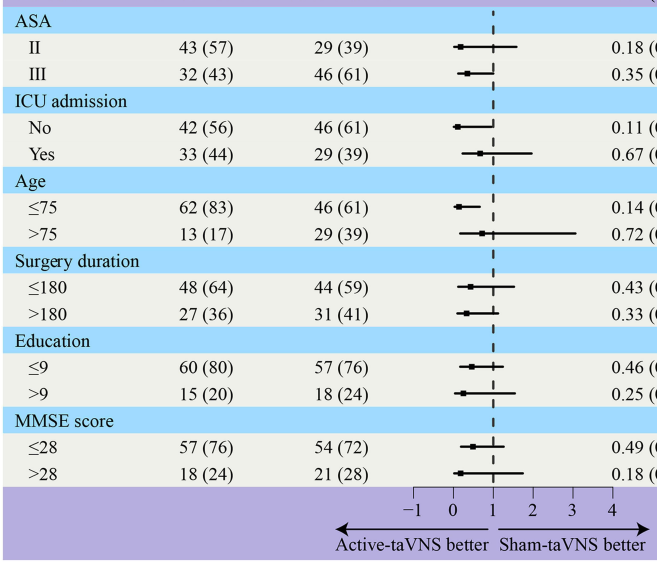

Figure 2 Forest plot of the subgroup analysis for the primary outcome.
Abbreviations: taVNS, transcutaneous auricular vagus nerve stimulation; OR, odds ratio; CI, confidence interval; ASA, American Society of Anesthesiologists; ICU, intensive care unit; MMSE, Mini-Mental State Examination.

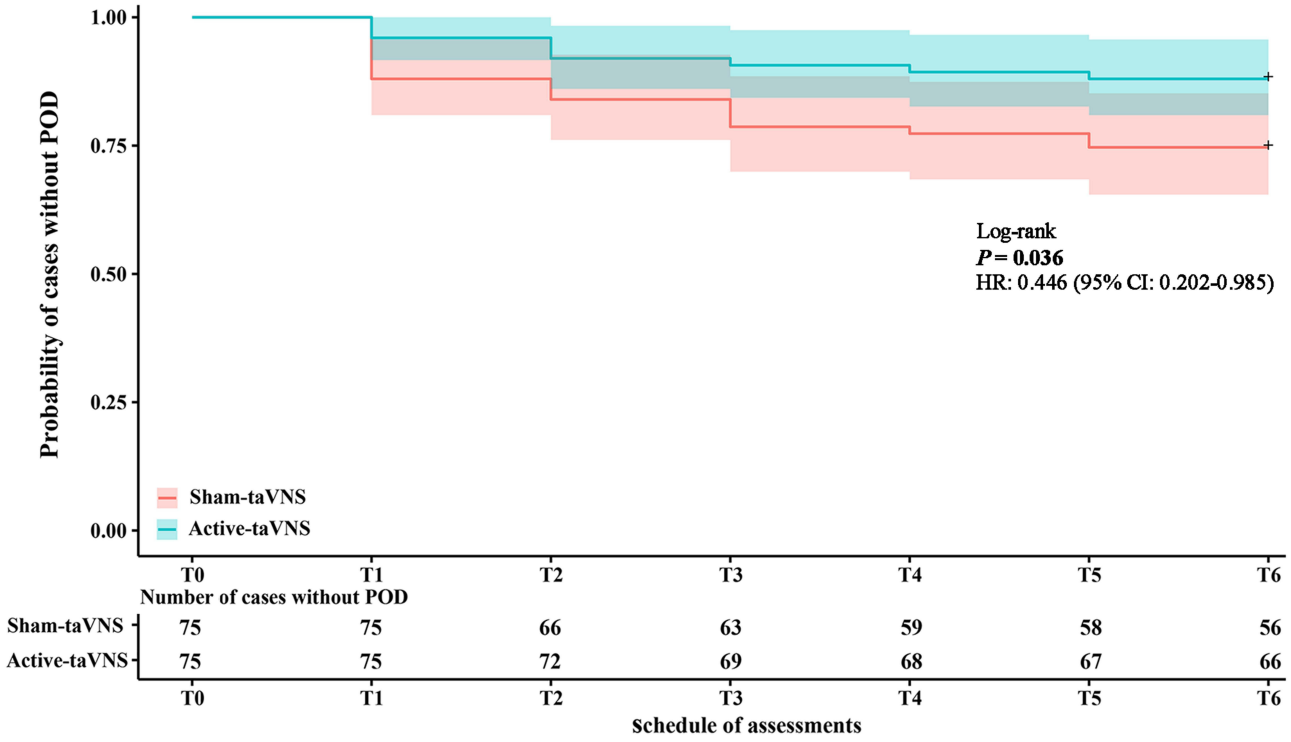

Figure 3 Kaplan-Meier curve showing intent-to-treat analysis of the cumulative incidence of POD during postoperative days 1 to 3 in the active-taVNS and sham-taVNS groups.
Note: Bold font represented *P* value < 0.05.
Abbreviations: POD, postoperative delirium; HR, hazard ratio; taVNS, transcutaneous auricular vagus nerve stimulation.

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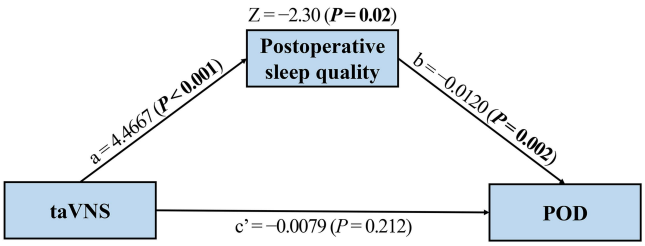

Figure 4 Proposed models investigating mediated effects. The mediating effect of postoperative sleep quality on reducing the incidence of POD through taVNS.
Note: Bold font represented *P* value < 0.05.
Abbreviations: taVNS, transcutaneous auricular vagus nerve stimulation; POD, postoperative delirium.

prevention.[29,30] In this study, the use of taVNS throughout the entire surgical process resulted in a POD incidence of 12%, representing a 52.6% reduction compared to the sham-taVNS group.

Extensive investigations of vagus nerve stimulation in epilepsy and Alzheimer's disease have unveiled its capacity to markedly enhance cognitive performance,[31,32] heralding a paradigm-shifting therapeutic avenue for cognitive disorders. Clinical investigations have even identified cognitive enhancement in healthy adults following VNS treatment.[33] In an animal of POCD, it also confirmed that VNS can significantly enhance cognitive function in rats.[34] However, the impact of VNS on cognitive function in the perioperative medical field remains relatively underexplored. Over the past decade, studies on taVNS have consistently demonstrated the utility of the concha and tragus, regions innervated by the auricular branch of the human vagus nerve, as valuable gateways for non-invasive brain stimulation.[35,36] Therefore, it is theoretically viable to apply taVNS to prevent POD.

The precise mechanism by which taVNS ameliorates cognitive dysfunction remains unclear. Surgery and anesthesia spark acute inflammation, hurting neurons and driving POD.[37] Animal data show VNS curbs this via anti-inflammatory and antioxidant pathways;[38–40] taVNS likely cuts POD risk by blocking postoperative inflammation. Therefore, we chose to provide continuous stimulation throughout the surgery to reduce the inflammatory response and stress induced by the procedure. Unfortunately, no inter-group differences in CRP or NLR were detected. Early post-operative values are dominated by surgical stress, easily masking the subtle anti-inflammatory effects of taVNS. Moreover, taVNS is thought to act mainly through central neuro-immune circuits, so peripheral markers may not mirror central changes.[41] Single-session tVNS boosts episodic memory—enhancing both recall and learning—by promoting dentate-gyrus LTP.[42] Via LC-driven noradrenaline, it sharpens cognitive control and associative memory.[43] Jongkees et al show it also refines sequential responses, as GABAergic inhibition suppresses errors.[44]

Postoperative sleep disruption—by impairing memory consolidation and directly eroding cognitive integrity—can powerfully precipitate delirium. Over 40% of patients complained about poor sleep quality during the first night following surgery, and the sleep problems continued several days after operation.[45] Evans et al identified insufficient sleep on the first night after surgery as an early predictor of subsequent POD.[46] Even brief periods of sleep deprivation, such as a single night, can lead to significant reductions in hippocampal activity, which is crucial for memory encoding. Wang et al found hospitalized sleep disturbances increased the incidence of POD.[47] As early as 2018, the PADIS Guidelines recommended that nonpharmacological interventions aimed at sleep promotion may help prevent POD.[48] Conversely, POD may also cause acute de novo sleep disturbances, adding further complexity. At present, it is difficult to define the true relationship between them, it is more likely a bidirectional effect rather than a definitive causal relationship. POD and sleep disturbances appear interlinked through shared pathophysiology. Perioperative systemic inflammation disrupts the blood–brain barrier, permitting inflammatory cytokines to enter the brain and activate microglia and astrocytes; neuroinflammation is considered one of the key pathological mechanisms of POD.[49] Animal study shows that sleep deprivation can evoke a "cytokine-storm"-like systemic response and provokes central neuroinflammation plus oxidative stress, causing neuronal injury and contributing to POD.[47,50,51] The cholinergic anti-inflammatory reflex—a vagus-nerve-mediated neuro-immune checkpoint—can be engaged by VNS to suppress pro-inflammatory microglial polarization and reduce oxidative stress, offering a unified therapeutic target.[52] We conducted a mediation analysis and

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found that postoperative sleep quality played a significant mediating role in the effect of taVNS on POD, further supporting the negative effect of sleep disturbances on POD.

This trial's strengths include its blinded, sham-controlled design, high data completeness, and use of validated tools to assess POD across a broad surgical population, enhancing generalizability. Limitations include a small sample size, warranting cautious interpretation and further large-scale studies. Follow-up was limited to 3 days, which may miss later-onset POD. Additionally, no objective biomarkers or imaging (eg, MRI or PET) were used to explore taVNS effects; combining taVNS with neuroimaging in future studies could clarify its potential mechanisms and support personalized interventions.

Conclusion

TaVNS shows potential to prevent POD in elderly patients undergoing major non-cardiac surgery, possibly through improving postoperative sleep quality. It is worth noting that systemic inflammatory markers (CRP, NLR) did not change, raising the possibility that the preventive effect of taVNS might involve central neuromodulatory mechanisms rather than systemic inflammation. We propose that this non-invasive neuromodulation technique could be incorporated into perioperative care as a preventive strategy for POD. Future large-scale randomized controlled trials are warranted to confirm these findings.

Data Sharing Statement

The raw data generated or analyzed during this study can be made available by the corresponding author upon reasonable request.

Ethics Approval and Informed Consent

This study was conducted in strict accordance with the ethical principles of the Declaration of Helsinki and was approved by the Ethics Committee of the Second Affiliated Hospital of Nanjing Medical University (Ethics approval number: 2024-KY-216-02). All procedures performed in the study involving humans followed the ethical standards of the institutional and national research committee. Written informed consent was obtained from either participants or legal surrogates before enrolment.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest. The sponsor had no role in the design, methods, data collection, analysis, and preparation of this manuscript.

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