Clinical Interventions in Aging

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CLINICAL TRIAL REPORT

Transcutaneous Auricular Vagus Nerve Stimulation and Pectoral-Intercostal Fascial Block for the Prevention of Chronic Postsurgical Pain in Elderly Patients Undergoing Off-Pump Coronary Artery Bypass Grafting: A 2×2 Factorial, Double-Blinded, Randomized Clinical Trial

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Background: Chronic postsurgical pain (CPSP) is common after off-pump coronary artery bypass grafting (OPCABG) in elderly patients. This trial investigated the efficacy of perioperative transcutaneous auricular vagus nerve stimulation (taVNS) and pectoral-intercostal fascial block (PIFB) for CPSP prevention.

Methods: In this 2×2 factorial trial, 260 elderly patients (≥60 years) undergoing OPCABG were randomized to taVNS + ropivacaine PIFB, taVNS + placebo PIFB, sham taVNS + ropivacaine PIFB, or sham taVNS + placebo PIFB groups. The primary outcome was CPSP incidence at 3 months postoperatively. Several secondary outcomes were evaluated. Logistic regression was employed to analyze risk factors associated with CPSP. Lastly, mediation analyses were performed to explore the mediating factors between interventions and CPSP.

Results: The overall incidence of CPSP was 34.6%. No interaction was found between taVNS and PIFB. Compared with sham taVNS, taVNS significantly reduced CPSP incidence (28.6% vs 40.9%, $P = 0.036$), alleviated acute pain and improved recovery quality. PIFB did not reduce overall CPSP incidence (30.2% vs 38.8%, $P = 0.143$), though it alleviated acute pain on postoperative day 1 and reduced moderate-to-severe CPSP. Risk factors for CPSP included preoperative anxiety, pain catastrophizing, acute postoperative pain, and high IL-6 levels. Mediation analysis indicated taVNS's benefits were partially mediated by reducing acute pain (19.3%) and IL-6 (20.4%).

Conclusion: Perioperative taVNS significantly reduced CPSP incidence and enhanced postoperative recovery in elderly OPCABG patients, partly mediated by alleviating acute pain and inflammation. Single-shot PIFB showed limited preventive effect on overall CPSP.

Keywords: postoperative pain, vagus nerve stimulation, nerve block, aged, randomized controlled trial

Introduction

Chronic postsurgical pain (CPSP) is defined as pain that develops or increases in intensity after a surgical procedure and persists beyond the normal healing period, typically lasting for at least three months.[1] Reported overall incidence rates of

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CPSP range from 3% to 85%, with moderate-to-severe pain accounting for 5% to 25%,[2] depending on the type of surgery and the definition of CPSP applied. Among these, the incidence of CPSP is particularly high following median sternotomy for cardiac surgery.[3,4] With the rapidly aging population in China, coronary heart disease (CHD) has become one of the most serious threats to public health. An increasing number of elderly patients with CHD are undergoing coronary artery bypass grafting. Among these patients, CPSP represents one of the critical factors affecting postoperative recovery and long-term quality of life.

Known risk factors for CPSP include younger age,[3] female sex,[3] pre-existing chronic pain,[5] preoperative psychological factors such as anxiety,[6,7] depression,[5,7] and pain catastrophizing,[6] acute postoperative pain[5–7] and postoperative inflammatory response.[8] Among these, our previous study confirmed that in elderly patients undergoing OPCABG, preoperative anxiety and depression are independent risk factors, with acute postoperative pain partially mediating this relationship.[9] Given that age and sex are non-modifiable, individualized interventions targeting acute pain and systemic inflammation—the key mediators in pain chronification—represent a strategic approach to preventing CPSP.

Vagus nerve stimulation (VNS) is an established neuromodulatory therapy approved by the FDA for the treatment of epilepsy, depression, and anxiety disorders.[10] Transcutaneous auricular vagus nerve stimulation (taVNS) non-invasively targets the auricular branch of the vagus nerve and can produce effects comparable to those achieved with invasive VNS.[11] TaVNS has been demonstrated to modulate multiple pathways, including cholinergic function,[12] inflammatory responses,[13] neuroplasticity,[14] and cerebral hemodynamics.[15] Its ability to alleviate chronic pain through regulation of autonomic function and the cholinergic anti-inflammatory pathway has been confirmed,[16,17] positioning it as a promising mechanism-based intervention in the perioperative setting—particularly in elderly patients with coronary heart disease, who frequently exhibit pre-existing vagal dysfunction. Although a study has shown that perioperative taVNS can reduce acute postoperative pain,[18] its potential for preventing CPSP remains unknown.

Perioperative regional nerve blocks play an increasingly important role in the prevention of postsurgical pain. By blocking noxious stimulus transmission during and after surgery, nerve block interrupts the sustained afferent signaling that may lead to neuroplastic changes and central sensitization—key mechanisms underlying the transition from acute to chronic pain.[19] In patients undergoing median sternotomy for cardiac surgery, the pectoral-intercostal fascial block (PIFB) can simultaneously block nociceptive input from multiple intercostal nerve segments. This technique effectively reduces intraoperative requirements for opioid analgesics and vasoactive agents, while providing effective analgesia for up to 12 hours postoperatively.[20] However, the benefits of PIFB in preventing CPSP remain inconsistent. Further well-designed clinical trials are essential to clarify its preventive efficacy and optimize interventional strategies for high-risk populations.

To improve research efficiency and minimize costs, this trial was designed as a 2×2 factorial study to evaluate the impact of perioperative taVNS and preoperative PIFB on CPSP. Furthermore, it aimed to explore the potential mediating roles of acute postoperative pain and inflammatory biomarkers in the pathogenesis of CPSP.

Materials and Methods

The trial was a randomized, double-blinded, 2×2 factorial clinical trial conducted at The Second Hospital of Hebei Medical University, China. The study protocol complied with the declaration of Helsinki, was approved by the Institutional Ethics Committee of the Second Hospital of Hebei Medical University (2024-R569), and was registered in http://www.chictr.org.cn (ChiCTR2400089192) on September 5th,2024 before inclusion of the first patient.

Patients

Patients aged 60 years or older who underwent elective first-time off-pump coronary artery bypass grafting (OPCABG) at the Second Hospital of Hebei Medical University between September 2024 and June 2025 were eligible for inclusion. Patients were excluded if they had auricular skin lesions, inflammation, or ear disease (eg, tympanic membrane perforation); a history or presence of neurological or psychiatric disorders; visual or hearing impairments or communication difficulties; preexisting non-cardiac chronic pain requiring pharmacological treatment; a history of drug or alcohol abuse or allergy to local anesthetics; or participation in another interventional study within the past three months.

Randomization and Blinding

Randomization was conducted by an independent researcher, using a computer-generated block randomization sequence with a block size of 8. Participants were assigned in a 1:1:1:1 ratio to one of four groups: taVNS + ropivacaine PIFB, taVNS + placebo PIFB, sham taVNS + ropivacaine PIFB, or sham taVNS + placebo PIFB. Allocation codes were sealed in sequentially numbered opaque envelopes. Upon enrollment, an unblinded researcher—an anesthesiologist with over 10 years of experience in regional anesthesia—opened the envelope, prepared the assigned intervention, and performed all taVNS and PIFB procedures but was not involved in follow-up or data analysis. Prior to the study, this researcher received standardized training specific to the protocol to ensure consistency in the electrical stimulation parameters and the fascial plane injection technique. Patients, surgeons, anesthesiologists, follow-up staff, and statisticians were blinded to both interventions. Final unblinding occurred only after data analysis was completed and confirmed by all researchers.

Interventions

TaVNS (TENS 7000, Compass Health Brands, Middleburg Heights, OH, USA) was performed five times during the perioperative period: following baseline assessment on the day before surgery, prior to anesthesia induction on the day of surgery, and between 9:00 and 12:00 a.m. on postoperative days (POD) 1 to 3. Stimulation was delivered to the cymba conchae of the left ear to minimize potential cardiovascular side effects.[21] The stimulation was delivered at 25 Hz with a 200 μs pulse width for 30 minutes, a protocol optimized for activating Aβ afferent fibers while minimizing discomfort and neural habituation.[22] The stimulation intensity was adjusted to elicit a tingling sensation without causing pain or discomfort. In the sham group, patients received brief stimulation for 30 seconds until a tingling sensation was perceived, after which the stimulation was discontinued. Patients were informed that stimulation had started and that they might not always feel a tingling sensation throughout the procedure.

Bilateral PIFB was performed after tracheal intubation. Under ultrasound guidance, the second and fourth intercostal spaces were identified bilaterally, and the needle was inserted 2–2.5 cm lateral to the sternal border. Local anesthetic was deposited in the plane between the pectoralis major and internal intercostal muscles, with 10 mL of 0.375% ropivacaine injected at each site, for a total of 40 mL bilaterally. In the placebo group, an equivalent volume of normal saline was injected following the same procedure.

Procedures

Baseline assessments were performed the day before surgery by clinical physicians, who were trained and supervised by a senior researcher (>10 years experience) in standardized scale administration and pain identification. Preoperative anxiety and depression were assessed using the Hospital Anxiety and Depression Scale (HADS),[23] pain catastrophizing using the Pain Catastrophizing Scale (PCS),[24] sleep quality using the Pittsburgh Sleep Quality Index (PSQI),[25] and cognitive function using the Mini-Mental State Examination (MMSE).[26] Sociodemographic data, such as age, sex, body mass index (BMI), marital status, history of smoking, alcohol consumption, prior surgery, comorbidities, and medications, were extracted from electronic medical records.

All patients underwent a standardized anesthetic protocol. Anesthesia was induced with midazolam (0.01–0.03 mg/kg), sufentanil (0.5–0.8 μg/kg), rocuronium (1 mg/kg), and etomidate (0.2–0.3 mg/kg). Anesthesia was maintained with combined intravenous and inhalational anesthesia, including continuous infusion of propofol (1–3 mg/kg/h), intermittent boluses of rocuronium and sufentanil, and routine administration of the vasoactive agent nitroglycerin (0.5–1 μg/kg/min). Heparin (1.5 mg/kg) was administered for anticoagulation prior to vascular anastomosis, and protamine was administered at a 1:1 ratio to heparin for reversal after completion of vascular reconstruction. After surgery, all patients were transferred to the cardiothoracic intensive care unit (ICU) with endotracheal intubation. Postoperative analgesia was managed by the surgical team via intravenous infusion, with the goal of maintaining a Numeric Rating Scale (NRS) score below 4. To account for the lack of a standardized protocol, we recorded the specific types and dosages of all postoperative analgesics used for the first 7 days after surgery. For quantitative comparison, all opioid doses were converted into intravenous morphine equivalent consumption (MEC) based on the following conversion ratios: morphine (i.v.) 10 mg = dezocine (i.v.) 10 mg = pentazocine (i.v.) 30 mg = butorphanol (i.v.) 2 mg = nalbuphine (i.v.) 10 mg.

Intraoperative characteristics, including the number of grafts, duration of surgery and anesthesia, incidence of hypotension and hypothermia, analgesic consumption, blood loss, and blood product transfusion volume, were obtained from the anesthesia information management system. Hypothermia was defined as an intraoperative body temperature <35.5 °C lasting for more than 15 minutes,[27] and hypotension was defined as an intraoperative systolic blood pressure <70 mmHg lasting for more than 15 minutes.[28]

Primary and Secondary Outcomes

The primary outcome of this study was the incidence of CPSP, which was assessed 3 months after surgery via telephone follow-up. CPSP was defined according to the International Association for the Study of Pain criteria as outlined in the International Classification of Diseases, Eleventh Revision (ICD-11). Patients were considered to have CPSP if they reported persistent pain at the surgical site within the past 3 months and denied any alternative causes for the pain, such as infection or tumor. Pain intensity was evaluated using the NRS, based on the worst pain experienced during the preceding week (0 = no pain, 1–3 = mild, 4–7 = moderate, 8–10 = severe). Patients were also asked to indicate the location of pain, categorized as chest wound, leg wound, or both.

Secondary outcomes included acute postoperative pain, incidence and duration of postoperative delirium, and quality of recovery. Acute pain was assessed daily at 9:00 to 12:00 a.m. on POD 1–3, 5, and 7 prior to electrical stimulation intervention. Patients rated the worst pain intensity experienced within the past 24 hours using the NRS. Those still intubated at the time of assessment were considered lost to follow-up. The time-weighted average (TWA) pain score was calculated to evaluate overall acute postoperative pain. Delirium was screened once daily from POD 1 to 7 at 9:00 to 12:00 a.m. using the Confusion Assessment Method (CAM),[29] and the number of days with delirium was recorded. Quality of recovery was evaluated on POD 7 using the Quality of Recovery-15 questionnaire (QoR-15),[30] which yields a score ranging from 0 to 150, with higher scores indicating better recovery. Additional secondary outcomes included postoperative analgesic consumption, postoperative complications, transfusion of blood products, time to tracheal extubation, length of ICU stay, and postoperative day 1 inflammatory markers (IL-6, IL-1β, and TNF-α). All these data were obtained from electronic medical records.

Statistical Analysis

Assuming no interaction between taVNS and ropivacaine PIFB and that their effects are independent, the sample size was calculated using a factorial design without interaction. Based on a preliminary pilot study, for taVNS as the main effect, the incidence of CPSP was 25.0% (3/12) in the taVNS group and 40.0% (6/15) in the sham taVNS group. For ropivacaine PIFB as the main effect, the incidence of CPSP was 23.1% (3/13) in the ropivacaine PIFB group and 42.9% (6/14) in the placebo PIFB group. Setting $\alpha = 0.05$, power = 0.8, and accounting for a 5% loss to follow-up, a total of 278 patients were required. Therefore, we planned to enroll 280 patients, with 70 patients per group. Sample size calculations were performed using G*Power 3.1.

An intention-to-treat (ITT) analysis was performed including all randomized patients who were allocated intervention, underwent surgery, and completed follow-up for the primary outcome. Baseline and intraoperative characteristics of patients lost to follow-up after surgery were also examined. A logistic regression model was constructed to evaluate the interaction between taVNS and ropivacaine PIFB on the primary outcome. To adjust for potential confounding, covariates including sex, age, BMI, preoperative chronic pain, pain catastrophizing, anxiety, and depression were incorporated. Covariates were selected based on previously reported risk factors and clinical relevance associated with CPSP. In the absence of a significant interaction, the perioperative characteristics and outcomes were analyzed separately according to taVNS and ropivacaine PIFB. Normality of all continuous variables was assessed using histograms and the Shapiro–Wilk test. Normally distributed data are presented as mean ± standard deviation and compared using independent samples t-tests; non-normally distributed data are reported as median [interquartile range] and compared using the Mann–Whitney *U*-test; categorical data are summarized as number (frequency) and compared using Chi-square or Fisher's exact tests.

Additionally, a hierarchical multivariable logistic regression model was developed to identify risk factors for CPSP. The predictors included the two interventions, clinically relevant variables, and those with $P < 0.1$ in the univariate analysis. Three incremental models were constructed: Model 1 adjusted for primary interventions and demographics; Model 2 added

preoperative and intraoperative clinical characteristics; and Model 3 further expanded to include postoperative clinical indicators. The predictive performance of these models was evaluated using Nagelkerke R^2. Exploratory mediation analyses were further conducted to determine whether the effect of taVNS on pain reduction was mediated through secondary outcomes (acute pain and immune response). Separate regression models were specified: linear regression with taVNS as the independent variable and each mediator as the dependent variable, and logistic regression with taVNS and the mediator as independent variables and CPSP as the dependent variable. The "mediation" package in R was employed to estimate total, indirect, and direct effects using nonparametric bootstrapping with 5000 iterations, reported with corresponding 95% confidence intervals (CIs). All models were adjusted for sex, age, BMI, preoperative chronic pain, PCS score, anxiety, depression, intraoperative hypotension and length of ICU stay. Statistical significance was defined as a two-tailed $P < 0.05$. All statistical analyses were conducted using R statistical software (version 4.3.1; The R Foundation for Statistical Computing).

Results

Between September 5, 2024, and June 20, 2025, a total of 665 patients were assessed for eligibility. Of these, 284 eligible participants provided consent and were randomly assigned to 1 of the 4 study groups (Figure 1). One patient did not allocate the PIFB due to ultrasound machine failure, and 2 patients missed one session of taVNS due to dyspnea and insufficient time before anesthesia, respectively. All remaining participants completed 5 sessions of either active or sham taVNS as well as the PIFB intervention. Sixteen patients were withdrawn due to conversion to CPB during surgery, 2 withdrew due to postoperative cerebral infarction, and 8 died during follow-up. Compared with participants who completed the study, those who withdrew had a higher prevalence of preoperative heart failure, longer operative and anesthesia durations, as well as greater intraoperative blood loss and higher transfusion requirements (Supplemental Table 1). Consequently, the ITT population for the primary outcome comprised 260 participants.

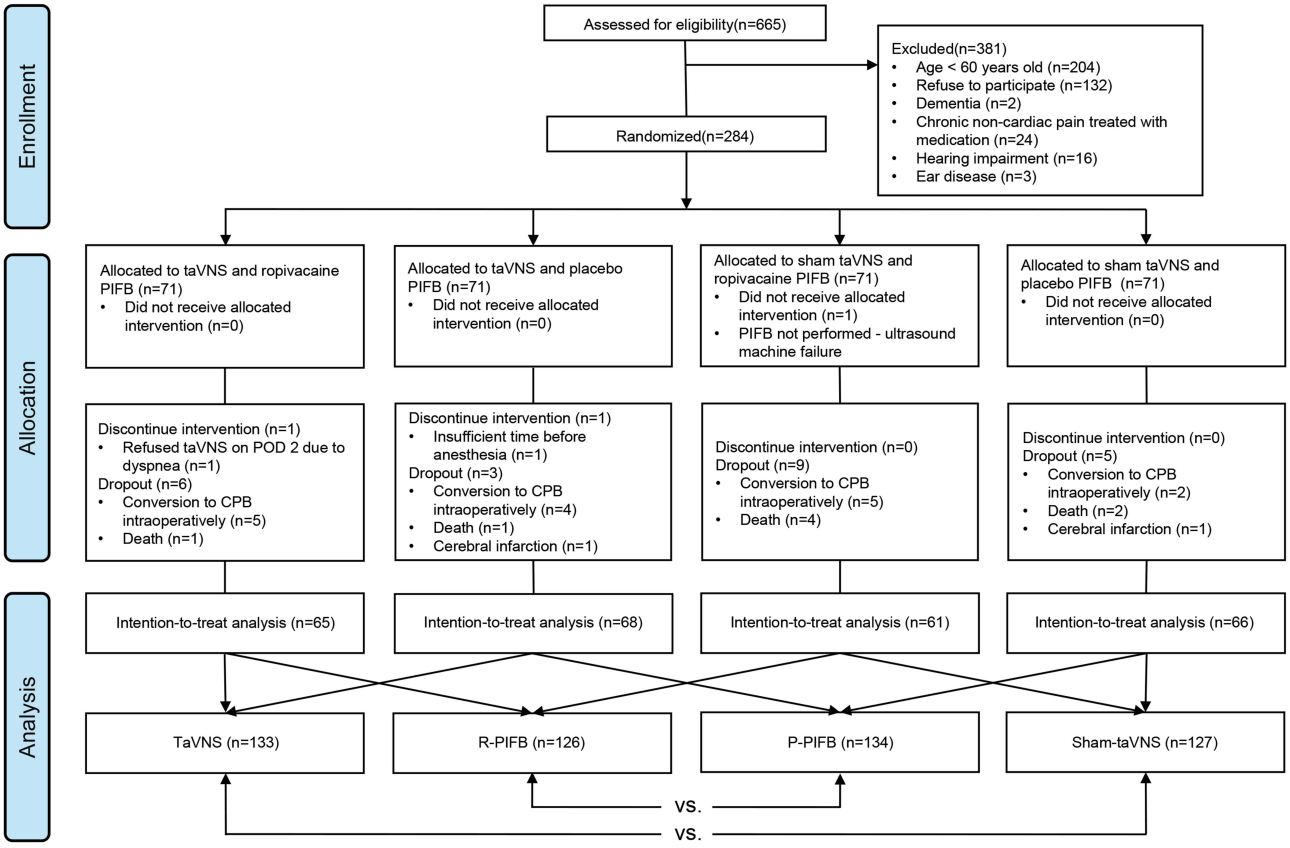

Figure 1 Study Flowchart.
Abbreviations: TaVNS, Transcutaneous Auricular Vagus Nerve Stimulation; PIFB, Pectoral-intercostal Fascial Block; POD, Postoperative Day; CPB, Cardiopulmonary Bypass.

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The participants were predominantly male (72.1%), with a mean age of 66.8 years. Preoperative cardiac pain was reported by 49.5% of participants, while 9.2% reported non-cardiac chronic pain. Logistic regression analysis revealed no statistically significant interaction between taVNS and PIFB ($P = 0.996$) (Table 1), indicating that the effects of the two interventions were independent; therefore, the perioperative characteristics and outcomes were analyzed separately. Baseline and intraoperative characteristics were well-balanced across the groups (Table 2). A comparison of baseline and intraoperative characteristics, including those who withdrew, is provided in Supplemental Table 2.

Primary Outcome

The overall incidence of CPSP was 34.6% (90/260), with the majority of cases occurring at the thorax incision (75.6%, 68/90), followed by the leg incision (5.8%, 15/90), and both sites concurrently (2.7%, 7/90). Approximately one-third of affected patients reported moderate-to-severe pain (36.7%, 33/90). CPSP incidence was significantly lower in the taVNS group compared with the sham-taVNS group (28.6% vs 40.9%, $P = 0.036$), whereas no statistically significant difference was observed between the ropivacaine PIFB and placebo PIFB groups (30.2% vs 38.8%, $P = 0.143$) (Figure 2A and B). No significant difference was observed in the pain locations between the two groups (Figure 2C and D). Notably, a higher proportion of mild pain and a lower proportion of moderate-to-severe pain were observed in the ropivacaine PIFB group compared with the placebo PIFB group ($P = 0.033$) (Figure 2E and F).

Secondary Outcomes

Participants with available pain scores at POD1-3, POD5 and POD7 were 55%, 78%, 93%, 98% and 100%, respectively. The average daily NRS score was calculated for each group to generate acute pain trajectories. Overall, the taVNS and sham-taVNS groups showed comparable patterns, although mean NRS scores were lower in the taVNS group on POD3 (3.37 ± 1.5 vs 3.83 ± 1.6, $P = 0.019$) and POD5 (2.85 ± 1.4 vs 3.27 ± 1.4, $P = 0.017$) (Figure 3A and B). In contrast, the ropivacaine PIFB group showed a significantly lower mean NRS score on POD 1 compared with the placebo PIFB group (3.69 ± 1.8 vs 4.78 ± 2.3, $P = 0.002$). For TWA pain scores, the taVNS group had significantly lower values than the sham taVNS group (3.52 ± 1.33 vs 3.89 ± 1.47, $P = 0.038$), whereas no significant difference was observed between the two PIFB groups (3.60 ± 1.44 vs 3.79 ± 1.37, $P = 0.301$).

Other secondary outcomes showed that although the incidence of delirium did not differ between the taVNS and sham taVNS groups, the duration of delirium was shorter in the taVNS group (2 [2–3] vs 3 [2–4], $P = 0.046$) (Table 3). Regarding postoperative analgesia, there were no significant differences in the categories of postoperative analgesics, total MEC, or the dosage of rescue morphine when comparing the taVNS and sham taVNS groups, as well as the ropivacaine PIFB and placebo groups. However, the frequency of supplemental morphine injections was significantly

Table 1 The Interaction Effects and Main Effects of TaVNS and PIFB

	Coefficient	SE	*P*	OR	95% CI
Interaction effects[a]					
TaVNS × PIFB	0.03	0.59	0.996	1.03	0.32–3.24
Main effects[b]					
TaVNS	−0.71	0.30	0.016	0.49	0.28–0.87
PIFB	−0.32	0.28	0.275	0.73	0.41–1.29

Notes: A *P* value < 0.05 was considered to indicate statistical significance. [a]Adjusted for taVNS, PIFB, sex, age, body mass index, preoperative chronic pain, pain catastrophizing scale score, anxiety and depression. Omnibus<0.001, R-squared=0.230; [b]Adjusted for sex, age, body mass index, preoperative chronic pain, pain catastrophizing scale score, anxiety and depression. Omnibus<0.001, R-squared=0.230.

Abbreviations: TaVNS, Transcutaneous Auricular Vagus Nerve Stimulation; PIFB, Pectoral-intercostal Fascial Block; SE, Standard Error; OR, Odds Ratio; CI, Confidence Interval.

Table 2 Baseline and Intraoperative Characteristics of 260 Surgical Patients Randomized to TaVNS or Sham taVNS and Ropivacaine PIFB or Placebo PIFB

	TaVNS (n = 133)	Sham taVNS (n = 127)	P value	R-PIFB (n = 126)	P-PIFB (n =134)	P value
Baseline characteristics						
Age, yrs.	67.1 ± 5.2	66.6 ± 5.3	0.430	67.1 ± 5.2	66.6 ± 5.3	0.476
Male	95 (71.4)	93 (73.2)	0.746	92 (73.0)	96 (71.6)	0.805
BMI, kg/m^2	25.7 ± 3.2	25.4 ± 3.0	0.365	25.5 ± 3.2	25.5 ± 3.1	0.993
Education level						
Illiteracy	11 (8.3)	14 (11.0)	0.697	12 (9.5)	13 (9.7)	0.996
Primary school	42 (31.6)	39 (30.7)		41 (32.5)	40 (29.9)	
Middle school	46 (34.6)	37 (29.1)		40 (31.7)	43 (32.1)	
High school and above	34 (25.6)	37 (29.1)		33 (26.2)	38 (28.4)	
Marital status						
Married	120 (90.2)	115 (90.6)	0.929	112 (88.9)	123 (91.8)	0.428
Death of a spouse	13 (9.8)	12 (9.4)		14 (11.1)	11 (8.2)	
Smoking	44 (33.1)	41 (32.3)	0.891	40 (31.7)	45 (33.6)	0.752
Alcoholism	20 (15.0)	13 (10.2)	0.245	13 (10.3)	20 (14.9)	0.265
History of surgery	37 (27.8)	26 (20.5)	0.167	33 (26.2)	30 (22.4)	0.475
EuroSCORE I	6 [5–7]	5 [4–6]	0.102	6 [5–7]	5 [4–6]	0.320
Medical history						
Hypertension	88 (66.2)	87 (68.5)	0.688	87 (69.0)	88 (65.7)	0.641
Diabetes	52 (39.1)	43 (33.9)	0.380	48 (38.1)	47 (35.1)	0.613
After PCI surgery	18 (13.5)	17 (13.4)	0.972	18 (14.3)	17 (12.7)	0.706
Heart failure	8 (6.0)	5 (3.9)	0.442	7 (5.6)	6 (4.5)	0.690
Old myocardial infarction	13 (9.8)	11 (8.7)	0.757	9 (7.1)	15 (11.2)	0.259
Arrhythmia	8 (6.0)	8 (6.3)	0.924	9 (7.1)	7 (5.2)	0.520
Cerebrovascular disease	27 (20.3)	24 (18.9)	0.776	27 (21.4)	24 (17.9)	0.475
Hypothyroidism	3 (2.3)	2 (1.6)	0.689	3 (3.4)	2 (1.5)	0.676
Type of medications taken	3 [3–5]	3 [2–5]	0.578	3 [2–5]	4 [3–5]	0.238
Preoperative chronic pain						
Cardiac chronic pain	60 (45.1)	68 (53.5)	0.174	62 (49.2)	66 (49.3)	0.994
Non-cardiac chronic pain	15 (11.3)	10 (7.9)	0.482	13 (10.3)	12 (9.0)	0.869
PCS score	9 [5–19]	10 [4–16]	0.769	8 [4–17]	11 [5–18]	0.362
Anxiety[a]	35 (26.3)	34 (26.8)	0.934	32 (25.4)	37 (27.6)	0.686
Depression[b]	29 (21.8)	25 (19.7)	0.674	25 (19.8)	29 (21.6)	0.721
MMSE score	25 [22–27]	26 [23–28]	0.115	25 [22–27]	26 [22–27]	0.389
PSQI score	5 [3–8]	5 [3–8]	0.939	5 [3–8]	5 [4–8]	0.610
Intraoperative characteristics						
Number of vascular grafts	3 [3–4]	3 [3–4]	0.496	3 [3–4]	3 [3–4]	0.730
Operation time, min	255 ± 45	260 ± 47	0.359	255 ± 45	260 ± 47	0.454
Anesthesia time, min	314 ± 50	320 ± 50	0.303	317 ± 48	317 ± 53	0.940
Hypotension[c]	42 (31.6)	35 (27.6)	0.478	31 (24.6)	46 (34.3)	0.114
Hypothermia[d]	12 (9.0)	16 (12.6)	0.352	9 (7.1)	19 (14.2)	0.103
Sufentanil consumption, mg	300 [215–445]	310 [200–485]	0.678	295 [188–423]	325 [230–481]	0.113
Blood loss, mL	300 [300–500]	300 [300–400]	0.062	300 [300–500]	300 [300–500]	0.956
Plasma transfusion, mL	400 [200–400]	400 [250–400]	0.964	400 [200–400]	400 [250–400]	0.156

(*Continued*)

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Table 2 (Continued).

	TaVNS (n = 133)	Sham taVNS (n = 127)	P value	R-PIFB (n = 126)	P-PIFB (n =134)	P value
Red cell transfusion, U	0 [0–0]	0 [0–0]	0.311	0 [0–0]	0 [0–0]	0.491
Autotransfusion, mL	300 [250–500]	250 [125–375]	0.171	363 [125–500]	250 [250–375]	0.329

Notes: Data are number (%), mean ± SD, or median [interquartile range]. A *P* value < 0.05 was considered to indicate statistical significance. [a]The Hospital Anxiety and Depression Scale-Anxiety score > 7; [b]The Hospital Anxiety and Depression Scale-Depression score > 7; [c]Intraoperative systolic blood pressure <70 mmHg lasting for more than 15 minutes; [d]Intraoperative body temperature <35.5 °C lasting for more than 15 minutes.

Abbreviations: TaVNS, Transcutaneous Auricular Vagus Nerve Stimulation; PIFB, Pectoral-intercostal Fascial Block; BMI, Body Mass Index; EuroSCORE I, European System for Cardiac Operative Risk Evaluation I; PCI, Percutaneous Coronary Intervention; PCS, Pain Catastrophizing Scale; MMSE, Mini-Mental State Examination; PSQI, the Pittsburgh Sleep Quality Index.

lower in patients who received taVNS (1 [1–2] vs 1 [1–3], $P = 0.041$). Furthermore, the taVNS group achieved higher QoR-15 scores (130 [118–133] vs 118 [117–126], $P = 0.034$), indicating better recovery. In the PIFB groups, the ropivacaine PIFB group received less postoperative albumin transfusion (20 [0–40] vs 40 [20–40], $P = 0.050$). Exploratory analysis of inflammatory markers on POD1 revealed a significant difference in IL-6 between the taVNS and sham-taVNS groups (104.6 ± 89.9 vs 154.2 ± 119.3, $P = 0.002$), whereas no significant differences were detected between the PIFB groups.

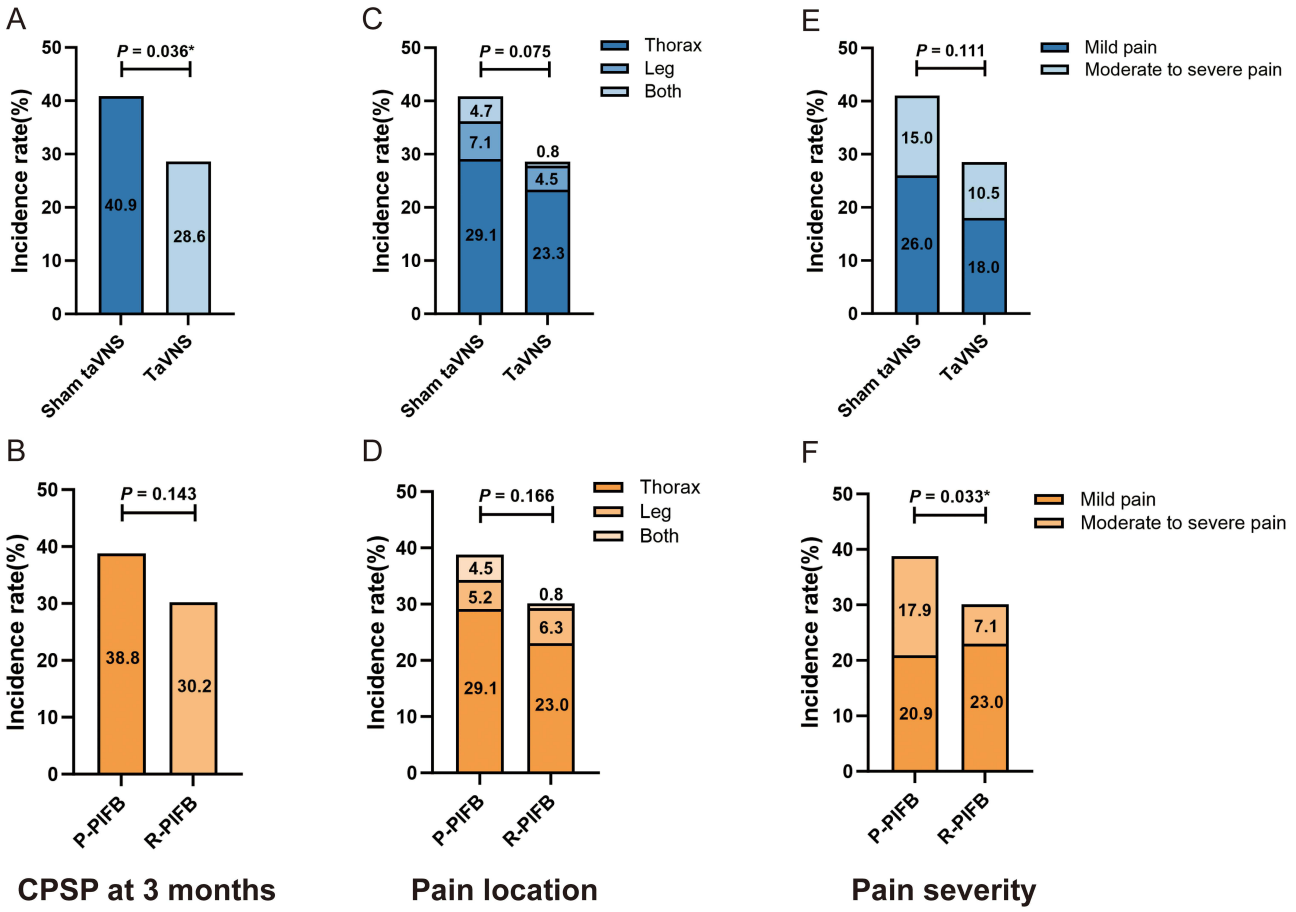

Figure 2 Primary outcomes according to taVNS and PIFB intervention. (**A** and **B**) Incidence rate of chronic pain at 3 months postoperatively; (**C** and **D**) Location of chronic pain; (**E** and **F**) Severity of chronic pain. *P < 0.05.

Abbreviations: TaVNS, Transcutaneous Auricular Vagus Nerve Stimulation; P-PIFB, Placebo Pectoral-intercostal Fascial Block; R-PIFB, Ropivacaine Pectoral-intercostal Fascial Block; CPSP, Chronic Post-surgical Pain.

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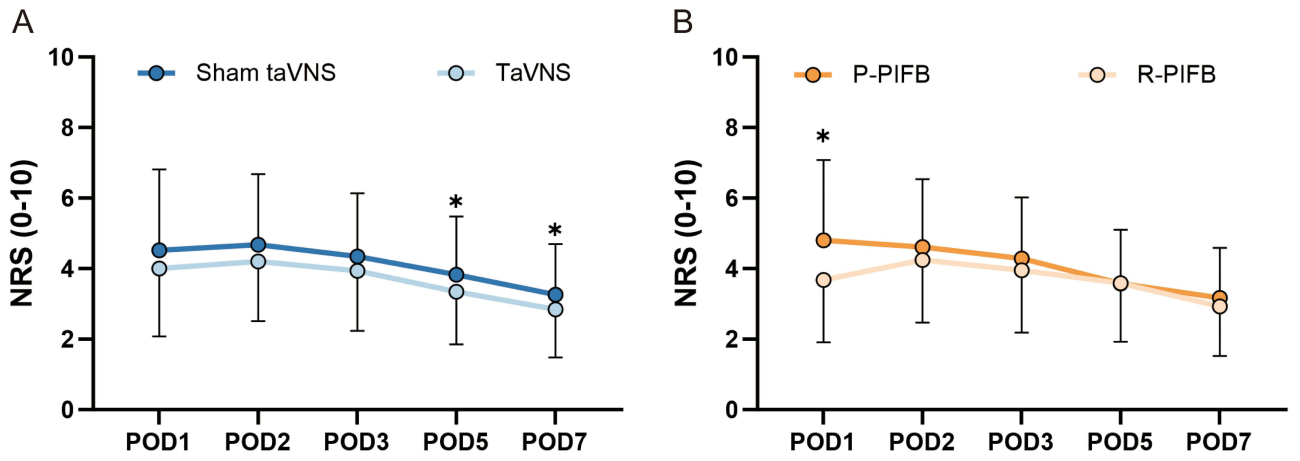

Figure 3 Comparison of postoperative acute pain scores. (**A**) Comparison of taVNS and sham taVNS. The TWA pain score was significantly lower in the TaVNS group compared to the Sham group (3.52 ± 1.33 vs 3.89 ± 1.47, P = 0.038). (**B**) Comparison of ropivacaine PIFB and placebo PIFB. There was no significant difference in TWA pain scores between the two groups (3.60 ± 1.44 vs 3.79 ± 1.37, P = 0.301). *P < 0.05.
Abbreviations: TaVNS, Transcutaneous Auricular Vagus Nerve Stimulation; PIFB, Pectoral-intercostal Fascial Block; TWA, Time-weighted Average; NRS, Numeric Rating Scale; POD, Postoperative Day.

Regression and Mediation Analysis

The results of the univariate analysis and collinearity diagnostics for variables planned for inclusion in the multivariable regression are presented in Supplemental Table 3. Multivariable logistic regression was conducted using a hierarchical approach, and the final model revealed that preoperative anxiety (OR 2.860, 95% CI:1.125–7.267; $P = 0.027$), higher preoperative PCS score (OR 1.089, 95% CI:1.038–1.142; $P < 0.001$), TWA pain score (OR 1.795, 95% CI:1.321–2.438; $P < 0.001$), and elevated IL-6 level on POD1 (OR 1.005, 95% CI:1.001–1.009; $P = 0.010$) were independently associated with an increased risk of CPSP (Table 4). The predictive performance of the models improved consistently, as evidenced by the progressive increase in Nagelkerke R^2 from Model 1 (0.048) to Model 3 (0.417).

Table 3 Secondary Outcomes of 260 Surgical Patients Randomized to TaVNS or Sham taVNS and Ropivacaine PIFB or Placebo PIFB

	TaVNS (n = 133)	Sham taVNS (n = 127)	P value	R-PIFB (n = 126)	P-PIFB (n =134)	P value
Postoperative delirium	44 (33.1)	50 (39.4)	0.292	43 (34.1)	51 (38.1)	0.509
Duration of delirium[a]	2 [2–3]	3 [2–4]	0.046	3 [2–3]	3 [2–3]	0.462
Scheduled Opioid Infusion						
Dezocine	11 (8.3)	11 (8.7)	0.910	8 (6.3)	14 (10.4)	0.235
Pentazocine	30 (22.6)	37 (29.1)	0.225	33 (26.2)	34 (25.4)	0.880
Butorphanol	10 (7.5)	8 (6.3)	0.699	10 (7.9)	8 (6.0)	0.532
Nalbuphine	96 (72.2)	89 (70.1)	0.708	91 (72.2)	94 (70.1)	0.712
Total dose (morphine eqv, mg)[b]	365 ± 153	383 ± 178	0.394	376 ± 169	372 ± 163	0.849
Rescue morphine						
Rate	48 (36.4)	54 (42.5)	0.311	43 (34.1)	59 (44.4)	0.092
Number of injections[c]	1 [1–2]	1 [1–3]	0.041	1 [1–2]	1 [1–2]	0.384
Total dose, mg[c]	11.7 ± 8.0	12.8 ± 8.4	0.490	12.0 ± 8.2	12.5 ± 8.3	0.736

(*Continued*)

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Table 3 (Continued).

	TaVNS (n = 133)	Sham taVNS (n = 127)	P value	R-PIFB (n = 126)	P-PIFB (n =134)	P value
Postoperative complications						
Pneumonia	51 (38.3)	52 (40.9)	0.668	45 (35.7)	58 (43.3)	0.212
Pleural effusion	15 (11.3)	13 (10.2)	0.786	11 (8.7)	17 (12.7)	0.304
Pneumothorax	3 (2.3)	7 (5.5)	0.172	4 (3.2)	6 (4.5)	0.585
Wound infection	1 (0.8)	1 (0.8)	1.000	1 (0.8)	1 (0.8)	1.000
Arrhythmia	26 (19.5)	31 (24.4)	0.344	22 (17.5)	35 (26.1)	0.092
Intra-aortic balloon pump	0 (0)	4 (3.1)	0.056	1 (0.8)	3 (2.3)	0.623
ICU readmission	2 (1.5)	2 (1.6)	1.000	3 (2.4)	1 (0.8)	0.357
Red cell transfusion, U	2 [1–4]	2 [2–5]	0.902	2 [1–4]	2 [2–4]	0.496
Plasma transfusion, mL	550 [400–900]	700 [425–1000]	0.553	450 [400–800]	700 [437–963]	0.835
Albumin infusion, g	20 [20–40]	20 [5–40]	0.826	20 [0–40]	40 [20–40]	0.050
QoR-15 Score	130 [118–133]	118 [117–126]	0.034	122 [118–130]	123 [117–131]	0.864
Time to extubation, h	19 [17–26]	20 [19–43]	0.393	20 [19–39]	19 [18–43]	0.258
Length of ICU stay, h	47 [37–92]	69 [47–96]	0.810	47.5 [40–96]	67 [44–91]	0.646
Inflammatory Factors at POD1[d]						
IL-6, pg/mL	104.6 ± 89.9	154.2 ± 119.3	0.002	127.9 ± 111.0	128.5 ± 105.2	0.970
IL-1β, pg/mL	2.54 ± 1.54	2.58 ± 1.45	0.886	2.45 ± 0.97	2.65 ± 1.81	0.342
TNF-α, pg/mL	1.74 ± 0.56	1.82 ± 0.70	0.370	1.70 ± 0.35	1.85 ± 0.79	0.101

Notes: Data are number (%), mean ± SD, or median [interquartile range]. A *P* value < 0.05 was considered to indicate statistical significance. [a]n=94; [b]Morphine equivalent consumption was calculated: morphine (i.v.) 10mg =dezocine (i.v.) 10 mg=pentazocine (i.v.) 30 mg=butorphanol (i.v.) 2 mg=nalbuphine (i.v.) 10 mg; [c]n=102; [d]n=189.

Abbreviations: TaVNS, Transcutaneous Auricular Vagus Nerve Stimulation; PIFB, Pectoral-intercostal Fascial Block; ICU, Intensive Care Unit; QoR-15, Quality of Recovery-15 Scale; POD, Postoperative Day.

Table 4 Hierarchical Logistic Regression Analysis of Perioperative Related Factors of Chronic Postsurgical Pain

	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)
TaVNS	0.572 (0.339–0.965)*	0.473 (0.263–0.851) *	0.565 (0.260–1.228)
PIFB	0.692 (0.410–1.168)	0.804 (0.451–1.433)	0.793 (0.374–1.678)
Male	0.868 (0.485–1.553)	0.800 (0.418–1.531)	0.865 (0.372–2.009)
Age	0.968 (0.920–1.018)	0.961 (0.908–1.018)	0.973 (0.897–1.056)
BMI	1.042 (0.951–1.142)	1.047 (0.945–1.159)	1.045 (0.922–1.184)
Preoperative cardiac pain		0.816 (0.454–1.464)	1.140 (0.538–2.417)
Preoperative non-cardiac pain		1.424 (0.536–3.785)	1.820 (0.491–6.741)
Preoperative anxiety		1.605 (0.788–3.270)	2.860 (1.125–7.267)*
Preoperative depression		1.074 (0.504–2.290)	2.192 (0.792–6.068)
Preoperative PCS score		1.093 (1.052–1.136)***	1.089 (1.038–1.142)***
Intraoperative hypotension		2.080 (1.109–3.902)*	1.400 (0.619–3.168)
TWA pain score			1.795 (1.321–2.438)***
Length of ICU stay			1.008 (0.997–1.019)
IL-6 at POD1			1.005 (1.001–1.009)**

Notes: Model 1: Adjusted for TaVNS, PIFB, and demographic variables (Male, Age, BMI), Nagelkerke R^2=0.048; Model 2: Adjusted for variables in Model 1 plus preoperative clinical characteristics (Preoperative cardiac/non-cardiac pain, anxiety, depression, and PCS score) and intraoperative hypotension. Nagelkerke R^2=0.253; Model 3: Adjusted for variables in Model 2 plus postoperative clinical markers (TWA pain score, Length of ICU stay, and IL-6 at POD1), Nagelkerke R^2=0.417. *P<0.05, **P<0.01, ***P<0.001.

Abbreviations: OR, Odds Ratio; CI, Confidence Interval; TaVNS, Transcutaneous Auricular Vagus Nerve Stimulation; PIFB, Pectoral-intercostal Fascial Block; BMI, Body Mass Index; PCS, Pain Catastrophizing Scale; TWA, Time-Weighted Average; ICU, Intensive Care Unit; POD, Postoperative Day.

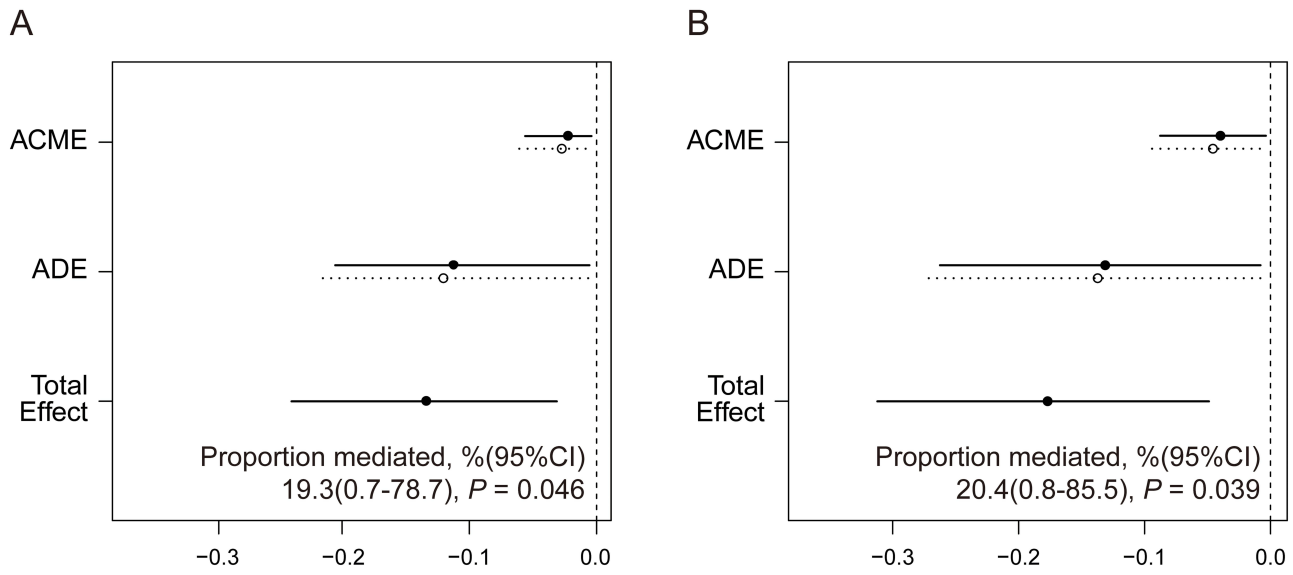

Figure 4 Mediation analysis between taVNS and CPSP. Adjusted for sex, age, body mass index, preoperative chronic pain, pain catastrophizing, anxiety, depression, intraoperative hypotension and length of Intensive Care Unit stay. (**A**) Mediation analysis for TWA pain score; (**B**) Mediation analysis for IL-6 at POD1.
Abbreviations: TaVNS, Transcutaneous Auricular Vagus Nerve Stimulation; PIFB, Pectoral-intercostal Fascial Block; ACME, Average Causal Mediation Effect; ADE, Average Direct Effect; CI, Confidence Interval; TWA, Time-Weighted Average; POD, Postoperative Day.

Mediation analyses demonstrated that both acute pain and immune response were significant mediators in the relationship between taVNS and CPSP (Figure 4 and Supplemental Table 4). The proportion mediated was 19.3% for TWA pain scores (95% CI: 0.7–78.7; $P = 0.046$) and 20.4% for IL-6 levels (95% CI: 0.8–85.5; $P = 0.039$).

Discussion

This randomized, double-blind, factorial trial demonstrated that perioperative taVNS significantly reduced the risk of CPSP at three months in elderly patients undergoing OPCABG. In addition, taVNS alleviated acute postsurgical pain and improved postoperative recovery quality. Although preoperative PIFB did not significantly reduce the overall incidence of chronic pain, it was associated with a lower proportion of moderate-to-severe pain and a reduction in acute pain on POD1. Furthermore, our findings suggest that both acute pain and the acute immune response partially mediate the beneficial effect of taVNS on the development of CPSP. This study represents a significant advancement from our prior observational work.[9] While our previous study identified preoperative psychological factors as prognostic determinants and acute pain as a mediating pathway, the present randomized controlled trial translates these findings into an effective intervention. By demonstrating the causal preventive effect of taVNS on CPSP and revealing its potential mechanism, this study moves beyond risk identification to provide evidence for a feasible, non-invasive preventive strategy.

Consistent with our findings, the efficacy of taVNS in alleviating perioperative pain has been supported by previous studies. A randomized controlled trial in patients undergoing perianal surgery demonstrated that taVNS administered preoperatively and again 24 hours postoperatively effectively reduced pain during the first defecation and decreased the requirement for postoperative opioids.[31] Similarly, in patients undergoing thoracoscopic surgery, continuous intraoperative taVNS was shown to alleviate acute postoperative pain and lower the incidence of chronic pain at three months.[32] Interestingly, consistent with our findings, this study did not observe a reduction in postoperative opioid consumption. This may be related to patients' expectations regarding surgical pain and the standardized postoperative pain management protocol implemented by the surgical team. Although the effects of taVNS on acute postsurgical pain have been extensively investigated, evidence regarding its efficacy in preventing CPSP remains limited. Our study primarily focused on CPSP, and the results obtained through a rigorous trial design provide reliable evidence supporting taVNS as a promising noninvasive neuromodulatory therapy in perioperative pain management.

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PIFB has been recognized as an important strategy for preventing acute postoperative pain. A growing body of evidence indicates that preoperative PIFB reduces postoperative pain scores and opioid consumption. For instance, consistent with our findings, a randomized controlled trial involving 110 elderly patients undergoing OPCABG demonstrated that preoperative PIFB significantly reduced pain scores at 6 hours, 12 hours, and 1 day postoperatively.[33] Furthermore, two additional studies in cardiac and breast surgery confirmed that preoperative PIFB markedly decreased both intraoperative and postoperative opioid requirements.[34,35] Similarly, preoperative PIFB has been considered to exert pre-emptive analgesic effects by blocking nociceptive signal transmission and preventing central sensitization, a critical mechanism underlying the development of CPSP. However, in the present study, PIFB did not demonstrate a preventive effect on CPSP, nor did it show overall efficacy in reducing acute pain beyond the first postoperative day. These findings suggest that a single preoperative block may be insufficient to disrupt the transition from acute to chronic pain. A possible explanation is that the duration of analgesia provided by a single-shot PIFB does not coincide with the critical window of postoperative pain sensitization. A single injection typically offers approximately 24 hours of regional analgesia, whereas the intense inflammatory response and nociceptive input triggered by median sternotomy often persist for 72 hours or longer.[36] This transient blockade is insufficient to counteract "hyperalgesic priming," a process where persistent inflammatory mediators, such as pro-inflammatory cytokines and chemokines, continue to sensitize peripheral nociceptors even after the local anesthetic effect has subsided.[37] Once the block resolves, these ongoing nociceptive stimuli may rapidly trigger central sensitization and structural remodeling within the spinal dorsal horn, ultimately contributing to the development of chronic pain. Recent evidence suggests that the use of continuous PIFB in patients undergoing cardiac surgery can provide effective postoperative analgesia for up to 72 hours.[38] Future investigations should explore whether continuous PIFB techniques, repeated blockade, or the use of longer-acting local anesthetics could enhance the durability of analgesia and more effectively mitigate the risk of CPSP.

In this study, preoperative anxiety, pain catastrophizing, higher TWA pain scores, and elevated IL-6 levels were identified as independent risk factors for CPSP. These findings are consistent with previous reports.[6,7,9,39] Psychological factors such as anxiety and catastrophizing may not only amplify pain perception through activate the systemic stress response[40] but also disrupt descending pain modulatory systems,[41] thereby increasing vulnerability to pain chronification. As a key pro-inflammatory cytokine, IL-6 is elevated by the defensive systemic inflammatory response triggered by surgical trauma.[42] This elevation subsequently exacerbates peripheral sensitization and sustains central sensitization, ultimately driving the chronification of pain.[43] Collectively, these findings highlight that effective management of CPSP requires multimodal preventive strategies rather than interventions targeting a single mechanism. An integrative approach should include psychological optimization, aggressive acute pain control, and modulation of the perioperative inflammatory response. Future studies could further refine predictive models by incorporating psychological assessments, biomarker profiles, and acute pain trajectories, thus facilitating the development of individualized interventions.

Our mediation analysis suggests that the synergistic analgesic and anti-inflammatory properties of taVNS may contribute to its long-term protective effect against CPSP, underscoring its potential as a mechanism-based intervention. The transition from acute to chronic pain is a complex, multifactorial process involving a series of functional, structural, and immunological changes within the nervous system. Among these, sustained increases in neuronal excitability leading to central sensitization represent one of the core mechanisms.[19] Our mediation analysis indicates that the protective effect of taVNS against CPSP may depend on coordinated regulation of the nervous and immune systems.[44] On the neural level, taVNS enhances descending pain inhibition,[45] reduces acute nociceptive input, and consequently limits activity-dependent neuroplastic changes in the spinal cord. On the immune level, activation of the cholinergic anti-inflammatory pathway suppresses the systemic release of pro-inflammatory cytokines[46] such as IL-6. Importantly, these two processes are closely interconnected. Intense nociceptive input can aggravate local inflammatory responses, while systemic inflammation lowers the activation threshold of nociceptive neurons, thereby amplifying pain signaling.[19] By concurrently attenuating acute nociceptive transmission and reducing trauma-induced inflammation, taVNS helps prevent the neuroplastic alterations that drive central sensitization, ultimately reducing the risk of transition from acute to chronic pain.

Limitations

This study has several limitations. First, it was conducted at a single center with a uniform surgical approach, which may limit the generalizability of the findings. Future studies are needed to validate these results in more diverse surgical populations. Second, due to real-world constraints, postoperative analgesic regimens could not be fully standardized across all participants. While this may have introduced variability, it also enhances the external validity of our findings by reflecting routine clinical practice. We attempted to account for this by analyzing the main categories of analgesics used. Third, the diagnosis of CPSP was not confirmed by pain specialists, which may have increased the risk of misclassification. Moreover, both psychological symptoms and pain outcomes were assessed through patient self-report. Despite standardized training of follow-up personnel, variability in patients' willingness or ability to accurately disclose their conditions may have introduced unmeasured bias. Finally, follow-up was limited to 3 months postoperatively. Longer-term assessments at 6 or 12 months, or beyond, are essential and warrant further investigation.

Conclusion

In summary, this study demonstrated that perioperative taVNS significantly reduced the incidence of chronic postsurgical pain at three months after OPCABG, while also improving acute pain control, shortening delirium duration, and enhancing overall recovery quality. Although PIFB did not significantly reduce the overall incidence of CPSP, it alleviated early postoperative pain and lowered the proportion of patients experiencing moderate-to-severe pain. Mediation analyses further suggested that the protective effects of taVNS were partly mediated through its analgesic and anti-inflammatory mechanisms. Future multicenter studies with larger sample sizes are warranted to confirm the efficacy of taVNS and to further explore optimized PIFB approaches (eg, continuous blockade or the use of long-acting local anesthetics) in reducing CPSP.

Declarations

An unauthorized version of the Chinese MMSE was used by the study team without permission, however this has now been rectified with PAR. The MMSE is a copyrighted instrument and may not be used or reproduced in whole or in part, in any form or language, or by any means without written permission of PAR (www.parinc.com).

Data Sharing Statement

The datasets supporting the findings of this study are accessible from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

The study protocol complied with the declaration of Helsinki was approved by the Institutional Ethics Committee of the Second Hospital of Hebei Medical University, Shijiazhuang, China. Informed written consent was obtained before the beginning of the baseline tests.

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 that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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