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Effect of Transauricular Vagus Nerve Stimulation on postoperative pain management in Video Assisted Thoracic Surgery: protocol for a randomized controlled clinical trial

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Study protocol

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Posted Date: November 11th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-9650565/v1

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Additional Declarations: No competing interests reported.

Effect of Transauricular Vagus Nerve Stimulation on postoperative pain management in Video Assisted Thoracic Surgery: protocol for a randomized controlled clinical trial

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ABSTRACT

Introduction: Transcutaneous auricular vagus nerve stimulation (taVNS) is a novel pain management technique that has gained popularity in recent years due to its non-invasive nature and ease of operation. Current literature has substantiated its efficacy in managing pain syndromes and chronic pain. However, there is a paucity of evidence regarding its effectiveness in treating acute postoperative pain. This project aims to explore the efficacy of taVNS in postoperative pain management, with a focus on video-assisted thoracic surgery(VATS). Pain scores will be assessed using a visual analogue scale (VAS, 0-100mm) before and after the administration of taVNS, respectively.

Methods: This double-blind, single-center, randomized controlled clinical trial aims to enroll 116 patients (n=58) scheduled to undergo VATS (including segmentectomy and lobectomy) under general anesthesia at Peking Union Medical College Hospital. Participants will be divided into an intervention group (receiving taVNS) and a sham intervention group (receiving sham-taVNS), and will undergo a 1-hour intervention on the first postoperative day. The primary outcome is the pain relief rate, defined as a reduction of 15mm or 30% in the VAS (1-100mm) score immediately before and after the intervention on the first postoperative day. Secondary outcomes include: the proportion of patients with inadequate analgesia within three days after intervention; the difference in VAS scores immediately before and after the intervention on the first postoperative day; the specifics and frequency of additional analgesic measures taken by patients from the first to the third postoperative day after intervention; immediate changes in heart rate variability before and after the intervention, based on time-domain and frequency-domain measurements; the difference in RCSQ scores on the night of surgery and the night after intervention; the incidence of taVNS-related adverse effects within three days after intervention. The follow-up period for this study will be three days after surgery.

Ethics: Ethical approval of this study has been granted by the Ethics Committee of Peking Union Medical College Hospital, Chinese Academy of Medical Sciences. Informed consent will be obtained from all the participants before enrollment.

Trial registration: The trial was registered with ClinicalTrials.gov (registration number: NCT06912399) on March 30, 2025. The registration website is https://register.clinicaltrials.gov.

Key words: taVNS, postoperative pain, VATS, heart rate variability

INTRODUCTION

Background and Rationale

The vagus nerve, a major element of the autonomic nervous system, regulates various physical functions in the human body, including pain, stress, neuronal plasticity, prokinetic effect, anti-inflammatory effect, etc[1]. For its extensive physical functions, VNS has been widely applied in different fields to treat different diseases, including brain diseases like epilepsy and depression, cardiovascular diseases like heart failure, and digestive system diseases[2-5]. Based on the anatomical research, which shows that the auricular branch of the VN (ABVN) is the only branch reaching the body surface, the concept of transcutaneous auricular vagus nerve stimulation (taVNS) has been proposed in the past decade[6]. Theoretically, transcutaneous auricular neuromodulation has a potential role in providing analgesic effects. Possible mechanisms include reducing inflammation, subcortical modulation of locus coeruleus or noradrenergic signaling, activation of serotonergic and endorphinergic analgesic pathways[7]. A recent study found that taVNS is capable of increasing Conditioned Pain Modulation (CPM) , which means a conditioning stimulus on one part of the body can modulate the pain-inducing stimulus on another part of the body[8] in healthy subjects, thus further underpinning the application of taVNS in pain control[9]. A review in 2021 drew a conclusion that taVNS can have a clinically significant influence on pain syndromes based on available evidence. [10]. A systematic review in 2024 indicated that taVNS could be an effective intervention for relieving pain intensity in chronic pain conditions[11]. All of these evidence confirmed the validity of treating pain syndrome with taVNS.

Postoperative pain is a thorny but unavoidable problem after surgery, which is mostly treated by extra opioid use. However, there is increasing evidence of opioid-involved side effects, such as PONV, respiratory depression, and hyperalgesia, undermining the recovery of general anesthesia[12]. As a result, more approaches to postoperative pain management are required. Generally speaking, taVNS has strengths of ease of use, barely any invasiveness, and reduced side effects[13], which allows taVNS to be applied as a supplement to drug treatment for pain syndrome, hence less use of drugs. It deserves the efforts of anaesthesiologists to find its role in today's perioperative multimodal analgesia. To date, however, there exists little evidence for the effectiveness of using taVNS for postoperative pain management. A previous clinical trial found that taVNS exerted a beneficial effect on rebound pain after femoral nerve block in patients undergoing anterior cruciate ligament reconstruction (ACLR). The incidence and duration of rebound pain, the need for postoperative additional analgesics, and the number of complications were reduced at the same time[14]. A randomized controlled trial in the UK demonstrated that taVNS was capable of reducing perioperative pain in patients undergoing surgery for orthopaedic trauma through autonomic modulation, which was quantified with heart rate variability[15]. This evidence implies that taVNS may have a promising future in postoperative pain management.

Thoracic surgery is commonly associated with inescapable surgical injury accompanied by a high level of pain during the postoperative period, which has been demonstrated in a number of studies and scientific literature[16]. VATS has been prevailing in the field of thoracic surgery in recent decades, as well as become a better choice for pulmonary wedge resection and even more complex procedures like pulmonary lobectomy, as a result of its less surgical trauma and lower incidence of postoperative complications[17]. In order to facilitate the observation of pain intensity changes after surgeries as well as the enrollment of participants, we plan to choose VATS as the study subject, which has a considerable postoperative pain and larger patient populations.

Strengths and Limitations

This project employs taVNS, an emerging clinical technique, to explore its application beyond currently established indications. By expanding the scope of taVNS, we introduce this technology into the field of anesthesiology, providing a novel neuromodulation approach for perioperative management.Focusing on non-pharmacological interventions for acute postoperative pain, this study offers new insights into multimodal analgesia, aligning with modern pain management strategies. Specifically, we target postoperative pain in VATS, complementing the Enhanced Recovery After Surgery (ERAS) protocol commonly used in thoracic surgery. In addition, this study incorporated heart rate variability as an objective secondary outcome measure, which has rarely been addressed in other similar studies.

However, this study only includes heart rate variability as an objective indicator, thereby limiting its ability to objectively and comprehensively evaluate the intervention effects. Additionally, this study can not precisely determine the optimal stimulation duration and parameters for achieving the best intervention outcomes. Since only the stimulation duration is standardized, the intervention effects may be influenced by individual differences in stimulation parameters.

METHOD AND ANALYSIS

Study Design

This clinical study is a single-center randomized controlled trial. The groups are (1) the taVNS group and (2) the sham-taVNS group. Eligible participants will be invited to join this clinical trial through phone calls several days before the surgery or visits on the first day of hospitalization by a staff member. Informed consent forms will be required from all participants before enrollment. After participants are sifted for eligibility and all the baseline data and questionnaires are collected, randomization will begin. The patient will undergo surgical treatment within one week after admission, and receive a one-hour intervention therapy between 8 a.m. and 12 a.m. of the first day after the surgery.

This study employed complete randomization. The study coordinator will use computer-generated random numbers to allocate subjects in a 1:1 ratio to either the taVNS group or the sham-taVNS group. The randomization results will be sealed in opaque envelopes. An unblinded staff member will open the envelopes to reveal the group assignments. The intervention will be administered by a trained unblinded personnel.

This study strictly adheres to a double-blind design. To ensure complete confidentiality of group allocation from the anesthesiologists analyzing the data, a dedicated data manager uninvolved in the study's data analysis will be responsible for randomization and group assignment procedures.

Study Sites

This clinical trial will be conducted at Peking Union Medical College Hospital (PUMCH), Beijing, China.

Description of Study Intervention

Given the availability of taVNS devices and compliance of participants, participants enrolled will have a commercial transcutaneous electrical nerve stimulation unit (tVNS501,RISHENA,Changzhou,China) attached to their left outer ear after VATS. The stimulation pulses will target the cymba concha, which is 100% dominated by the auricular branch of the vagus nerve[18]. Stimulation pulses will be 25Hz in frequency according to current clinical research[19], 500μs in pulse width, which has been suggested to be most biologically active[20], with their amplitude increasing to the maximum amount that the patients can tolerate without pain[19].

For the taVNS group, electrical stimulation will be initiated at 0mA and gradually increased until the subject reports a 'tingling' sensation within 20s after the start. Then the current will be reduced to the level just below this certain threshold(0.6-1mA) where the patients will not report an obvious pain, and continue for the time required. For the sham-taVNS group, electrical stimulation will be initiated at 0mA and gradually increase until the subject reports a 'tingling' sensation within 20 seconds after the start, the same as the taVNS group, but then the device will terminate stimulation 15 seconds after discharge. This procedure learns from a previous study[15].

Participants are going to undergo a 1-hour intervention on the first postoperative day. Pain score will be assessed by VAS immediately before and after the administration of taVNS, respectively. During the intervention period, patients will be asked to avoid additional analgesic measures as much as possible. If such measures are necessary, they must be recorded in detail.

The investigators will document any additional analgesic measures taken by the patients within three days after the intervention, including: The name, dosage, and administration method of analgesic medications; Any physical analgesic measures employed. In addition, the following data will be documented: Occurrence of taVNS-related adverse effects; RCSQ (Richard-Campbell Sleep Questionnaire) scores before and after intervention; Ambulatory electrocardiogram (MCDD-01,MCDD-02,Semacare,Shenzhen,China) during the intervention period.

Throughout the intervention period, the researcher responsible for the intervention will stay with the participant at all times to ensure the smooth conduct of the intervention.

Statistical Power and Sample Size

We assume the proportion of achieving pain relief in the taVNS group to be 60%, and 30% in the sham-taVNS group, according to the data in a previous ta-VNS associated clinical trial[15]. 53 subjects per group will provide 90% power to detect MCIDs with a significance of 0.05 (two-tailed) (PASS 15.0, CNSS, UT, USA). Allowing for a 10% dropout, the sample size is determined to be 116 (58 in each group) in this clinical study.

Eligibility Criteria

All interested patients who are going to have Video-assisted Thoracic Surgery (VATS) under general anesthesia will be further assessed for eligibility by our team members through a face-to-face consultation in accordance with the inclusion and exclusion criteria below:

Inclusion criteria:

1. Age ≥18 years;
2. ASA physical status I-III;
3. No prior taVNS treatment;
4. Scheduled for VATS, including segmentectomy and lobectomy;
5. Postoperative VAS score ≥30 mm at any time on the day of surgery;
6. Patient and family members capable of understanding the study protocol and willing to participate

Expected Participant Characteristics

Characteristic	Expected study population	Rationale or considerations
Age	Adults meeting the trial's age eligibility criteria	Defined according to the target surgical population and eligibility criteria
Sex	Male and female	Both sexes will be eligible, subject to the study criteria
Gender	Not separately collected	Gender identity is not currently recorded as a separate variable
Race, ethnicity, and ancestry	Chinese participants; specific ethnicity/ancestry not separately collected	The study is conducted at a single center in China
Socioeconomic status	Not routinely collected	Socioeconomic status was not included in the prespecified data collection plan
Geographic location	China	Single-center trial conducted at Peking Union Medical College Hospital, Beijing, China

Table 1 PRO EDI table: Expected Participant Characteristics

Exclusion criteria:

1. Psychiatric disorders or other conditions impairing cooperation;
2. Chronic use of corticosteroids or opioids
3. Scheduled for bilateral VATS (video-assisted thoracic surgery);
4. History of thoracic surgery;
5. Chronic pain, autoimmune diseases, or persistent infections.

Withdrawal criteria:

1. Patient request;
2. Surgery cancellation or modification resulting in ineligibility；
3. Severe perioperative complications or adverse events;
4. Significant intervention-related adverse effects.

Safety

Based on the traditional belief that VN efferent fibers leading to the heart mostly occur on the right side[21,22], theoretically, it is safer to perform taVNS in the left ear with the intention of avoiding heart-related side effects like palpitations[23]. That is why we decide to attach the taVNS device to the left ear of the participants. Actually, however, right-sided VN stimulation does not come with more adverse events in some studies[24]. Apart from heart-related side effects, tVNS was reported to have common side effects like tingling or pain around the stimulation site, and less common side effects which have been observed in <1% of the study population, including gastrointestinal discomforts, headache, facial drooping, dizziness, vocal hoarseness, and nasopharyngitis [25]. As a result, despite that tVNS has been confirmed safe and well tolerated in systematic reviews[26], the investigators are supposed to bear in mind that studies in this field are far from sufficient. The study team will take full responsibility for any adverse reactions or adverse outcomes resulting from the intervention in this study.

Effect Measures

Within 48 hours after surgery, pain measurement (especially postoperative acute pain) with VAS is validated, subjective, and also well understood by patients[27-29]. As a result, the intensity of pain will be measured by a visual analogue scale (VAS) immediately before and after the intervention. The reason for using VAS(0-100mm) rather than a numerical rating scale (NRS), which is more commonly used in clinical work, is that VAS is favored in studies for its greater accuracy with a range from 1-100mm (compared with 1-10 in NRS).

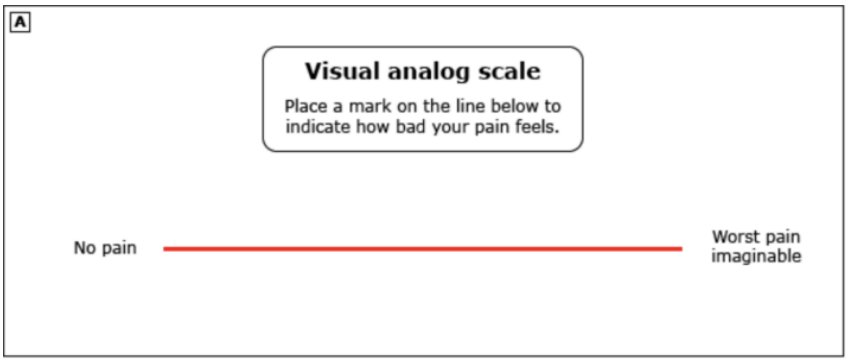


Figure 1 Example of Visual Analog Scale

Primary outcome measure

The primary outcome is the proportion of achieving pain relief. We define VAS decreasing by over 15mm or 30% as achieving pain relief according to median clinician-perceived minimal clinically important differences (MCIDs) on postoperative pain management, which is reported in a previous study[30]. Before taking VAS, all participants are informed of the instructions of VAS, and then they need to draw a line on the scale representing their immediate pain intensity. After the intervention, all participants need to take the VAS again. Then, the difference between the two VAS scores can be calculated to see if this participant fits the standard of achieving pain relief. Then the proportion of achieving pain relief can be calculated.

Secondary outcome measures

Secondary outcomes include:

(1) The proportion of patients with inadequate analgesia within three days after intervention;
Note: “Inadequate analgesia” was defined as meeting at least one of the following criteria: 1) a Visual Analogue Scale (VAS) score of ≥40 mm at any assessment during the three-day post-intervention period; or 2) the requirement for supplemental analgesic medication in the ward due to pain, or the occurrence of ineffective patient-controlled analgesia (PCA) button presses after the intervention.
(2)The difference in VAS scores immediately before and after the intervention on the first postoperative day;
(3)The specifics and frequency of additional analgesic measures taken by patients from the first to the third postoperative day after intervention;
(4)Immediate changes in heart rate variability before and after the intervention, based on time-domain and frequency-domain measurements;
Note: Time-domain measurements of heart rate variability include RR intervals, SDNN (standard deviation of NN intervals, estimating overall heart rate variability), and RMSSD (root mean square of successive differences between normal heartbeats). Frequency-domain measurements include high frequency (HF, reflecting vagal nerve activity) and low frequency (LF, reflecting arterial baroreceptor sensitivity).
(5)The difference in RCSQ scores(measuring sleep disturbance) on the night of surgery and the night after intervention;
(6)The incidence of taVNS-related adverse effects within three days after intervention.

Schedule of Activities

The span of this clinical trial for each participant will not last for more than 4 days with 3-4 individual visits. Details of activities are shown below.

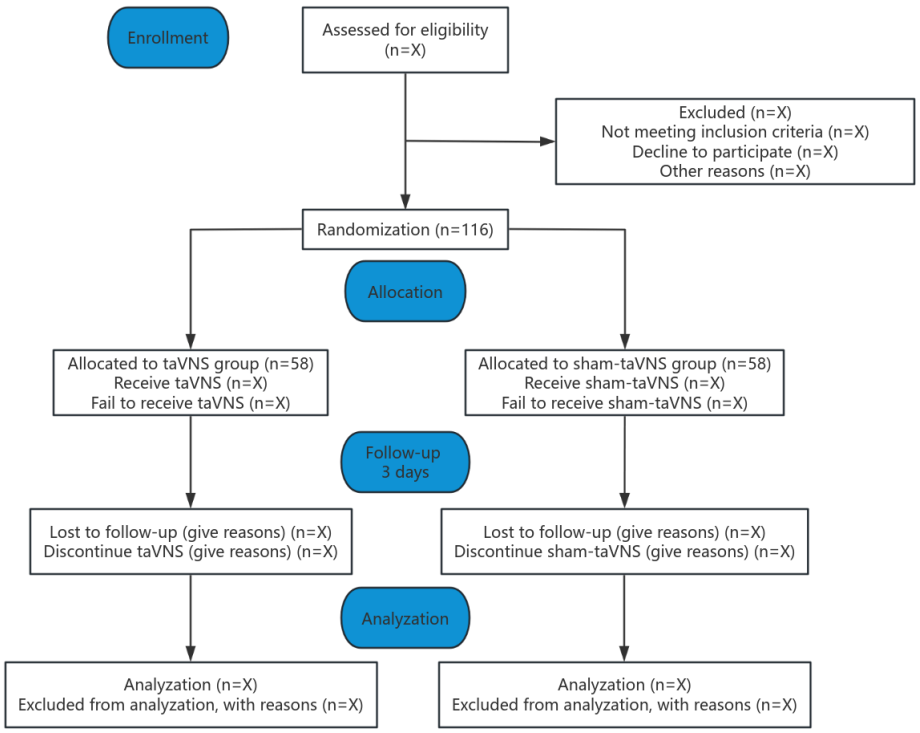


Figure 2 Flow chart over the study procedures.

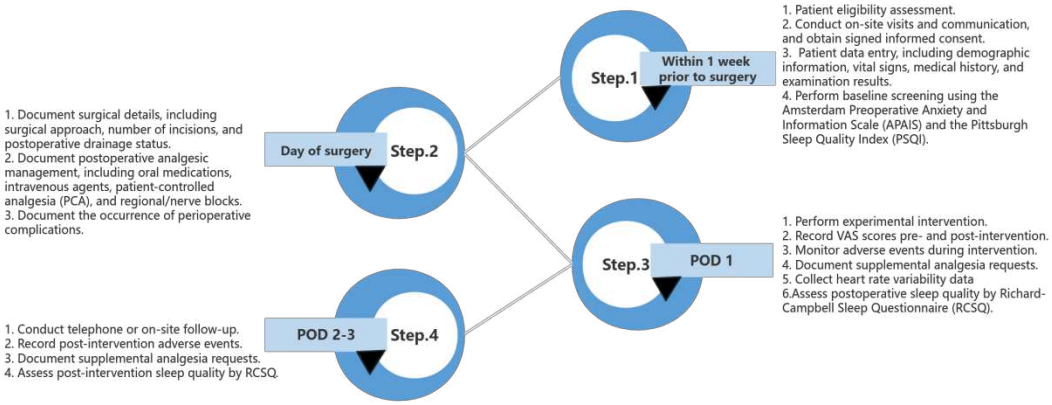


Figure 3 Schedule of activities over the clinical trial.

Participant timeline: Schedule of enrollment, interventions, and assessments.

	TRIAL PERIOD					
	Enrollment			Post-randomization		Close-out
TIMEPOINT	**$-t_7$ to 0**	**$-t_1$**	**0**	**t_1**	**t_2**	**t_2**
ENROLLMENT:						
Eligibility screen	X					
Informed consent	X					
Surgery		X				
Randomization			X			
INTERVENTION/ COMPARATOR:						
TaVNS			X			
Sham-taVNS			X			
ASSESSMENTS:						
[List baseline variables and tests]	X	X	X			
[List outcome variables and tests]			X	X	X	X

Table 2 SPIRIT figure——Participant timeline: Schedule of enrollment, interventions, and assessments.

Data Analysis

In the analyses of group differences (taVNS group and sham-taVNS group), all analyses will be blinded to group allocation. Categorical variables (achieving pain relief or not) in primary outcome analysis will be analyzed by $\chi 2$ test or Fisher's exact test, which will be presented as numbers and percentages in a chi-square table. With regard to baseline and secondary outcome analysis, the Shapiro–Wilk test will be used to test the normality of continuous variables. Then, continuous variables with a normal distribution will be tested by Student's t-test. Those with skewed distribution will be tested by the Mann-Whitney U-test. Results will be reported as reported as mean±standard deviation or median and interquartile ranges (IQR). We assume a P value<0.05 to be considered statistically significant. All the analyses will be assisted by SPSS software version 22.0 (IBM, NY, USA). If a participant withdraws from the study prematurely, only the baseline data and outcome-related data already collected will be included in the statistical analysis.

ETHICS AND DISSEMINATION

This clinical trial shall be conducted according to the SPIRIT statement. The Ethics Committee of Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, has approved the study (K25C0847). This trial has been registered with ClinicalTrials.gov (NCT06912399).

Our team will take advantage of public propaganda in the hospital to boost the impact of our study, thus drawing more potential participants into our study. The results will be submitted to peer-reviewed journals, as well as presented at national or international meetings. Throughout the study, our team will actively cooperate with the cardiothoracic surgery department in PUMCH. The participant data from this study will not be made publicly available. After the study is completed, all study-related participant data will be sealed and stored by the research personnel of this study.

MONITORING

The data monitoring of this study will be undertaken by the corresponding author of this article. The corresponding author will determine the advancement of the study process and the timing of its termination, and will be responsible for the authenticity of the study data and the results. In addition, the progress of this study will be periodically reported to the The Ethics Committee of Peking Union Medical College Hospital, Chinese Academy of Medical Sciences for review.

AUTHOR' CONTRIBUTIONS

All authors are affiliated with Peking Union Medical College Hospital. Tao Xu (first author) was responsible for the study design and manuscript writing; Lu Che (second corresponding author) was responsible for manuscript revision; Li Xu (first corresponding author) was responsible for providing the research concept and financial support.

FUNDING STATEMENT

The funding for this study will be provided by Yichang Humanwell Pharmaceutical Co., Ltd. (China), with project number PUMCHAIIT-2025-06.

COMPETING INTERESTS STATEMENT

There is no conflict of interest between the manufacturers(RISHENA, Semacare) that provide the medical devices and the manufacturer(Yichang Humanwell Pharmaceutical Co., Ltd.) that provides the funding support in this study.

PATIENT AND PUBLIC INVOLVEMENT

Patients or the public will not be involved in the design, or conduct, or reporting, or dissemination plans of our research.

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