Efficacy of transcutaneous auricular vagus nerve stimulation on radiotherapy-related neuropathic pain in patients with head and neck cancers (RELAX): protocol for a multicentre, randomised, double-blind, sham-controlled trial

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ABSTRACT

Introduction Radiotherapy-related neuropathic pain (RRNP) is one of the most distressing complications after radiotherapy for head and neck cancers. Drug therapy is not sufficiently effective and has limitations in terms of dose titration period and side effects. Transcutaneous auricular vagus nerve stimulation (taVNS), which stimulates the auricular branches of the vagus nerve through electrical impulses, has been proven to have analgesic effects in certain diseases. However, it is unknown whether taVNS can relieve RRNP.

Methods and analysis This is a multicentre, randomised, double-blind, parallel, sham-controlled trial. We will include adult patients newly diagnosed with neuropathic pain after radiotherapy for head and neck cancers. One hundred and sixteen individuals will be recruited and randomly assigned in a 1:1 ratio to receive taVNS or sham stimulation. The interventions will last for 7 days, twice daily for 30 min each. The primary efficacy outcome is pain reduction on day 7. The secondary outcomes are changes in functional interference, psychological distress, fatigue, quality of life and serum inflammatory factors. The study may provide a new early intervention strategy for RRNP among patients with head and neck cancers.

Ethics and dissemination This study has been approved by the Medical Research Ethics Committee of Sun Yat-sen University (SYSKY-2022-109-01) and will be conducted in strict accordance with the Declaration of Helsinki. Ethical approvals will be obtained separately for all centres involved in the study. Study results will be published in peer-reviewed academic journals. The database of the study will be available from the corresponding author on reasonable request.

Trial registration number NCT05543239

INTRODUCTION

Pain is a common adverse event after radiotherapy for head and neck cancers1 and can be divided into acute nociceptive pain and chronic neuropathic pain.2 Previous studies have mostly focused on treatment for acute nociceptive pain which is mainly caused by mucositis3 4 while there has been a lack of high-quality studies about chronic neuropathic pain that is difficult to relieve in clinical practice.5 6

Radiotherapy-related neuropathic pain (RRNP) is a severe, long-lasting chronic pain and it is one of the most distressing post-complications from radiotherapy for head and neck cancers. It is a late-onset adverse effect with an onset time ranging from 6 months to 20 years after radiotherapy,6 7 which mainly results from cranial neuralgias, brachial plexopathy and cervical plexopathy.8

Studies have shown that the prevalence of neuropathic pain in patients with cancer pain

⇒ This is the first trial to test the efficacy of transcutaneous auricular vagus nerve stimulation (taVNS) on radiotherapy-related neuropathic pain (RRNP) in patients with head and neck cancers.
⇒ The trial will examine the potential impact of taVNS on emotion, psychology and quality of life of patients with RRNP.
⇒ Since the trial will be conducted in southern China, where the population is mainly Chinese, it may limit the generalisability of the study results for Western countries.
⇒ Given the long follow-up period, this may result in more data loss and may influence some secondary results.
is as high as 31–45%. In addition to the painful feelings, RRNP produces psychological and emotional disturbances that jeopardise quality of life.

There are few effective treatments for RRNP. Previous studies have shown that some analgesics such as amitriptyline, carbamazepine, and non-steroidal anti-inflammatory drugs (NSAIDs) are ineffective for RRNP. Our previous study of pregabalin versus placebo in the treatment of RRNP showed that patients in the pregabalin group have better pain intensity reduction than those in the placebo group, which is the only randomised controlled trial currently available for the treatment of RRNP for head and neck cancers. However, 41.6% of patients still failed to achieve at least 30% pain relief even with standard doses of pregabalin, and the use of pregabalin requires a dose titration process and some side effects such as dizziness, limb oedema and obesity may also follow. Moreover, previous studies have shown that more than 60% of chronic pain patients report inadequate pain control with drug therapy. Therefore, the ideal management strategy for RRNP should not rely solely on medication but should employ a biopsychosocial approach using pharmacological and non-pharmacological interventions.

Vagus nerve stimulation (VNS) has been proven to attenuate systemic inflammatory responses via a unique ‘parasympathetic anti-inflammatory pathway’. Acetylcholine, the principal vagal neurotransmitter, significantly attenuated the release of pro-inflammatory cytokines (tumour necrosis factor (TNF)-α, interleukin (IL)-1β and IL-6) in lipopolysaccharide-stimulated human macrophage cultures. Inflammatory responses, especially inflammatory factors such as TNF-α, IL-1β and IL-6 are proven to be involved in nerve injury and central sensitisation which play an important role in pathological processes of neuropathic pain. It is suggested that VNS may improve chronic neuropathic pain by inhibiting the inflammatory response.

Transcutaneous auricular VNS (taVNS) works by stimulating the auricular branches of the vagus nerve (mainly located in the concha cavity and conchae) through electrical impulses. Previous studies have shown that taVNS can increase the pain threshold in healthy individuals and relieve a variety of pains including migraine, cluster headache and musculoskeletal pain in patients with systemic lupus erythematosus. The taVNS can also improve psychological disorders and fatigue. In addition, it is well tolerated with few adverse events (AE). Existing evidence has suggested a potential application of taVNS in the treatment of RRNP, but a randomised study is still needed to validate it.

Accordingly, we designed this multicentre, randomised, double-blind, parallel-group, sham-controlled trial to evaluate the efficacy of taVNS on RRNP in patients with head and neck cancers.

METHODS

Design

The efficacy of taVNS on RRNP in patients with head and neck cancers (RELAX) study is a multicentre, randomised, double-blind, parallel-group, sham-controlled trial, which will be conducted at four centres of China: Sun Yat-sen Memorial Hospital, Sun Yat-sen University Cancer Center, The Affiliated Brain Hospital of Guangzhou Medical University and The Zhongshan City People’s Hospital. The trial flow chart and the follow-up schedule are shown in figure 1 and table 1, respectively. This protocol follows the Recommendations for Interventional Trials guidelines. A Standard Protocol Items: Recommendations for Interventional Trials checklist is provided in the online supplemental file 1. This trial has been started on 16 September 2022 and is scheduled to end in December 2024.

Participants

Patients with head and neck cancers who meet the following eligible criteria will be recruited: Inclusion criteria

- Male or female patients aged ≥18 years with an estimated survival of at least 5 months.
- Prior radiotherapy for histologically confirmed head and neck cancers ≥6 months prior to study entry (the head and neck cancer is defined as soft tissue tumours or cancer arising from the mucosal surfaces of the lips, oral cavity, pharynx, larynx and cervical oesophagus; the nose, paranasal sinuses, salivary glands, thyroid gland and parathyroid glands).
- Pain for at least 4 weeks with an average intensity of 4 or more on an 11-point Numeric Rating Scale (NRS) in the screening period, and pain locations in accordance with radiated innervated areas, for example, head, face, neck and arms.
- Neuropathic pain is defined according to clinical history, symptoms, physical signs and a score ≥12 in the Chinese version of the Leeds Assessment of Neuropathic Symptoms and Signs questionnaire by two trained and experienced neurology specialists.
- With informed consent.

Exclusion criteria

- Current diagnosis of tumour recurrence or metastasis and evidence of tumour-associated pain.
- Patients with non-radiotherapy induced neuropathic pain; for example, postherpetic neuralgia, diabetes mellitus, HIV infection, spinal cord injury and other neurological disease.
- Use of carbamazepine, gabapentin, pregabalin, taVNS or transcranial magnetic stimulation within the last 30 days prior to study entry.
- Other ongoing treatments for neuropathic pain including antidepressants with norepinephrine and serotonin reuptake inhibition, calcium channel δ2-δ ligands and other anticonvulsant medications, and topical lidocaine.
Concomitant medication that may cause an adverse interaction with pregabalin, including sedatives (e.g., benzodiazepines).

- Significant renal impairment: plasma creatinine >1.5 mg/mL and creatinine clearance <60 mL/min.
- History of anaphylactic response to pregabalin.
- Ulceration of the auricle skin.
- Diagnosis of mental illness, peptic ulcer, atrioventricular III degree block, heart rate <50/min, heart rate corrected QT interval >450 ms.
- Patients with cardiac pacemakers or implanted ECG monitoring equipment.

- Evidence of severe systemic diseases.
- Subjects with any other condition which, in the investigator’s judgement, might interfere the outcome of the study.
- Cognitive function and language skills are insufficient to complete study questionnaires.
- Pregnant or lactating women.

**Withdrawal or drop-out criteria**

Any patient can withdraw at any time for any reason in conditions that they wish to do so without any consequences, and the investigator will ensure that the patient’s...
that the intensity of this treatment method may not be felt and the therapeutic device is placed in an opaque airtight pouch that is invisible to both the clinician and the patient during use. To provide additional assurance that the outcome assessors would not inadvertently uncover a subject's treatment allocation, all participants were reminded not to mention any aspects of the stimulation procedures to the assessors. Case Report Forms containing data relevant to the stimulation were maintained in a separate location. Data analysts will be blinded to the allocated treatment group. Unless emergencies happen, which the investigator considers necessary to conceal the unblinding codes, the randomisation code will be unblinded after the completion of data analysis. Blinding will be monitored by asking participants ‘Do you believe that the taVNS device was functioning properly?’ through a telephone review after the treatment period.

## Intervention
For all participants, after cleaning the skin of the concha with an alcohol pad, electrodes will be placed on the concha of the left ear (figure 2). Stimulation pulses (frequency 30 Hz, pulse width 300 µs) will be generated by a commercial transcutaneous ear VNS device (tVNS 501, Jiangsu, China) (figure 2).

For the taVNS group (Arm A), the amplitude will increase within 30s until the participant develops a tingling sensation and then decrease to the maximum tolerable amount without pain within 15s.

For the sham taVNS group (Arm B), the amplitude will also increase within 30s until the participant develops a tingling sensation, but then decrease to zero stimuli within 15s.

All participants will be informed that the target stimulus has been reached and they may or may not experience any sensations from the stimulation. All patients receive intervention for 30min, twice a day (between 9:00 to 10:00 and 15:00 to 16:00), for seven consecutive days. The device is housed in an opaque bag throughout the treatment.

All enrolled patients will receive a basal dose of pregabalin (75mg two times per day) for analgesia, which was maintained constant during the study intervention.

<table>
<thead>
<tr>
<th>Table 1 Schedule of events and examinations</th>
</tr>
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<tbody>
<tr>
<td>Haemoglobin WBC counting Platelet counting/AST/ALT/ BUN/Cr/ Na+/K+</td>
</tr>
<tr>
<td>Baseline (day 0)</td>
</tr>
<tr>
<td>Day 7</td>
</tr>
<tr>
<td>Telephone review (week 2, 4, 8 and 12±1 day)</td>
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<tr>
<td>Week 1±1 day</td>
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**Note:** WBC, white blood cell; WHOQOL-BREF, brief version of The WHO Quality of Life.
period (7 days). Other treatments for radiation-induced brain injury are allowed and prescribed by trial clinicians after evaluation. Certain medicines are forbidden during the intervention period (eg, antiepileptic medications, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, topical lidocaine and benzodiazepines). During the study, participants are permitted to take rescue drugs (eg, NSAIDs, cyclo-oxygenase-2 inhibitors, acetaminophen and opioids) to alleviate unbearable breakthrough pain.

Treatment adherence
To enhance intervention adherence, researchers will provide free clinical evaluation and taVNS treatment. Telephone interviews will be conducted in the weeks 2, 4, 8 and 12 after the treatment. If the patient missed more than two times (20%) of stimulation, they will be excluded from the per-protocol (PP) analysis.

Outcome assessment
Primary outcome
The primary efficacy outcome is the pain reduction at day 7, measured by the NRS, with which patients evaluated the average pain in the last 24 hours from 0, indicating no pain, to 10, indicating ‘pain as bad as you can imagine’. The use of NRS complies with the recommendations of the Initiative on Methods, Measurement and Pain Assessment in Clinical Trials guidelines.14

Secondary outcomes
All secondary endpoints will be assessed at baseline, day 7 and week 16 by the trained assessors who does not know the group allocation.

The Chinese version of the Brief Pain Inventory-Short Form (BPI-SF)30 is used to assess pain severity and inference, which has been widely used in neuropathic pain.14 31 The pain severity score is assessed as the mean of the four pain items (ie, pain at its worst, least, average and now).32 The functional inference is measured by the BPI Interference in seven items, which include general activity, mood, walking ability, work, social relations, sleep and life enjoyment.

The Chinese version of the short form of the Profile of Mood States (POMS-SF)33 has been recommended as a core outcome measure of emotional functioning in chronic pain clinical trials.14 It is a 30-item scale to evaluate patients’ mood states.

The Chinese version of WHOQOL-BREF34 is a brief version of The WHO quality of life (WHOQOL), which has been widely used in clinical studies on cancer and neuropathic pain.35 36 In the questionnaire, a total of 26 items assess four domains of quality of life.
The Chinese version of the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) is widely used to assess various chronic disease-related fatigue states. It is a self-report scale, with a higher total score representing less fatigue.

The Patient Global Impression of Change (PGIC) is a single-evaluation of the patient’s overall symptom change on a 7-point scale (1=very much improved; 2=much improved; 3=minimally improved; 4=no change; 5=minimally worse; 6=much worse; 7=very much worse). Treatment success is defined as ‘much’ or ‘very much’ improved.

The Clinical Global Impression of Change (CGIC) is a single-item questionnaire that asks the investigator to evaluate the subject’s overall symptom change on a 7-point scale (1=very much improved; 2=much improved; 3=minimally improved; 4=no change; 5=minimally worse; 6=much worse; 7=very much worse). Treatment success is defined as ‘much’ or ‘very much’ improved.

Exploratory outcome
The serum inflammatory factors include TNF-α, IL-1β, IL-6 and IL-10. Whole blood was centrifuged and serum was then stored at −80°C. The inflammatory factors were detected by ELISA in the laboratory. The change in these factors from baseline to day 7 will be calculated to evaluate the potential inflammatory response mechanism of taVNS on RRNP.

Safety evaluation
The record of AE will be conducted from the first electrical stimulation to the end of the trial and then be used to evaluate their potential associations with taVNS by a trained neurologist. The investigator is responsible for the detection and documentation of events meeting the criteria and definitions detailed below. A treatment-emergent AE is defined as any undesirable event that takes place after the first electrical stimulation of the taVNS and prior to the last protocol-arranged contact with the patient. Open-ended and non-leading verbal questioning of the participant will be used to enquire about AE/SAE occurrence. If there is any doubt as to whether a clinical observation is an AE, the event should be recorded. All AE reported by the participants or observed by the investigator or his staff will be recorded in detail. Data on the use of concomitant medications and rescue medications, as well as adherence to the study treatment, defined as taking 80% or more of the full course of taVNS treatment were also collected.

Study procedures
The face-to-face interview will be conducted by an assessor blinded to the intervention at days 0, 7 and week 16 of the regimen. There are three stages for this trial:

► Stage 1. Day 0.

This stage refers to the day between the signing of the consent form and the first taVNS (or sham) treatment. BPI-SF, POMS-SF, FACIT-F, WHOQOL-BERF, and serum inflammatory factors will be assessed as the baseline data.

► Stage 2. Treatment period.

This stage will start from day 1 of this trial, and last for 7 days. At the beginning of this stage, 1:1 randomisation will be carried out to divide patients into taVNS or sham taVNS groups. Patients will receive taVNS or sham taVNS treatment for seven consecutive days. After the last treatment, NRS, BPI-SF, POMS-SF, FACIT-F, WHOQOL-BERF, PGIC, CGIC and serum inflammatory factors will be assessed.

► Stage 3. Follow-up period.

This stage will start from day 8 and continue to week 16 of this trial. During this stage, patients will stop stimulation and perform pregabalin dosage adjustments based on the pain relief with a maximum dosage of four capsules two times per day. The pain and drugs or rehabilitation treatment information during this stage were obtained through telephone review (week 2, 4, 8 and 12). BPI-SF, POMS-SF, FACIT-F, and WHOQOL-BERF, will be assessed on week 16 by face-to-face interview.

Data management and monitoring
The study data will be stored in the researcher’s department at Sun Yat-sen University, which will be responsible for research data monitoring and auditing. The auditing will be conducted annually and independent of investigators and the sponsor. The paper data will be stored in a locked cabinet in the office which is locked when no research personnel is present and the database will be stored in Sun Yat-sen University and be password-protected. Data will be coded once entered into the computer and the file will be password-protected and accessible only by investigators. All private participant data will be coded and protected. When disseminating the results, no individuals will be identified or identifiable.

Sample size
Sample size calculation was based on the primary outcome: the change of score in pain at day 7 assessed by an 11-point NRS. According to our preliminary study of taVNS for RRNP and the previous trial of pregabalin for the treatment of RRNP in patients with head and neck cancers, 52 participants per group will be recruited to have 90% power to detect a between-group difference of 0.9 in the change of score in pain, SD of 1.4 and a one-sided type I error rate of 2.5%. Taking into account an estimated 10% dropout rate, this trial plans to include 116 participants, with 58 participants in each group.

Statistical analysis plan
The data will be presented as mean and SD or median and IQR for continuous variables according to its distribution and numbers with percentages for categorical variables.

The primary analysis will be conducted according to the intention-to-treat (ITT) principle, which will include all patients who were randomised. After the normality test, the Student’s t-test or the Mann-Whitney U test will be used to compare the difference in primary outcome between the two groups. Missing data for the primary outcome will
be imputed with a Markov chain Monte-Carlo multiply imputation approach with the assumption of missing-at-random. Sensitivity analyses using a last observation carried forward imputation as well as the complete case of the ITT population will be performed to evaluate the primary outcome. The PP analysis will also be applied to the primary outcome as another sensitivity analysis. The PP set is defined as ITT patients who completed the study with evidence of receiving ≥80% course of taVNS treatment and no other significant protocol violations.

For secondary outcomes, the absolute rate differences with 95% CIs are calculated for responder status (≥30% pain relief) and treatment success rates for PGIC and CGIC using the Newcombe-Wilson score method and comparison between groups will be performed with the Cochran-Mantel-Haenszel test. For other continuous secondary endpoints, the Student’s t-test or the Mann-Whitney U test will be applied in the ITT and PP set without imputation of missing data. The safety set includes all patients who received at least one electrical stimulation of the taVNS and will be used to compare the safety of treatment. Adverse effects, use of concomitant drugs and rescue drugs are compared between groups using χ² or Fisher’s exact tests.

Furthermore, subgroup analyses will be performed to evaluate the potential relationship between some clinical factors with the outcomes, including the different cancer types, and the use of chemotherapy and corticosteroids, based on the analysis of our previous research. Analysis of variance or linear mixed-effect model will also be used for repeated measurements to evaluate the potential longitudinal trend of efficacy.

Several factors associated with RRNP that might also have an impact, such as radiation-induced brain necrosis, seizure symptoms and dysphagia, these will be reported with the appropriate descriptive methods. Meanwhile, multivariable analyses or subgroup analyses will be conducted to control or identify the potential influence of these variables on the efficacy of the intervention.

Statistical analyses will be performed by independent statisticians who are blinded to the allocation information. All the statistical analyses will be performed using R Project for Statistical Computing V.3.4.2.

Patient and public involvement
No patients or the public are involved in the design, conduct, reporting and dissemination plans of this research.

DISCUSSION
The RELAX study will be the first randomised controlled trial to evaluate the efficacy of taVNS on RRNP among patients with head and neck cancers. In addition, we will explore the potential impact of taVNS on mood, psychology and quality of life in these populations.

Despite the increasing number of studies, there is no clear consensus regarding the optimal parameters that need to be adopted for taVNS research. Moreover, the effects of taVNS in RRNP have yet to be assessed. Our stimulation parameters are based on a published study showing that taVNS can help reduce pain in patients with systemic lupus erythematosus, in which taVNS on concha of the left ear at 30 Hz and 300 µs showed a good analgesic effect. The amplitude was increased to the maximum amount tolerated by the participant without pain and taVNS was well tolerated with few AE attributed to the stimulation.

The duration of taVNS treatment has varied across studies, from 4 days to several weeks, and there has been no research on the effect of taVNS on RRNP treatment so far. According to our previous trial of pregabalin in the treatment of RRNP, pregabalin requires a titration period of 7 days, while the NRS pain score of the experimental group in this period only decreases by 0.62 points, which is far from satisfactory, while rapid dosage increase will bring more side effects. How to reduce the pain intensity within 1 week is a key problem in clinical practice. Therefore, we set 7 days as the trial course and the pain reduction at day 7 as the primary endpoint. Furthermore, previous studies have shown that VNS can reduce inflammation and may have long-term analgesic effects. Therefore, we design 16 weeks as the follow-up endpoint.

For the sham taVNS group, we use the same stimulation pulses as the taVNS group, the amplitude is also increased within 30s until the participant develops a tingling sensation, but then decreases to zero stimuli over 15s. This control strategy is called ‘transient sham stimulation’, based on the previous study showing that the method could facilitate the binding of both participants and investigators to avoid expectation bias and determine the true efficacy of transcutaneous electrical nerve stimulation for use in clinical populations.

Considering the temporal difference in vagal excitability, we give stimuli at 9:00 to 10:00 and 15:00 to 16:00 to minimise the differences in stimulus periods. All stimulation processes are carried out by trained physiotherapists according to the operation protocols to ensure that the patients complete the prescribed course of treatment and that possible side effects are detected timely to improve treatment compliance.

The RELAX trial will be carried out in four centres in China to explore the efficacy of taVNS in the treatment of RRNP among patients with head and neck cancers and may provide a new early intervention strategy for this high-incidence and serious disease.

Limitations
There are some possible study limitations. First, this trial will be conducted only in southern China, where the population is mainly Chinese, due to differences in race, there may be differences in sensitivity to electrical stimulation, which may limit the generalisability of the study results for Western countries. Second, we have set a follow-up period of 16 weeks. A longer follow-up period...
may result in more data loss, which increases the difficulty in the medication management and rehabilitation during the follow-up and may affect some secondary results. However, our team has accumulated experience in follow-up and patient management in our previous study of pregabalin, which will effectively promote participant retention and complete follow-up.

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Contributors

YT and Q-YS conceived and designed the study. XZ and YL drafted the manuscript. XR, XY, YD, and HL contributed to the revision of the manuscript. All authors approved the submission of this manuscript.

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Competing interests

None declared.

Patient and public involvement

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

Patient consent for publication

Informed consent was obtained from all subjects involved in the study.

Provenance and peer review

Not commissioned; externally peer reviewed.

Supplemental material

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