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STUDY PROTOCOL

Effects of Patient-Controlled Transcutaneous Electrical Acupoint Stimulation on Cancer Induced Bone Pain Relief in Patients with Non-Small Cell Lung Cancer: Study Protocol for a Randomized Controlled Trial

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Background: Transcutaneous Electrical Acupoint Stimulation (TEAS) therapy opens up the possibility for individuals with Cancer-induced bone pain (CIBP) to receive a home-based, patient-controlled approach to pain management. The aim of this study is designed to evaluate the efficacy of patient-controlled TEAS (PC-TEAS) for relieving CIBP in patients with non-small cell lung cancer (NSCLC).

Methods/Design: This is a study protocol for a prospective, triple-blind, randomized controlled trial. We anticipate enrolling 188 participants with NSCLC bone metastases who are also using potent opioid analgesics from 4 Chinese medical centers. These participants will be randomly assigned in a 1:1 ratio to either the true PC-TEAS or the sham PC-TEAS group. All participants will receive standard adjuvant oncology therapy. The true group will undergo patient-controlled TEAS intervention as needed, while the sham group will follow the same treatment schedule but with non-conductive gel patches. Each treatment course will span 7 days, with a total of 4 courses administered. There will be 4 assessment time points: baseline, the conclusion of weeks 4, 8, and 12. The primary outcome of this investigation is the response rate of the average pain on the Brief Pain Inventory (BPI) scale at week 4 after treatment. Secondary outcomes include pain related indicators, quality of life scale, mood scales, and routine blood counts on the assessment days. Any adverse events will be promptly addressed and reported if they occur. We will manage trial data using the EDC platform, with a data monitoring committee providing regular quality oversight.

Discussion: PC-TEAS interventions offer an attempt to achieve home-based acupuncture treatment and the feasibility of achieving triple blinding in acupuncture research. This study is designed to provide more rigorous trial evidence for the adjuvant treatment of cancer-related pain by acupuncture and to explore a safe and effective integrative medicine scheme for CIBP.

Trial Registration: ClinicalTrials.gov NCT05730972, registered February 16, 2023.

Keywords: bone cancer pain, TEAS, transcutaneous electrical nerve stimulation, patient-controlled analgesia, integrative medicine, home-based treatment

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Introduction

Cancer-induced bone pain (CIBP) constitutes a significant issue in non-small cell lung cancer (NSCLC). The prevalence of bone metastasis in NSCLC varies from 20% to over 60%,[1–4] with 80% of these patients encountering CIBP.[4,5] Pain stands as one of the most prevalent skeletal-related events of bone metastasis, exerting a detrimental impact on both quality of life (QoL) and performance status.[3] While radiation therapy serves as the foremost recommended standard for alleviating painful bone metastases, its application remains limited to patients with a constrained count of metastases. The conventional therapeutic approach to managing CIBP primarily relies on pharmaceutical intervention. Drawing from adjuvant anticancer therapy and bone-protective treatment, pharmacological analgesic regimens adhere to the World Health Organization (WHO) three-level analgesia ladder, encompassing non-opioid and opioid treatments.[6] Nonetheless, up to 45% of early-stage cancer patients and 75% of advanced cancer patients encounter inadequate pain control at least once.[7] The challenges of opioid-related side effects (such as constipation, nausea, and vomiting) as well as opioid use disorders further complicate the pursuit of optimal cancer pain management.[8–10]

Integrative medicine constitutes a vital aspect of patient-centered care, and the evidence-based fusion of acupuncture and analgesics holds the potential to address unmet needs in cancer pain management. Acupuncture, acupressure, and transcutaneous electrical nerve stimulation (TENS) have all received recommendations for cancer pain management within several evidence-based guidelines, including the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines.[11] Transcutaneous electrical acupoint stimulation (TEAS), which merges acupoint stimulation with TENS therapy, boasts noninvasiveness, quantifiable electrical stimulation, and treatment flexibility in contrast to traditional acupuncture methods. Although the analgesic effect of TEAS has been widely confirmed,[12–15] currently studies involved TEAS treatment on chronic cancer pain management strategies are lacking. There have been researches with small samples proved the effectiveness of TEAS on nonspecific cancer pain,[16,17] and a research involving 159 patients with cancer-related pain treated with chronic opioids was carried out by our group.[18,19] It showed that the 3-week application of TEAS in patients with CRP receiving chronic opioid therapy resulted in a statistically significant reduction in pain scores, but the observed reduction was of uncertain clinical significance. The relevant studies still face challenges including inadequate sample size, suboptimal methodology, and a notable risk of bias.[20] Focusing on specific types of cancer pain can mitigate bias arising from the heterogeneity of cancer types and treatment regimens, and several cases have demonstrated the feasibility of TEAS as a treatment for CIBP,[21,22] so we takes the bone pain associated with non-small cell lung cancer into consideration in the design of this randomized clinical trial. Significantly, the intervention mode was innovated into patient-controlled transcutaneous electrical acupoint stimulation (PC-TEAS), which integrates the advantages of patient-controlled analgesia (PCA) and family therapy, distinguishing itself from the fixed-frequency TEAS treatment in previous studies.

Methods

Objectives

The primary objective of this study was to evaluate the efficacy of PC-TEAS combined with potent morphine in relieving CIBP in patients with NSCLC, aiming to investigate the therapeutic significance of PC-TEAS as an adjuvant therapy for bone metastasis cancer pain. Additionally, the potential advantages of PC-TEAS were comprehensively assessed by observing and comparing changes in daily oral morphine equivalents (OMED), quality-of-life scores, mood scale scores, adverse events, and other indicators among the participants. The goal is to establish a safe, effective, reproducible, and generalizable integrated medicinal acupuncture treatment regimen for the clinical analgesic management of CIBP in NSCLC.

Design

This exploratory study is a multicenter, prospective, triple-blind randomized controlled clinical trial (ClinicalTrials.gov identifier: NCT05730972). In accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) and the Consolidated Standards of Reporting Trials (CONSORT) guidelines and checklists, the study will be conducted in 4 Chinese hospitals: the Third Affiliated Hospital of Zhejiang Chinese Medical University, Sir Run Run Shaw Hospital of the Medical College of Zhejiang University, Zhejiang Cancer Hospital, and Wenzhou Central Hospital. This trial will be conducted in accordance with the Declaration of Helsinki. (Supplement 1: SPIRIT checklist)

Participants and randomization

This study aims to enroll 188 patients with NSCLC bone metastases who are receiving potent opioid analgesia (Figure 1). The enrolment will take place at the Departments of Acupuncture and Oncology in each center. Patients will be identified either at presentation in secondary care or retrospectively via discharge coding, poster adverts or online promotion. The eligible patients will undergo screening based on inclusion and exclusion criteria. They will also receive information

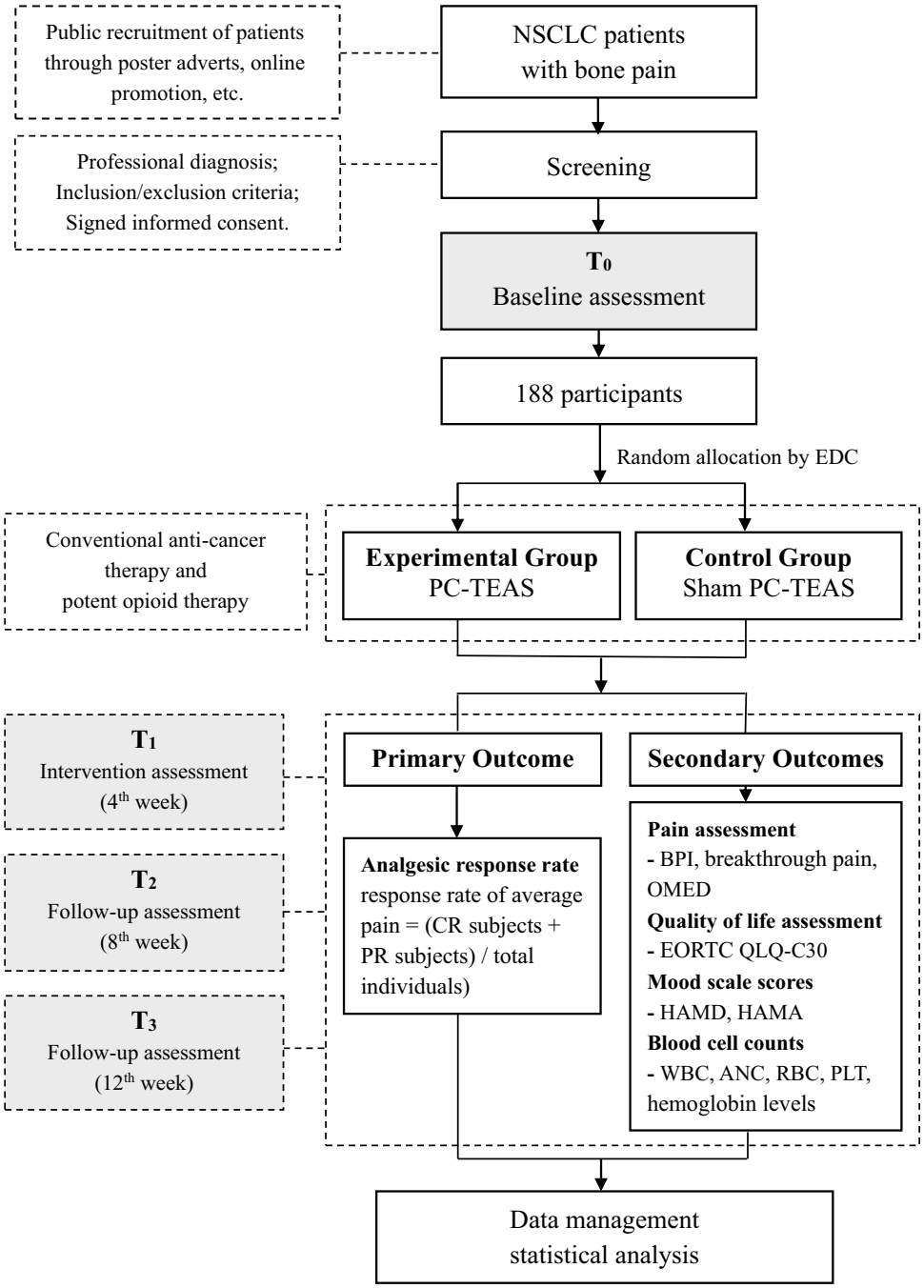

Figure 1 Flow diagram of the randomized clinical trial.

Notes: EDC, refers to the randomization system in the electronic data capture platform; (i. pain score decrease of ≥ 2 and no increase in OMED; ii. pain score no increase and decrease of ≥ 25% in OMED).

Abbreviations: BPI, brief pain inventory; OMED, daily oral morphine equivalents; EORTC QLQ-C30, the European organization for research and treatment of cancer quality of life of cancer patients questionnaire; HAM-D, Hamilton rating scale for depression; HAM-A, Hamilton rating scale for anxiety; WBC, white blood cell count; ANC, absolute neutrophil count; RBC, red blood cell count; PLT, platelet count; CR, complete response (pain score of 0 and no increase in OMED); PR, partial response.

about the trial's overview and their informed consent. Following their consent, baseline data collection on eligible participants will be carried out by data collectors in accordance with the case record form (CRF). Participants eligible for inclusion in the study were required to meet the following diagnostic criteria: ① Primary non-small cell lung cancer (stage I–IV), including adenocarcinoma, squamous cell carcinoma, and large cell carcinoma, was diagnosed pathologically and/or cytologically in accordance with the WHO diagnostic criteria. ② Bone metastases were diagnosed by emission computed tomography (ECT) examinations, or confirmed by bone lesion needle biopsy or cytology. The diagnostic process followed the guidelines provided by *the Expert Consensus in Clinical Diagnosis and Treatment of Bone Metastases and Bone-Related Diseases resulting from Malignant Tumors*. Patients will also need to meet the following inclusion criteria: ① Age between 18 and 80 years, with no gender limitations. ② Having fulfilled the diagnostic criteria and received a definite diagnosis of CIBP. ③ Regular prescription of potent opioid analgesics. ④ Anticipated survival of at least 3 months, with no clear contraindications to opioid therapy. ⑤ Stable vital signs and an ECOG-PS score of 2 points or lower; capability to accurately assess their own pain; willingness to collaborate with investigators to complete study assessments. ⑥ Provision of signed informed consent. The following patients are excluded from being enrolled in this study: ① Patients definitively diagnosed with pain unrelated to lung cancer. ② Patients who received local radiation therapy or surgery targeting bone metastases within 2 weeks before enrolment or will receive such treatment during the intervention period. The surgeries included vertebroplasty, radio-particle implantation, neurological lesions, and other minimally invasive interventions. ③ Patients with venous thrombosis in the upper and lower extremities (below the elbow/knee joint), active cerebrovascular disease, severe cardiopulmonary dysfunction, or respiratory depression. ④ Patients with pacemaker implantation or metallic implants in vivo. ⑤ Patients with skin lesions at the acupoints, poor skin condition, or other situations that are not suitable for treatment with PC-TEAS. ⑥ Patients with opioid hypersensitivity. ⑦ Patients with psychiatric disorders or severe cognitive deficits. ⑧ Patients who participated in other clinical trials that could influence the evaluation of the results of this study. Patients can withdraw or discontinue prematurely from the study for any of the following reasons: ① Active request for withdrawal by subjects. ② Occurrence of serious adverse events during the study. ③ Development of severe complications or deterioration during the study. ④ Severe noncancer pain affecting outcome observation. ⑤ Inability to undergo trial observation.

In alignment with the principles of central randomization and block randomization, a 1:1 randomization using a block size of 4 will be conducted. A total of 188 participants will be randomly assigned to 2 groups: the PC-TEAS and sham PC-TEAS group. This assignment will be carried out using the randomization system integrated into the DAP Electronic Data Capture (EDC) platform. The randomization numbers and specific groupings will be known and managed solely by independent investigators responsible for randomization at the data management center. The EDC platform's randomization system will generate a randomization number for each eligible participant who has given consent. Subsequently, the participant will receive a therapeutic instrument prelabelled with the corresponding randomization number. Two investigators in each research center, with over 3 years of qualification by the practicing physician, will then provide training in the operation of patient-controlled analgesia (PCA) to the participants.

In this triple-blind study, the physicians in charge, investigators, and trial participants (PCA subjects) will be blinded to group allocation. Data collectors, outcome assessors, and statisticians will not be involved in any clinical procedure steps and will not know the specific grouping. Each step of the control group operation (sham PC-TEAS) will be identical to that of the test group, which has a normal screen display but is unable to output current normally. The endpoint adjudication committee, consisting of the principal investigator, a database manager, and a statistician, will adjudicate the locking and unblinding of the database upon the trial's completion. Blinding can be broken prematurely in the event of an emergency, such as the occurrence of a serious adverse event that cannot be judged to be related to the trial operation or not, or if the participant does not adapt to PC-TEAS, requiring emergency discontinuation. Unblinding will be executed by the investigator or physician in charge after obtaining consent from the principal investigator. When unblinding is required prematurely, the randomization manager will perform it, recording the time and reason for the unblinding. And the data monitor will be notified as soon as possible. Once unblinded prematurely, the subject will discontinue participation in the

study, and their trial data will not be used in the efficacy evaluation analysis, although it will still be included in the safety analysis dataset.

Intervention

Patients in both groups will receive routine adjuvant therapy in oncology, including chemotherapy, immunotherapy, targeted therapy, pharmacological analgesia (especially potent opioid analgesia), and nutritional support. This study will employ a patient-controlled TEAS intervention. Participants will be trained in the indiscriminate operation of TEAS by investigators and PCA therapy will be administered on demand at home using the corresponding PC-TEAS instruments.

In the true PC-TEAS group, the distal acupoint group on limbs and the *Jiaji* acupoint group on the trunk will be selected and treated by patient-controlled TEAS based on the painful area. Patients experiencing pain above the navel will have the option of bilateral LI4 (*Hegu*) - TE5 (*Waiguan*) stimulation, along with the corresponding *Jiaji* acupoints in the relevant segments. For patients with pain below the navel, the option of bilateral ST36 (*Zusanli*) - SP6 (*Sanyinjiao*) stimulation and the corresponding segmental *Jiaji* acupoints will be provided. The localization of acupoints will adhere to the 2006 national standards of the People's Republic of China (GB/T12346-2006) for Acupoint Names and Localization. The investigator will determine the spinal cord segment corresponding to the painful area for each participant, following the American Spinal Injury Association (Asia) atlas. Subsequently, the investigator will guide the participant in selecting the appropriate acupoint group and the standardized TEAS operation, ensuring that the patient is able to engage in effective home-based self-management therapy. The investigators are professional acupuncture-moxibustion physicians who had been certified for medical practitioners for more than 3 years. Patients will receive self-controlled treatment as needed, without restrictions on timing and with no upper limit on the number of sessions. However, it is recommended to document the time and frequency of treatments in a pain log.

After routine skin disinfection, the two pairs of electrode patches will be applied to the corresponding *Jiaji* acupoint groups bilaterally, and followed by the bilateral distal acupoint groups (Figure 2). Once the Huatuo® SDZ-IIB portable electroacupuncture therapy instrument, prelabeled with a random number corresponding to each patient, is attached, treatment will commence using a modulated wave at a frequency of 20/100 Hz and a current stimulation intensity within the individual patient's tolerance range. A single session of PC-TEAS treatment is expected to last for 30 minutes. Each course of treatment consists of 7 days, comprising a minimum of 3 days or 5 treatment sessions per course. A total of 4 treatment courses will be administered. Conversely, participants in the control group will undergo the same procedures as those in the true PC-TEAS group. The electroacupuncture apparatus will feature normal screen displays, and the gel patch will have an identical appearance but will be nonconductive, preventing the normal output of current.

To ensure compliance with the treatment, investigators will regularly update the batteries and gel patches, and perform quality checks on the instrument during the treatment period. Additionally, the investigators will promptly contact and instruct participants through telephone, web platforms, or face-to-face interactions to ensure that the subjects can operate the device correctly. SMS reminders will also be sent to patients to prompt them to return for their visit before the follow-up day. After the final quality check of the machine, participants who have completed the full follow-up visit will be provided with a Huatuo® SDZ - IIB portable electroacupuncture therapy instrument.

If a participant experiences breakthrough pain during the trial, immediate opioid rescue doses should be administered promptly, and their administration should be thoroughly documented in the pain log and CRF sheet. Generally, treatment of PC-TEAS will not be discontinued in the case of breakthrough pain. However, in the event of serious adverse events such as primary disease progression, severe skin lesions, or resulting intolerance to ongoing PC-TEAS treatment, the participant will discontinue PC-TEAS treatment when necessary and be unblinded prematurely. Further details can be found in the blinded section of the preceding text.

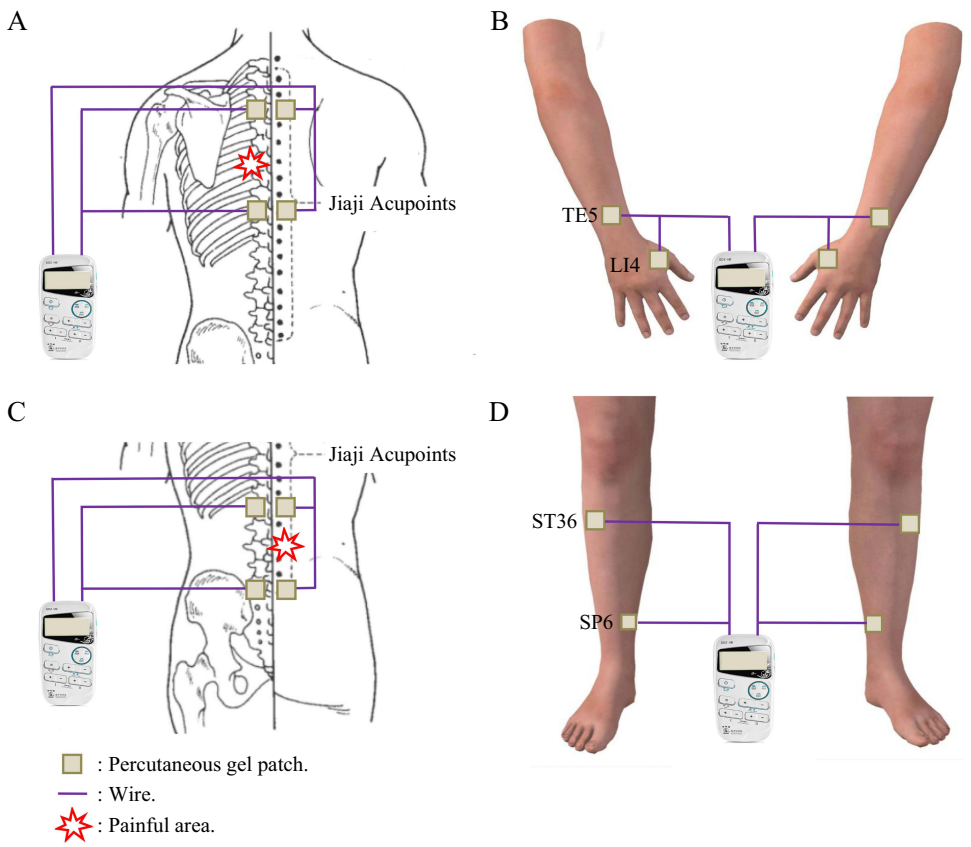

Figure 2 Schematic diagram of transcutaneous electrical acupoint stimulation (TEAS) operation.
Notes: (**A**) and (**B**) Patients with pain in sites above the navel, can be treated with the option of bilateral *Jiaji* acupoint group (cervical / thoracic spine segments) and bilateral upper extremity distal acupoint group (LI4, *Hegu* - TE5, *Waiguan*); (**C** and **D**) Patients with pain below the navel can be treated with the option of bilateral *Jiaji* acupoint group (lumbar segments) and bilateral lower extremity distal acupoint group (ST36, *Zusanli* - SP6, *Sanyinjiao*).

Outcomes and Data Collection

This project consists of four time points (T_0 to T_3) and is presented in Table 1. It has a treatment period of 4 weeks and a follow-up period of 8 weeks, a total of 12 weeks of observation from randomisation. Outcome evaluations will be measured at T_0 baseline (on the day of randomization, which can coincide with the first day of treatment), T_1 after intervention (end of week 4), at T_2 follow-up assessment (1 month after end of treatment), and at T_3 follow-up assessment (2 months after the end of treatment). The population characteristics including gender, age, body mass index, diagnostic results, TNM staging of NSCLC, and specific treatment options, will be collected before treatment.

Primary Outcome

Response rate for average pain on the Brief Pain Inventory - Severity (BPI-S) after 4 weeks of treatment. According to *the International Consensus on Palliative Radiotherapy Endpoints for Future Clinical Trials in Bone Metastases*,[23] the degree of therapeutic response for bone metastatic pain can be classified as follows: complete response (CR, pain score of 0 and no increase in OMED), partial response (PR, i. pain score decrease of ≥ 2 and no increase in OMED; ii. pain score no increase and decrease of ≥ 25% in OMED), pain progression (PP, i. grade ≥ 2 increase in pain score with no decrease in OMED; ii. grade ≥ 1 increase in pain score with ≥ 25% increase in OMED) and indeterminate response (IR, cases not classified as CR/PR/PP). Subjects with CR or PR will be considered pain responders; while subjects whose pain progressed or is indeterminate are non-responders. This trial aims to statistically calculate the rate of average pain responders after treatment to comprehensively evaluate the effect of PC-TEAS adjuvant analgesic treatment.

Table 1 SPIRIT - Phases of Trial and Data Collection

		Study Period					
	TIMEPOINT	**Enrolment**	**Allocation**	**Treatment**		**Follow-Up**	
				T0 / Baseline	**T1 / 4th Week**	**T2 / 8th Week**	**T3 / 12th Week**
ENROLMENT	General characteristics	×					
	Eligibility screen	×					
	Informed consent	×					
	Randomisation		×				
INTERVENTIONS	True PC-TEAS/Sham PC-TEAS[a]			├──────┤			
ASSESSMENTS	Brief pain inventory (BPI)			×	×	×	×
	Daily oral morphine equivalent (OMED)			×	×	×	×
	Frequency of breakthrough pain			×	×	×	×
	European organization for research and treatment of cancer quality of life of cancer patients questionnaire (EORTC QLQ-C30)			×	×	×	×
	Hamilton rating scale for depression (HAM-D)			×	×	×	×
	Hamilton rating scale for anxiety (HAM-A)			×	×	×	×
	Tri-lineage cell counts in blood[b]			×	×	×	×
	Acupuncture expectation assessment			×			
	Blinded assessment				×		
	Safety evaluation				×	×	×
	Compliance assessment				×	×	×

Notes: The baseline condition will be assessed before the TEAS intervention. Results of the treatment phase will be expected to be assessed the day after completion of true PC-TEAS or sham PC-TEAS treatment. The results of the follow-up phase are expected to be evaluated on the last day of each period. ×: Both groups will be implemented. [a] The control group will administered sham TEAS treatment. [b] Blood trilineage cell counts specifically refer to the white blood cell, absolute neutrophil, red blood cell, hemoglobin, and platelet count.

Secondary Outcome

1. The pain intensity of BPI on assessment days (baseline, week 4, 8, and 12).[24] Changes from baseline in average pain intensity, worst pain, least pain, and present pain during the past week will be recorded at each time point. Additionally, the impact of pain on daily functioning, including general activity, walking ability, work performance, sleep, relationships, enjoyment of life, and mood, will also be documented.
2. The frequency of fulminant pain during the past week on assessment days (baseline, week 4, 8, and 12). Note the amount of breakthrough pain at each corresponding time point and document the changes from baseline.
3. OMED on assessment days (baseline, week 4, 8, and 12).[25] The daily oral morphine equivalent dose over the past 24 h will be recorded for both groups at each testing time point. Equivalent morphine dose conversions will be

established in accordance with the NCCN clinical practice guidelines for adult cancer pain (version 3.2022). For instance, fentanyl transdermal patch (25 mcg/h) will be considered approximately equal to oxycodone (30 mg/d), parenteral morphine (20 mg/d), and oral morphine (60 mg/d).

4. The Quality of life measured using EORTC QLQ-C30 scores on assessment days (baseline, week 4, 8, and 12). The European Organization for Research and Treatment of Cancer (EORTC) Quality of Life of Cancer Patients questionnaire (EORTC QLQ-C30, v. 3.0) is a cancer-specific 30-item questionnaire.[26,27] The focus will be on the 5 functional scales, 8 symptom scales, one financial scale, and one global health inventory index scores, as well as changes from baseline in these scales.
5. The mood scale scores of Hamilton Rating Scale for Depression (HAM-D) and Hamilton Rating Scale for Anxiety (HAM-A) on assessment days (baseline, week 4, 8 and 12). HAM-A is one of the most widely used rating scales to measure the severity of perceived anxiety symptoms.[28] HAM-D is a standardized scale for the measurement of the severity of depressive symptoms,[29] initially designed to yield a total score based on 17 of its 21 items.[30] The scores of anxiety/depression and its change during the previous 2 weeks from baseline will be recorded.
6. The trilineage cell counts in blood on assessment days (baseline, week 4, 8 and 12). The white blood cell count, absolute neutrophil count, red blood cell count, haemoglobin level, and platelet count, along with their respective changes, were observed. The data, can be obtained from the routine blood test results of the participants with advanced cancer, will be recorded 3 days before and after the assessment day. And these records will not require the extra collection of biological specimens.

Acupuncture Expectation Assessment and Blinded Assessment

At baseline, the experiences of subjects in both groups who have previously received acupuncture-related treatments will be collected, offering 3 options: “have done”, “not have done”, and “unclear’. with the 3 options of “effective, ineffective, unclear”. This assessment aims to determine whether the previous experience of acupuncture treatment and individual treatment preferences introduce bias to the results. After the treatment concludes, a blinded assessment will be conducted in both groups of patients. Participants will be asked to indicate the group they believe they were assigned to, choosing from “test group”, “control group”, and “unclear.” This will determine the success of the blinding procedure.

Compliance and Safety Assessment

Compliance will be assessed at weeks 4, 8, and 12, to determine whether subjects have completed the treatment steps or follow-up procedures. In case of discontinuation or withdrawal, the specific time and reason will be promptly recorded. PC-TEAS, as a non-invasive treatment, has demonstrated its safety. However, it is important to proactively prevent common adverse events associated with adjuvant anticancer therapy and promptly address them if they occur. In the event of adverse events, the responsible physician and investigator should provide appropriate treatment. The investigator will complete the adverse event record form, note any concomitant medications if necessary, and promptly report to the coordinator at the research center. In the case of a severe adverse event, whether trial-related or not, immediate first aid measures should be taken. The principal investigator-led steering committee must be notified by telephone within 24 h, and they will decide whether to terminate the patient’s clinical trial if necessary. Discontinuation due to serious adverse events should still be followed up, and the endpoint outcome should be documented.

Data Processing and analysis

The CRF form has been developed under the guidance of the steering committee. It comprises various existing classical scales, including the BPI scale, HAM-D, HAM-A, and EORTC QLQ-C30. Data collectors, who are uniformly trained, will gather participant data and complete corresponding paper CRF forms promptly on each assessment day. Subsequently, they will register the information on the EDC platform within 48 hours. The responsibility for data management lies with the data management team, assisted by the DAP EDC platform, ensuring the authenticity, completeness, and accuracy of clinical trial data. Using the EDC platform, status changes will be applied to participants who discontinue or withdraw from the trial midway. All previously collected data, including follow-up visits and specific reasons for withdrawal from the trial, will be fully preserved. The study will be coordinated by a designated coordinator

at each center, with regular quality oversight provided by the data monitoring committee (DMC). At each quality monitoring stage, the site's principal investigator will submit the completed CRF with the participants' initials for the current stage. Personnel from the data management center will perform double data entry based on these CRFs and address any conflicting data through inquiries to the investigators. Following the entry and review of all data, the endpoint adjudication committee will make the final decision regarding trial termination and database locking. Statistical analysis will be conducted by a statistical team not involved in the prior study. They will utilize statistical software such as SPSS 11 and R 2.2, producing a comprehensive written statistical analysis report. Upon completion of the study, the steering committee will prepare a study summary report, encompassing the introduction, research purpose, methods, results, and conclusions. The investigators at each center will sign this report. The principal investigator for the grant will archive both the study summary report and the final dataset. Publication or presentation of the findings in any form requires the express written consent of the principal investigator and cannot be disclosed to unauthorized individuals.

Estimation of Sample Size

Based on the results of our previous study, sample size estimation was performed using PASS 15. We set equal sample sizes for both groups (k=1), checking level α= 0.05 (two-sided), and test efficacy β=80%. The average pain response rate ((number of CR subjects + PR subjects)/total number of individuals) was 45.23% in the true PC-TEAS group after treatment, while the sham PC-TEAS group exhibited a response rate of 24.32%. Considering a dropout rate of 20%, we determined that each of the two groups would require 94 samples, resulting in an expected total of 188 patients. To ensure sufficient participation, we took into account expert opinions and the annual target patient population of each research center in advance. We identified four centers and adopted a patient-controlled manipulation approach, which ensured operational flexibility and enhanced patient compliance.

Statistical Analysis

The statistical team at the Department of Epidemiology and Health Statistics, School of Public Health, Zhejiang Chinese Medical University, will assume responsibility for developing and implementing the Statistical Analysis Plan (SAP) for this trial. Statistical calculations were conducted on the full analysis set population using SPSS 11 and R 4.2.2. Missing data will be addressed through multiple imputation. Measurement data will be presented as either the mean ± SD or the median (interquartile range), and counting data will be expressed as rates or constituent ratios (%). Unless otherwise specified, all hypothesis tests will be two-sided with a significance level of α = 0.05. Between-group comparisons of quantitative data will be carried out using t–tests, analysis of variance (in cases of homogeneity of variance and normal distribution), or Kruskal–Wallis rank sum tests (in situations of non-normal distribution). Qualitative data will be analysed using the chi-square test or Fisher's exact probability method. For hierarchical data, the Kruskal–Wallis rank sum test or CMH test will be employed. Additionally, subgroup analyses will be conducted to explore between-group differences in pain scores among NSCLC patients with specific subtypes or different types of cancer pain.

Validity and reliability

A uniform standard operating procedure (SOP) and an investigator brochure, developed by the steering committee, explain in detail each question in the trial. They also provide explicit wording that should not be used, as it may affect the assessment. For PCA operation training, videos of the operational steps have been recorded. These videos can be repeatedly viewed by investigators and participants for learning purposes. A dedicated training meeting, organized by the steering committee, will be held one month prior to the formal start of the clinical trial. The aim of this meeting is to uniformly train all investigators. The training sessions will primarily focus on the trial protocol and SOPs. Each researcher will be well aware of their division of labor and specific implementing rules, ensuring standardization in all aspects of the trial. The site principal investigators will be responsible for coordinating the trial's progress. They will follow a strict randomization approach and maintain a triple-blind setting. Trial data collection and statistics will be carried out by dedicated data collectors who are not involved in the intervention. They will use telephone and network methods for data collection. The Electronic Data Capture (EDC) platform will be managed specifically by the data management team. To ensure data reliability, double data entry will be employed, along with timely clarification of

questions and answers. Monthly quality monitoring will be rigorously implemented by the DMC to ensure validity and standardization in each trial session. A specialized SAP will be developed by the dedicated statistical team, ensuring the validity of outcome measures and the accuracy of statistical procedures.

Ethics and dissemination

Prior approval from the ethics committee of each center should be obtained before the trial starts. Dissemination and patient recruitment will take the form of posters, websites, etc. All eligible patients will be provided with informed consent to obtain their informed consent and/or to disclose personal and/or health data before inclusion in the trial. To protect participants' privacy, only patient initials will appear on the CRF forms, in statistics, and in shared data. The participant's age will be recorded on the CRF instead of the participants' dates of birth. This study does not involve biological specimens but is required to collect and assess changes in indicators in participants' existing routine blood counts, with the additional terms of consent issued together in the informed consent form. We will regularly check for side effects or adverse effects that may be caused by PC-TEAS treatment and take the necessary precautions. If damage occurs and is identified to be related to this study by the Hangzhou Medical Association, the subject group will provide compensation. Information about this study has been published on ClinicalTrials.gov and the WHO trial registry dataset (https://trialsearch.who.int/Trial2.aspx?TrialID=NCT05730972). The findings will be published in Chinese or English journals and reported on ClinicalTrials.gov.

Roles and responsibilities

This is an investigator-sponsored study. The steering committee is led by the principal investigator, Y.L., and provides theoretical support for this study. The steering committee issues the investigator brochure and operational step videos, offers uniform training for investigators and data collectors, and assumes responsibility for communication and management by other committees. Matters related to the study at each center will be coordinated by personnel at the coordinating center. They will oversee the progress of participant inclusion and take charge of managing patients' adverse events. The endpoint adjudication committee will decide on database lock and the unblinding and unmasking process, among other responsibilities. The data management team primarily consists of staff from the Department of Public and Health at Zhejiang Chinese Medical University. A dedicated individual will be responsible for managing the randomization system, while a data reviewer will perform double data entry to ensure accuracy. An independent DMC, separate from investigators and sponsors, will monitor data authenticity and the standardization of operations at each stage to ensure the clinical trial's quality. The ethics committee will appoint a dedicated person, independent of the investigators and sponsor, to manage funding and conduct semi-annual audits of the trial's progress. The statistical committee will be accountable for creating the SAP, preparing the statistical report, and conducting the statistical analysis of the study's outcomes.

Plans for communicating Important Protocol Amendments to relevant Parties

In case of a significant protocol change, the steering committee will initiate an application, seeking consent that has been approved by the relevant ethics committee. Additionally, other committees, such as the DMC, investigators, and participants, will be duly informed. An updated information response will also be executed on ClinicalTrials.gov.

Discussion

So far, researches on TEAS for treating cancer-related symptoms have mainly focused on postoperative complications[12,31,32] and the effectiveness of TEAS in treating chronic cancer pain is underreported and insufficiently described. Two clinical trials (involving 35 patients) suggested that transcutaneous electrical stimulation exhibits analgesic effect in the management of non-specific cancer-related pain. Our group conducted a randomized clinical trial involving 159 patients with cancer-related pain who were undergoing long-term opioid therapy. The 3-week application of TEAS treatment in the patients resulted in a statistically significant reduction of 0.78 in pain scores, but the observed reduction was of uncertain clinical significance. In order to potential minimize bias resulting from heterogeneity in cancer species and treatment regimens, it is imperative to conduct further investigations into the role

of TEAS within specific cancer subtypes. A case report in 2009 presented that TEAS successfully alleviated BICP in a late-stage cancer patient,[21] and the feasibility of TEAS treatment was demonstrated by a trail recruited 24 participants. Their findings suggested that further work is required on an increased sample size and refining the control arm before evaluating TENS in cancer bone pain.[22] Due to the high incidence of bone metastasis in primary non-small cell lung cancer, reaching approximately 60%, and the majority of patients suffering from cancer-induced bone pain (CIBP),[1–5,33] this randomized controlled trial with larger sample size will focus on patients with NSCLC induced bone pain associated with potent opioid administration. The study design and methodology were also refined in this study, incorporating blinding assessment and the intervention strategy of PC-TEAS. It will conclude the analgesic effect of PC-TEAS more scientifically and is beneficial to explore more effective modes of TEAS intervention.

The TEAS treatment is easily manipulable, and its percutaneous, non-invasive treatment characteristics consider the safety and comfort of patients, while ensuring therapeutic effectiveness. TEAS treatment has few limitations regarding body position, and it does not impact patients' daily lives and activities. Building upon the unique advantages of TEAS treatment and combining the concepts of patient-controlled analgesia (PCA) and home-based physical rehabilitation therapy (HBPT),[34,35] this study introduces an innovative treatment model: patient-controlled TEAS. Participants are instructed by the acupuncturist to select the intervention sites (acupoint groups) and the appropriate parameters. Then, patients or their family members can carry out PC-TEAS therapy, receiving flexible, quantifiable, and effective stimulation. This round-The-clock adjuvant TEAS treatment, different from conventional adjuvant therapy, can be tailored to the analgesic needs of patients with CIBP. It offers timely and adequate analgesic support to patients, easing the strain on physician care and medical resources. Furthermore, home-based treatment represents a growing trend in medicine. PC-TEAS treatment can be administered at home, reducing the transportation and medical care burden on patients while minimizing the need for repeated hospital admissions. Additionally, PC-TEAS therapy benefits cancer patients, particularly those experiencing moderate-to-severe pain and those in terminal stages, by allowing them to live more comfortably in familiar environments, and this enhancement in quality of life is paramount. Taken together, these points demonstrate the feasibility of PC-TEAS as a complementary alternative therapy in the clinical management of CIBP. The PC-TEAS treatment also paves the way for a feasible triple-blinded implementation. Clinical trials involving conventional acupuncture therapies often require interventionists to perform specific manipulations on patients. However, these manipulations almost never allow for the blinding of investigators, potentially leading to some degree of investigator bias. In this trial, a triple-blind approach is employed, ensuring that participants, investigators, and statisticians are all kept unaware of the specific subject groupings. Based on the participants' conditions, the investigators selected acupoint groups in accordance with the treatment protocol and provided consistent operational guidance to the patients. Participants who have received training are capable of administering PC-TEAS therapy on their own, thereby allowing for blinding of the interventionists. Simultaneously, data collectors are not involved in the actual intervention sessions, thus ensuring the objectivity of data acquisition and preventing the transmission of any predisposed opinions to the participants.

This study employed more rigorous planning for outcome measures. The BPI is a pain assessment tool intended for use with cancer patients, structured with two factors (pain intensity and pain interference). The BPI utilizes 0–10 numeric scales, prompting patients to rate their pain at the time of responding to the questionnaire (present pain), as well as its worst, least, and average levels over the previous week. It also inquiries about pain relief, pain quality, and the patient's perception of the underlying cause of the pain. Given that all participants in this study were treated with potent opioid analgesics, the aim is to ascertain whether PC-TEAS demonstrates analgesic effects based on drug analgesia. To achieve this, the response rate will be adopted as the primary outcome in accordance with the international consensus on palliative radiotherapy endpoints in bone metastasis clinical trials. The response rate allows for a comprehensive evaluation of both subjective average pain intensity and the objective equivalent of morphine administration, offering a thorough assessment of the role of palliative treatment. Furthermore, an assessment of other dimensions of pain will be conducted, including the frequency of breakthrough pain, along with changes in the daily oral morphine equivalent. Building upon the reduction in pain scores across BPI dimensions, when necessary, an analysis will be performed to determine the clinical significance of the magnitude of change in pain intensity.[36] Additionally, employing scales like the EORTC QLQ-C30, a multifaceted evaluation of the quality of life, emotions, and other patient situations related to

Cancer-Induced Bone Pain (CIBP) from non-small cell lung cancer (NSCLC) will be conducted. This comprehensive assessment will explore changes in cancer pain-related symptoms, aiming to uncover potential additional therapeutic effects of PC-TEAS.

To the best of our knowledge, it holds significance to discover complementary treatment modalities beyond opioid therapy for the alleviation of CIBP. Such modalities can offer diverse treatment options for integrative medicine and the palliative care of cancer-related pain. We provide a novel regimen for the treatment of CIBP, which combines transcutaneous electrical acupoint stimulation therapy with the concepts of PCA and home-based treatment, with the expectation of achieving better adjuvant analgesic efficacy. We also present a more rigorous protocol for acupuncture randomized controlled clinical trials targeting cancer pain, along with a method to implement blinding in alternative medical studies, such as traditional Chinese medicine. Additionally, the selection of specific electroacupuncture stimulation parameters for further investigation warrants exploration, as does the potential application range of traditional electrical stimulation.

Limitations

First, because PCA participants generally lack a medical background, the standardization of PC-TEAS treatment heavily relies on comprehensive health education and operational training provided by investigators to the participants. Participants are required to record daily pain logs, which also required close follow-up and coaching. Second, for patients who have previously undergone TEAS treatment, distinguishing between sham PC-TEAS treatment and the actual treatment can be easy, potentially leading to a failure in blinding. Third, studies that focus on single cancer tumors with a single type of cancer pain might require more time to complete subject recruitment. Fourth, the primary outcome indicators were designed to be too stringent, and positive results may not occur.

Trial Status

This trial is planned to be implemented from May 2023 to December 2025. Recruitment began on May 16, 2023, and is anticipated to end in December 2025. The study's recruitment phase is currently ongoing. The study is projected to be completed by May 2026, and thus far, 9 participants have been recruited into the study.

Abbreviations

BPI, Brief Pain Inventory; CIBP, Cancer induced bone pain; CR, Complete response; CRF, Case record form; CRP, Cancer-related pain; DMC, Data monitoring committee; ECT, Emission computed tomography; EDC, Electronic Data Capture; EORTC QLQ-C30, The European Organisation for Research and Treatment of Cancer Quality of Life of Cancer Patients Questionnaire; GAD-7, The Generalized Anxiety Disorder; IR, Indeterminate response; NCCN, The National Comprehensive Cancer Network; NSCLC, Non-small cell lung cancer; OMED, Daily oral morphine equivalents; PCA Patient-controlled analgesia; PHQ-9, The Patient Health Questionnaire; PP, Pain progression; PR, Partial response; SAP, Statistical analysis plan; SOP, Standard operation procedure; PC-TEAS, Patient-controlled transcutaneous electrical acupoint stimulation; TENS, Transcutaneous electrical nerve stimulation; WHO, World Health Organization.

Data Sharing Statement

The data generated in this study, including the SAP and the full protocol, is available upon reasonable request. Researchers who wish to request the use of the data, along with a methodologically sound proposal, could be approved for data access by contacting the author Yi Liang via liangyiwww@126.com.

Ethics Approval and Consent to Participate

Approval was granted by the ethics committee of the Third Affiliated Hospital of Zhejiang Chinese Medicine University (No. ZSLL-KY-2021-021-01). Information will be provided verbally and in written form to eligible patients, and if applicable, to their legal guardians. Written informed consent will be acquired from each study participant or their legal guardian. Ongoing consent can be withdrawn at any point during the study.

Consent for Publication

Obtained.

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Disclosure

The authors report no conflicts of interest in this work.

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