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STUDY PROTOCOL

Transcutaneous Electrical Acupoint Stimulation for Opioid Tolerance in Hepatocellular Carcinoma and Proteomics Analysis: A Randomized Controlled Trial Protocol

Zhihui Luo[1,2,*], Huangan Wu[1,2], Jiaxi Pan[1,2,*], Hui-Rong Liu[1,2], Yan Huang[1,2], Hongxiao Xu[1,2], Qingyi Wang[1,2], Luyi Wu[1], Lu Zhu[1,2]

[1]Department of Acupuncture, Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai, People's Republic of China; [2]Shanghai Research Institute of Acupuncture and Meridian, Shanghai University of Traditional Chinese Medicine, Shanghai, People's Republic of China

*These authors contributed equally to this work

Correspondence: Lu Zhu, Shanghai Research Institute of Acupuncture and Meridian, Shanghai University of Traditional Chinese Medicine, No. 650 Wanping South Road, Xuhui District, Shanghai City, 200030, People's Republic of China, Email m15951891067@163.com; Luyi Wu, Department of Acupuncture, Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine, No. 110 Ganhe Road, Hongkou District, Shanghai City, 200437, People's Republic of China, Email luyitcm@163.com

Background: The current method for managing opioid tolerance is opioid rotation, but its effectiveness is limited. Transcutaneous electrical acupoint stimulation (TEAS) combined therapy has been shown to effectively relieve moderate-to-severe pain in patients with hepatocellular carcinoma (HCC), but there is insufficient evidence regarding its role in modulating opioid tolerance. Additionally, exosomal proteomics can aid in exploring the potential mechanisms of action of TEAS.

Methods: This single-center, patient-blinded, randomized controlled clinical trial will enroll 72 participants with moderate-to-severe cancer pain secondary to HCC. Participants will be randomly assigned to the observation group or the control group in a 1:1 ratio. On the basis of conventional Western medical analgesia, the observation group will receive TEAS treatment, while the control group will receive sham TEAS treatment. The treatment course will last for 2 weeks, followed by a 4-week follow-up period. The primary outcome is the opioid tolerance index after the treatment concludes in week 2. It quantitatively reflects the degree of opioid tolerance by measuring changes in opioid consumption over time. Secondary outcomes include the Numerical Rating Scale score, numbers of breakthrough pain, frequency of gastrointestinal side effects, quality of life evaluation, and protein biomarkers.

Conclusion: The expected results will clarify the efficacy of TEAS in alleviating opioid tolerance in patients with moderate-to-severe HCC-related pain. Exosome proteomics can provide exploratory insights into potential mechanisms underlying the efficacy of TEAS.

Ethics and Trial Registration: The Research Ethics Committee of the Yueyang Hospital of Integrated Traditional Chinese and Western Medicine has approved the study protocol (No. 2025–045). The trial has been registered with the International Traditional Medicine Clinical Trial Registry (http://itmctr.ccebtcm.org.cn/). Registration number: ITMCTR2025002162. Registered on June 9, 2025.

Keywords: hepatocellular carcinoma, transcutaneous electrical acupoint stimulation, opioid tolerance, serum exosomes, proteomics

Introduction

Hepatocellular carcinoma (HCC) originates from malignant proliferation of hepatocytes and is closely associated with chronic liver diseases such as hepatitis and cirrhosis.[1] The latest data indicates that there were approximately 860,000 new cases of liver cancer globally in 2022, resulting in over 750,000 deaths, positioning it as the third leading cause of cancer-related mortality worldwide.[2] About 80% of cancer patients experience varying degrees of pain during the course of the

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disease, with nearly one-third reporting severe pain, particularly in those with advanced HCC.[3,4] Tumor overgrowth stretches the liver capsule, stimulating sensory nerve endings distributed throughout the capsule and resulting in persistent dull or distending pain in the hepatic region. Furthermore, chronic inflammation triggered by tumor invasion into surrounding tissues, as well as pathological changes such as localized edema, ischemia, and hypoxia, can activate nociceptors and contribute to pain generation.[5,6] Studies have shown that HCC patients with pain face a reduced survival prognosis, underscoring the importance of adopting any safe and effective therapeutic strategies to alleviate pain in these patients.[7]

According to the World Health Organization (WHO)-recommended "three-tiered analgesic ladder" for cancer pain, opioids are recommended for the management of moderate-to-severe cancer pain.[8,9] Researches have shown that patients with severe cancer pain are prone to developing tolerance to opioid medications, which can subsequently trigger opioid-induced hyperalgesia. This condition forces patients to continuously increase their medication dosage or to rotate their opioid medications to maintain the same analgesic effect.[10,11] It is noteworthy that the liver serves as the primary organ for the opioids biotransformation, and cumulative dose escalation may lead to drug-induced liver injury or even severe complications such as hepatic encephalopathy.[12] Therefore, there is an urgent need in clinical practice to mitigate or control the development of opioid tolerance without affecting the analgesic effects of opioids, thereby improving adherence to anti-tumor therapy.

Transcutaneous electrical acupoint stimulation (TEAS) is a technique that delivers electrical pulses to acupoints through electrodes placed on the skin. Due to its simplicity and safety, TEAS is well accepted among patients. Several studies have reported that patients with advanced pancreatic cancer and postoperative gastric cancer exhibited pain relief evaluated by Visual Analog Scale or Numerical Rating Scale (NRS) scores after receiving TEAS, suggesting that this therapy has potential clinical application value.[13–15] Our previous study suggested that a 7-day TEAS intervention can significantly enhance analgesic effects and maintain for the following week in HCC patients with moderate-to-severe pain.[16] Although existing studies have confirmed the definite analgesic effect of TEAS in cancer pain management, whether this therapy can alleviate opioid tolerance and its underlying mechanisms remain unclear.

Opioid receptor phosphorylation and neuroinflammation are two major factors contributing to opioid tolerance. Mechanistically, phosphorylation modification of opioid receptors induces G-protein uncoupling, facilitates the recruitment of β-arrestins to the receptor sites, thereby mediating opioid receptor desensitization and initiating receptor endocytosis.[17] Under chronic exposure, the number of membrane-bound receptors decreases, thereby reducing drug responsiveness. Microglial activation within the central nervous system constitutes a critical process of neuroinflammation. It can attenuate the analgesic effect of opioids and facilitate the development of opioid tolerance by enhancing the release of IL-1β and activating the NLRP3 inflammasome.[18,19] In this context, circulating serum exosomes, as important mediators of peripheral-central pain and tolerance signaling, reflect systemic neuroendocrine alterations and are closely associated with mechanisms underlying opioid tolerance, including immunomodulation and systemic inflammation,[20,21] rendering them an ideal candidate for investigating the molecular mechanisms of opioid tolerance. Given that proteins constitute the core components of exosomes, proteomics-based strategies enable the systematic identification and quantitative profiling of the full proteome within exosomes, which is expected to provide scientific evidence for the objective evaluation and therapeutic strategy formulation of clinical cancer pain.[22]

Notably, TEAS may exert both specific effects and contextual effects. The ritual of electrode patch application and direct physician involvement may contribute to a certain placebo effect by enhancing patient expectations.[23–25] Therefore, this randomized controlled trial (RCT) has two aims. The primary clinical aim is to evaluate the clinical efficacy of TEAS in alleviating opioid tolerance among HCC patients with moderate-to-severe pain. The secondary mechanistic aim is to perform Label-free quantitative proteomic analysis of serum exosomes, in order to identify potential therapeutic targets underlying the protective effects of TEAS in alleviating opioid tolerance in HCC.

Methods

Study Design

This single-center, patient-blinded, randomized controlled clinical trial will enroll 72 participants aged 50–80 years with moderate-to-severe cancer pain secondary to HCC. Participants will be randomly assigned to the observation group or the

control group in a 1:1 ratio. On the basis of standard cancer pain medication, the observation group will receive TEAS treatment, while the control group will receive sham TEAS treatment, administered once daily, 6 days a week for 2 weeks, followed by a 4-week follow-up period. In accordance with the NCCN Clinical Practice Guidelines for Adult Cancer Pain, opioid therapy will serve as the baseline treatment. The primary outcome is the Opioid Tolerance Index (OTI). Secondary outcomes include the NRS score, numbers of breakthrough pain, frequency of gastrointestinal side effects, quality of life evaluation, and serum exosome proteomics. The study protocol has been developed in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)[26] and its extension (SPIRIT-TCM),[27] and will be implemented following the Consolidated Standards of Reporting Trials (CONSORT) statement.[28] The trial has been registered with the International Traditional Medicine Clinical Trial Registry (ITMCTR, http://itmctr.ccebtcm.org.cn/) under the registration number ITMCTR2025002162. The trial flow chart is presented in Figure 1.

Sample Size

In this study, stratified randomization will be employed for group allocation, with pain intensity serving as the stratification factor. Based on the NRS, participants will be categorized into two strata: moderate pain (NRS score

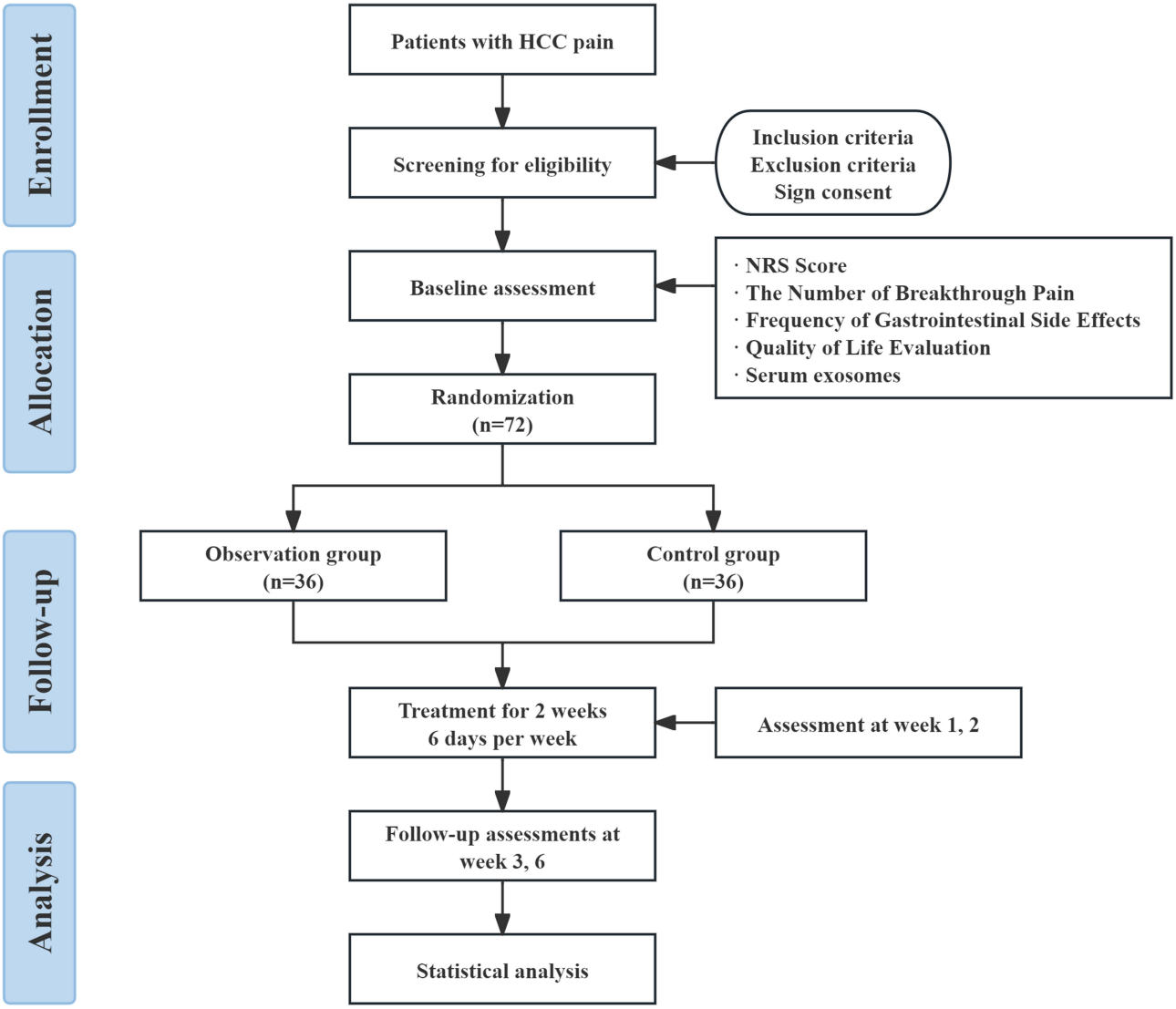

Figure 1 Trial flow chart.
Abbreviations: HCC, Hepatocellular Carcinoma; NRS, Numerical Rating Scale.

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4–6) and severe pain (NRS score 7–10). The sample size was estimated according to preliminary data. The primary outcome is the opioid tolerance index after two weeks of treatment; hence, the sample size calculation was performed using the method for comparing means between two independent groups. The mean opioid tolerance index was 4.8±1.1 in the control group and 3.6±1.1 in the observation group for the moderate pain stratum; for the severe pain stratum, the corresponding mean value was 5.6±1.4 in the control group and 4.2±1.4 in the observation group, respectively. A two-sided significance level of $\alpha = 0.05$ and a statistical power of $1\text{-}\beta = 0.80$ were adopted, with δ representing the expected mean difference between the two groups and σ denoting the standard deviation. The following formula is applied:

$$n = 2\left(Z_{\alpha/2} + Z_{\beta}\right)^2 \times \sigma^2/\delta^2$$

Based on the calculation, 15 participants wii be required per group in the moderate pain stratum, and 14 participants per group in the severe pain stratum, yielding a total of 58 valid samples for both strata combined. Considering an anticipated dropout rate of 20%, a total of 72 participants will be enrolled in this study.

Participants

Randomization and Blinding

Participants eligible for recruitment will be stratified into two groups according to the NRS: moderate pain (NRS score 4–6) and severe pain (NRS score 7–10). For each stratum, random allocation cards will be prepared and sealed in corresponding envelopes. Upon enrollment of eligible participants, the envelopes will be opened sequentially in the order of participant registration to reveal the group assignment, after which the treatment will be initiated.

The allocation results will be concealed from outcome assessors, supervising physicians, data analysts, and participants. However, TEAS operators are not blinded due to the necessity of specialized training for treatment administration. During the treatment sessions, participants will be equipped with standardized blackout eye masks to prevent visual observation of the procedure. Furthermore, to minimize the risk of unblinding resulting from inter-participant communication, participants will either be separated by medical cubicle curtains or assigned to individual rooms for treatment. To assess the success of blinding, within 5 minutes after the second week of treatment, participants will be informed that two therapy were used: one involving TEAS and the other a sham TEAS with a current intensity of 0.5 mA. They will then be asked to answer the question: "Do you believe you received TEAS over the past two weeks?" Responses will be recorded using one of the following options: "Yes", "No", or "Uncertain". All biological samples and datasets will be anonymized before analysis.

Recruitment

This trial, scheduled to be conducted from March 2025 to November 2027, will recruit patients diagnosed with moderate-to-severe cancer pain related to HCC through the WeChat account of Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, posted notices, and other appropriate channels. All participants and their family members will be fully informed of the trial's purpose, procedures, and potential risks. Written informed consent will be obtained from each participant prior to enrollment. All recruitment materials have been approved in advance by the hospital ethics committee (No. 2025–045).

Inclusion Criteria

1. Meeting the diagnostic criteria for HCC;[29]
2. Aged between 50 and 80 years, regardless of gender;
3. Classified as Child-Pugh class A or B;[30]
4. NRS score ≥ 4 within the 24 hours prior to screening;
5. Life expectancy greater than 3 months;
6. Conscious and able to assess their own pain and quality of life;
7. Willing to participate in the study and able to provide signed informed consent.

Exclusion Criteria

1. Patients with other physiological or pathological pain conditions;

2. Patients who had undergone tumor resection within the past 3–6 months;
3. Patients with severe complications, such as persistent ascites, intraperitoneal infection, gastrointestinal hemorrhage, hepatic failure, or intraperitoneal hemorrhage;
4. Patients with severe acute or chronic organic diseases or psychiatric disorders;
5. Patients with contraindications for TEAS, such as local skin lesions at local acupoints, heightened sensitivity to electrical stimulation, or those with cardiac pacemakers or cardiovascular stents;
6. Patients with a previous history of TEAS treatment;
7. Patients scheduled for surgery within the next 2 months.

Interventions

Basic Treatment

According to the WHO-recommended "three-tiered analgesic ladder", moderate cancer pain is managed with tramadol hydrochloride sustained-release tablets (0.1 g orally every 12 hours), while severe cancer pain is treated with morphine hydrochloride sustained-release tablets (10–30 mg orally every 12 hours). The initial dosage is determined based on the severity of the patient's cancer pain and their prior medication history. In cases of breakthrough pain occurring during treatment, morphine injections are administered in the oncology outpatient setting, with the specific dose adjusted according to the patient's NRS score. If a patient requires intervention for breakthrough pain more than three times per day, the dosage of the opioid medication is adjusted upward by 25% to 50% from the previous dose.

Observation Group

The TEAS intervention will be administered using a HANS-200A stimulator (Nanjing Jisheng Medical Technology Co., Ltd., China). Acupoints include bilateral Hegu (LI 4), Taichong (LR 3), Neiguan (PC 6), Zusanli (ST 36), Qimen (LR 14), and Zhangmen (LR 13). Their localization is strictly determined in accordance with the WHO Standard Acupuncture Point Locations guidelines (2008),[31] with detailed location descriptions provided in Table 1 and Figure 2. The patients will be in a supine position and the operator will attach the first pair of aseptic square electrode patches (3 × 3 cm) with the anode and cathode placed at LI 4 and LR 3, respectively. A second pair of electrodes will be positioned with the anode at PC 6 and the cathode at ST 36, and a third pair will be placed with the anode at LR 14 and the cathode at LR 13. The electrodes will then be connected to an electrical stimulator. The stimulator will be turned on and set to a dilatational wave mode (alternating frequencies of 2/100 Hz), with stimulation intensity adjusted to a level deemed comfortable and tolerable by the patient (5–10 mA). Each session will last 30 minutes. Treatments will be conducted once daily, 6 days per week, over a period of 2 weeks. Details will be fully documented in accordance with the Standards for Reporting Interventions in Controlled Trials of Acupuncture (STRICTA).[32]

Control Group

The control group will consist of an identical TEAS procedure as the observation group, with the sole exception of the current intensity, which will be set at 0.5 mA level without therapeutic effect. This specific intensity is selected to

Table 1 Location of Acupoints

Acupoints	Location
Hegu (LI 4)	On the dorsum of the hand, radial to the midpoint of the second metacarpal bone.
Taichong (LR 3)	On the dorsum of the foot, between the first and second metatarsal bones, in the depression distal to the junction of the bases of the two bones, over the dorsalis pedis artery.
Neiguan (PC 6)	On the anterior aspect of the forearm, between the tendons of the palmaris longus and the flexorcarpi radialis, 3 cun proximal to the palmar wrist crease.
Zusanli (ST 36)	On the anterior aspect of the leg, on the line connecting ST35 with ST41, 3 cun inferior to ST35.
Qimen (LR 14)	In the anterior thoracic region, in the 6th intercostal space, 4 cun lateral to the anterior median line.
Zhangmen (LR 13)	On the lateral abdomen, inferior to the free extremity of the 11th rib.

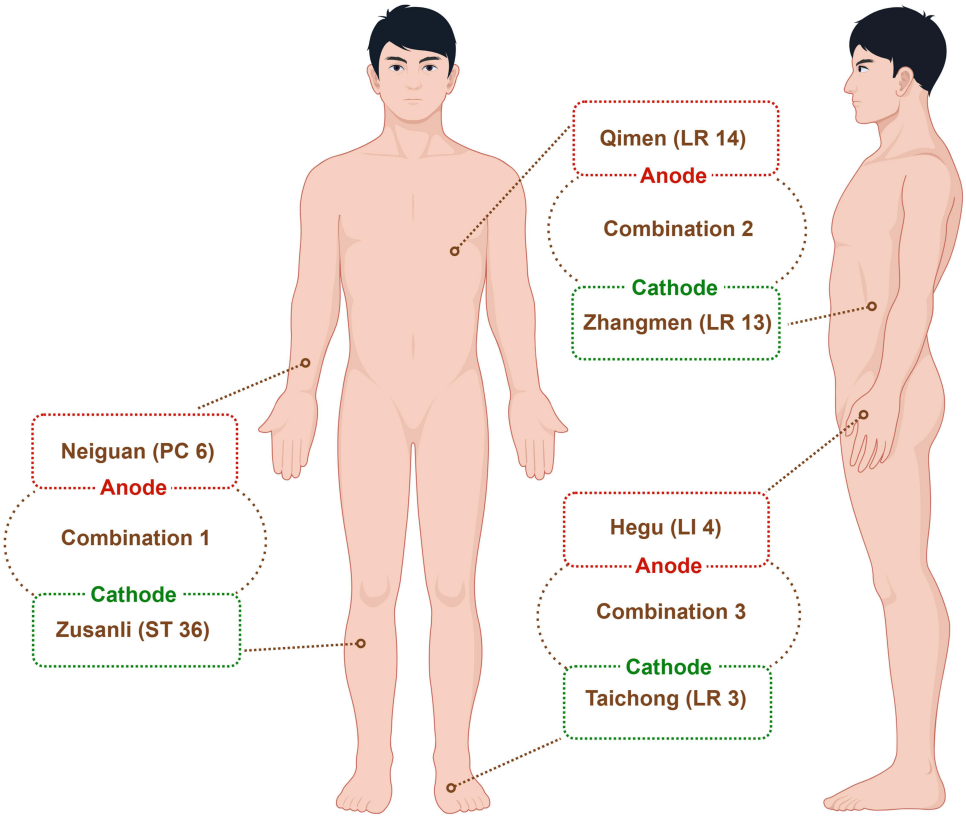

Figure 2 Location of the acupoints.

generate a perceptible but faint sensation without eliciting any meaningful therapeutic responses, as previously demonstrated in studies.[16,33] Employing such a low-current stimulus as a validated placebo control is a scientifically sound strategy that effectively preserves blinding within the trial.

All participants will be followed for 4 weeks after 2 weeks of treatment.

Outcomes and Measurements

The outcomes and measurements timepoints are presented in Table 2. Prior to randomization, a baseline assessment will be conducted, which includes demographic characteristics (gender, age, height, weight, occupation, education level), disease duration, past medical history, family history, allergic history, cancer stage, Child-Pugh classification, treatments received, pain intensity, analgesic usage, blood routine examination, and liver and kidney function tests.

Primary Outcome

The primary outcome will be assessed using the OTI. OTI is a composite, validated and practical metric that quantifies the degree of opioid tolerance, integrating four key parameters: total opioid dose, initial dose, final dose, and duration of opioid use.[34] An elevated OTI indicates decreased sensitivity to opioids, requiring higher doses to achieve equivalent analgesic effects. Clinical studies have demonstrated that post-treatment reductions in OTI and opioid consumption in patients with cancer pain suggest an improvement in opioid tolerance.[35,36]

Since morphine is considered the gold standard among opioids, dose comparisons across different opioids are commonly referenced to morphine. Therefore, all opioid doses will be converted into morphine equivalent doses using standard conversion ratios to compute the total opioid dose. OTI is directly proportional to the total opioid dose over the 2-week treatment period and to the difference between the final (week 2) and initial (week 0) daily opioid requirements, while inversely proportional to the number of days between the start and end of treatment. A higher OTI value indicates

Table 2 Timepoints for Outcomes and Measurements

	Baseline	Treatment		Follow-up	
	Week 0	Week 1	Week 2	Week 3	Week 6
Primary outcome					
OTI			•		
Secondary outcomes					
NRS score	•	•	•	•	•
The number of breakthrough pain	•	•	•	•	•
Frequency of gastrointestinal side effects	•	•	•	•	•
Quality of life evaluation	•	•	•	•	•
Serum exosome proteomics	•		•		
Evaluation of blind method			•		
Safety evaluation	◄———	———	———	———	———►

Notes: •, required; ◄———►, required during this period.
Abbreviations: OTI, Opioid Tolerance Index; NRS, Numerical Rating Scale.

a greater increase in opioid dosage during the treatment period, and vice versa. The following calculation formula is applied:

$$\mathrm{OTI} = \lg\left[\text{Total opioid dose} \times \left(\text{Final dose} - \text{Initial dose}\right)/\text{Duration of opioid use}\right]$$

Secondary Outcome

1. NRS Score[37]
   This instrument employs an 11-point scale ranging from 0 to 10, where 0 represents "no pain" and 10 represents the "intolerable pain". Patients will be instructed to circle the number that best represented the intensity of their worst pain over the past 24 hours.
2. The Number of Breakthrough Pain
   The daily frequency of transient, intense pain flares, which occurred on the basis of persistent pain, will be documented. These episodes are defined as those with a NRS score of ≥ 4.[38]
3. Frequency of Gastrointestinal Side Effects
   The weekly frequency of nausea, vomiting, abdominal distension, constipation, diarrhea, and xerostomia will be recorded for each patient.
4. Quality of Life Evaluation
   The quality of life of patients will be assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30).[39] This instrument consists of two primary components: the functional scales and the symptom scales. Scores on the functional scales are positively correlated with the patient's health status, with higher scores indicating better overall functioning and well-being. Conversely, for the symptom scales, higher scores reflect more severe symptoms and a lower quality of life.
5. Serum Exosome Proteomics
   Quantitative analysis of serum exosomes derived from patients will be performed using label-free proteomics technology, aiming to explore the potential mechanisms underlying the alleviative effect of TEAS on opioid tolerance in HCC. In the morning (8:00–8:30 am), 5 mL of fasting venous blood will be collected from the patients, allowed to stand at room temperature for 30 minutes, then centrifuged at 4°C at 3000 rpm for 10 minutes, and the supernatant will be transferred to a cryopreservation tube and stored in a −80°C freezer for future use. The proteomics workflow will be conducted as follows: First, exosomes will be isolated, purified, and identified from the serum. The exosomes will then be resuspended in protein lysis buffer to extract proteins. Subsequent mass spectrometry analysis will be performed using a Label-Free approach to compare peptide signal intensities for relative quantification. A specific protein database will be constructed for quality control. Proteins will functionally

be annotated and quantitatively analyzed. Based on the results, differentially expressed proteins will be screened and subjected to bioinformatic analyses, including secondary GO classification, subcellular localization, and COG/KOG classification. Key regulatory proteins modulated by TEAS will be identified and validated using Parallel Reaction Monitoring (PRM). Benjamini-Hochberg correction for multiple testing will be further applied to adjust the derived P-values, and only functional categories and pathways with P-values < 0.05 will be considered as significant.

Items 1 to 4 will be assessed at baseline, during the treatment period in the 1st and 2nd weeks, and in the follow-up period at the 3rd and 6th weeks. Item 5 will be assessed at baseline and in the 2nd week of treatment.

Safety Evaluation

Adverse events (AEs) will be closely monitored and documented. These include, but are not limited to, dizziness, palpitation, shock, nerve injury, and dermal reactions to electrode patches, such as localized redness, pruritus, and allergic responses. Each event will be recorded in detail, encompassing its frequency, severity, duration, and the management measures taken. All AEs occurring during the study will be assessed by a qualified physician after each weekly treatment session and throughout the follow-up period.

Data Collection, Management and Monitoring

All data will be systematically documented and evaluated by investigators, who have completed a clinical practice training program prior to participant recruitment. The training encompasses instruction on the proper completion of the case report form (CRF) in an objective, accurate, and timely manner. Additionally, it includes guidelines for assessing the electronic CRF (eCRF) and entering the corresponding. The data monitor conducts regular audits of the study data to ensure the completeness and accuracy of all eCRF. The data for each participant will be stored in a centralized server, with access limited exclusively to the data monitor for data verification. Investigators will not have the capability to modify or access the data until the completion of participant enrollment, observation, and data collection for all participants. Quality controllers will be appointed to conduct regular reviews of both the completion status and the quality of research tasks performed. In addition, a Data Safety Monitoring Board (DSMB) will be established, composed of at least three professionals, including a statistician, a hepatologist, and an acupuncture expert. The study protocol will be adjusted according to any changes in research requirements and context to ensure the results are accurate, reliable, and clinically meaningful.

Data Analysis

Statistical analysis will be conducted according to the principles of intention-to-treat (ITT) and per-protocol (PP). ITT analysis involves statistical analysis of all participants who meet the study protocol requirements and are randomly assigned to the study, regardless of whether they completed the intended treatment, including those who withdrew or failed to complete the entire treatment course. In contrast, the PP analysis only examines those participants who strictly adhere to the study protocol, those who meet the study design, receive the full treatment, and complete follow-up as required. The results of these two analyses will be presented simultaneously, and the consistency between them will be assessed. If missing data arising from loss to follow-up or non-response are determined to be random, mean imputation will be applied for data handling. For participants who complete at least one follow-up visit but discontinue full study participation, the last observation carried forward method will be adopted in all outcome analyses.

Data will be analyzed using SPSS 26.0. Continuous variables will be expressed as means ± standard deviations, and categorical variables as proportions. A linear mixed-effects model will be used to assess the score changes in the OTI, NRS, QLQ-C30, number of breakthrough pain, and frequency of gastrointestinal side effects across treatments, including fixed effects for time, group, their interaction, and covariates such as age, sex, baseline OTI, and disease duration. Additionally, this model examines the correlation between the OTI changes and protein biomarkers, treating OTI variations as the dependent variable and protein biomarker changes in independent variables. Stratified analyses will

be used to explore differences in the efficacy of different treatment between moderate and severe patients according to NRS score (NRS score 4–6 for moderate and 7–10 for severe). $P < 0.05$ will be considered statistically significant.

Discussion

Opioids are the most widely used class of analgesics in clinical practice, significantly alleviating pain in cancer patients. However, the development of opioid tolerance, dependence, and adverse effects such as respiratory depression, constipation, nausea, and vomiting after long-term use not only diminishes analgesic effects but also complicates cancer treatment and poses potential risks. TEAS, when used as a complementary therapy in conjunction with existing analgesics, holds significant value in enhancing the efficacy for patients with pain due to HCC.

In recent years, TEAS has been widely used in clinical analgesia, demonstrating great efficacy for acute, chronic, and cancer-related pain. TEAS has been shown to effectively relieve pain in patients with mild to moderate bone metastases, with analgesic effects comparable to those of analgesic medications.[40] It also alleviates postoperative pain in gastric cancer patients and improves immune and gastrointestinal function.[14,15] A high-quality RCT indicated that acupuncture significantly reduces methadone maintenance doses and opioid craving.[41] Given the close pathological relationship between opioid tolerance and dependence, it is plausible that TEAS may also exert beneficial effects in alleviating opioid tolerance in HCC patients. Based on previous research, this protocol has optimized and selected six representative acupoints for soothing the liver, regulating qi, promoting blood circulation, and alleviating pain. Among them, LI 4 and ST 36 are classic acupoints known for their anti-inflammatory and analgesic effects, which are mediated through both peripheral and central pathways.[42–45] PC 6 not only reduces secondary hyperalgesia but also serves as a key acupoint for regulating gastrointestinal function, helping to alleviate opioid-induced adverse gastrointestinal reactions.[46] LR 3, LR 14, and LR 13, all located on the Liver Meridian, are selected to specifically address HCC-related pain. TEAS exhibits frequency-specific analgesic effects.[47] The 2/100 Hz has been proven to be the optimal treatment frequency in improving neuropathic radicular pain,[48] which also serves as a key rationale and basis for the selection of parameters in this study. The follow-up design enables not only the evaluation of short-term efficacy of TEAS but also the long-term sustained therapeutic outcomes. The 4-week follow-up period aligns with routine clinical management, minimizes dropout rates, and avoids excessive burden on participants in this study.

In terms of efficacy assessment, this trial uses the OTI as the main observation indicator, which allows for a clear comparison of the degree of tolerance differences among individual patients when using opioid medications, and facilitates quantitative analysis.[34] A decreased OTI indicates reduced opioid tolerance in patients, such that the same dose of opioids can produce a stronger analgesic effect. Since the severity of cancer pain is an important factor affecting opioid tolerance, we use the NRS to assess pain levels in HCC patients, which is a recognized core measurement tool related to pain,[49] and we record the incidence of breakthrough pain based on the NRS scoring criteria. Increased opioid tolerance and dosage can also lead to a higher frequency of gastrointestinal side effects in patients, which we also document, and we specifically employ the EORTC QLQ-C30 to comprehensively evaluate the quality of life of HCC patients.

On the other hand, exosomal protein biomarkers hold significant value in the assessment and treatment of pain associated with liver cancer. Exosomes are small extracellular vesicles, ranging from 30 to 100 nm in diameter, secreted by various living cells. Specific exosomal proteins not only promote the initiation and progression of HCC by mediating relevant signaling pathways but also act as key carriers of pain mediators involved in inflammatory and neuropathic pain processes.[50] In a mouse model of sciatic nerve injury, exosome levels change over time in the medial prefrontal cortex and nucleus accumbens, suggesting that exosome release can mimic pain-like behaviors and modulate pain thresholds.[51] Similarly, tumor-derived exosomes may carry algogenic substances, such as nerve growth factor and chemokines, which can activate nociceptors on peripheral nerve fibers and enhance the transmission of pain signals to the central nervous system, thereby exacerbating pain in HCC patients. Exosomal proteomics enables comprehensive analysis of protein composition and expression profiles in serum exosomes, offering preliminary and exploratory insights into intercellular communication and associated pathophysiological processes. As an exploratory analytical approach, this technique holds potential to uncover candidate molecular pathways underlying the effects of TEAS on cancer pain relief and opioid tolerance attenuation.

However, several limitations should be noted. First, due to the nature of TEAS procedures, it is not possible to blind the treatment operators, which may introduce subjective bias. To address this limitation, all outcome assessments will be performed by independent, evaluators who are not involved in treatment administration, thereby minimizing the risk of measurement bias. Secondly, as this is a single-center RCT focusing solely on patients with moderate-to-severe pain in HCC who exhibited opioid tolerance, the preliminary results cannot be directly extrapolated to other cancer types or non-cancer chronic pain populations, and large-scale multi-center studies are needed to verify the universality of the conclusions. Finally, although serum exosomal proteomics is used to explore mechanisms, the results may only reveal the correlation between protein biomarkers and HCC cancer pain, rather than a quantitative relationship between the two. Whether the selected differential proteins are the key substances through which TEAS exerts its effects needs to be validated through rigorous mechanistic experiments.

Conclusion

This protocol demonstrates favorable feasibility and carries significant clinical relevance for optimizing cancer pain management and mitigating opioid-related adverse reactions. The findings of this study will provide preliminary evidence regarding the efficacy and potential underlying mechanisms of TEAS in alleviating opioid tolerance among patients with moderate-to-severe HCC-related pain, thereby offering essential reference and guidance for future investigations in this field.

Trial Status

Participant recruitment is ongoing at the time of manuscript submission.

Abbreviations

AEs, Adverse Events; CONSORT, Consolidated Standards of Reporting Trials; CRF, Case Report Form; eCRF, Electronic Case Report Form; DSMB, Data Safety Monitoring Board; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; GDNF, Glial cell line-Derived Neurotrophic Factor; HCC, Hepatocellular Carcinoma; ITMCTR, International Traditional Medicine Clinical Trial Registry; ITT, Intention-To-Treat; NCCN, National Comprehensive Cancer Network; NRS, Numeric Rating Scale; OTI, Opioid Tolerance Index; PNI, Perineural Invasion; PP, Per-Protocol; PRM, Parallel Reaction Monitoring; RCT, Randomized Controlled Trial; SPIRIT, Standard Protocol Items: Recommendations for Interventional Trials; STRICTA, Standards for Reporting Interventions in Controlled Trials of Acupuncture; TCM, Traditional Chinese Medicine; TEAS, Transcutaneous Electrical Acupoint Stimulation; TRPV1, Transient Receptor Potential Vanilloid 1; WHO, World Health Organization.

Ethics Approval and Consent to Participate

The trial will comply with the Declaration of Helsinki. The Research Ethics Committee of the Yueyang Hospital of Integrated Traditional Chinese and Western Medicine has approved the study protocol (No. 2025-045). Written informed consent will be obtained from all participants prior to enrollment. A copy of the signed consent form will be given to the participant.

The trial has been registered with the International Traditional Medicine Clinical Trial Registry (ITMCTR, http://itmctr.ccebtcm.org.cn/) under the registration number ITMCTR2025002162. Date of first registration: June 9, 2025.

Author Contributions

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

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Disclosure

The authors report no conflicts of interest in this work.

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