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STUDY PROTOCOL

Efficacy and Safety of Electroacupuncture for Postherpetic Neuralgia and Biomarker Evaluation: A Study Protocol for a Multicenter, Randomized Trial

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Introduction: Postherpetic neuralgia (PHN) is a persistent neuropathic pain condition that endures for at least 3 months following the onset of herpes zoster, significantly impairing life quality of patients. Current PHN treatments demonstrate limited efficacy, and the lack of reliable severity biomarkers hinders effective clinical management. Electroacupuncture represents a promising therapeutic approach for PHN, though comprehensive evidence supporting its efficacy and safety is still needed. Furthermore, as objective indicators, the role of serum biomarkers in assessments still requires further investigation.

Methods: This multicenter, sham-controlled, randomized study will recruit 180 patients with PHN. Participants will be allocated in a 1:1:1 ratio to electroacupuncture, sham acupuncture, or waiting-list groups via multicenter stratified block randomization. Participants will receive 1-month of treatment and 3-month follow-ups. The electroacupuncture group and the sham acupuncture group will each receive 12 treatments. All participants will maintain their pre-enrollment medication. Primary outcome is Numerical Rating Scale; secondary outcomes include pain episode frequency, Hamilton Anxiety Scale, Hamilton Depression Scale, The Short-Form 36 Health Survey, and changes of biomarkers (Neuropeptide Y, Substance P, Tumor Necrosis Factor-α, Interleukin-10). A linear mixed-effects model will be used to analyze data at different time points to explore the efficacy of electroacupuncture and the correlation between serum biomarkers and pain intensity. The predictive value of biomarkers for refractory postherpetic neuralgia (NRS reduction <30% from baseline post-treatment) will be assessed using ROC curves.

Conclusion: The expected outcomes will clarify the efficacy and safety of electroacupuncture for PHN. The study will also analyze the correlation between serum biomarkers and pain symptoms and determine whether serum biomarkers can serve as prognostic indicators for refractory postherpetic neuralgia.

Trial Registration: ClinicalTrials.gov identifier: NCT06990854. Registered on June 3, 2025. (https://clinicaltrials.gov/study/NCT06990854).

Keywords: electroacupuncture, postherpetic neuralgia, biomarker, sham acupuncture, randomized controlled trial, study protocol

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Introduction

Postherpetic neuralgia (PHN), defined as persistent neuropathic pain lasting ≥3 months after herpes zoster rash healing, is the most prevalent and debilitating complication of varicella-zoster virus reactivation.[1,2] The diagnostic criteria primarily rely on the clinical history of zoster infection combined with characteristic pain persisting beyond cutaneous healing. However, standardized diagnostic serum biomarkers are lacking.[3] The condition manifests as burning, electric-shock-like pain with allodynia in affected dermatomes, significantly impairing physical function and quality of life.[4,5] Epidemiological studies indicate 5–30% incidence in herpes zoster patients, with risk escalating with age (>50% in patients >60 years) and immunocompromised status.[6,7] In China, the overall prevalence of herpes zoster is 6.15%, and the prevalence in individuals aged 70 years and older is 12.95%.[8] With an aging population, the challenges posed by PHN will gradually become more severe. Notably, 20–50% of patients with PHN develop chronic symptoms lasting >1 year.[1] The pathophysiological mechanisms involve dual peripheral and central nervous system alterations: peripheral nerve injury triggers an inflammatory cascade (IL-6, TNF-α), while central sensitization manifests as spinal cord hyperexcitability and thalamic plasticity changes.[5,9] Current treatment algorithms prioritize gabapentinoid drugs, tricyclic antidepressants, and lidocaine patches as first-line pharmacotherapy, yet <50% patients achieve ≥50% pain reduction.[10,11] Refractory cases often require interventional approaches, including nerve blocks and spinal cord stimulation, although these carry risks of complications and transient efficacy.[12,13] The clinical imperative persists for safer, more effective interventions to address PHN's multifactorial pathogenesis.[10]

Electroacupuncture (EA) is an alternative therapy that has been widely used in clinical practice to alleviate PHN.[14] Current research has found that, in the central nervous system, low-frequency electroacupuncture stimulates the expression of the anti-inflammatory factor IL-10 in spinal cord microglia.[15] This can promote the release of β-endorphins to exert an analgesic effect. Electroacupuncture can also exert analgesic effects by regulating astrocyte function in the rostral ventromedial medulla to inhibit central sensitization.[16] Peripherally, electroacupuncture can reduce the sensitization of peripheral nociceptors by decreasing the abnormal discharge of injured nerves.[17,18] Research has found that electroacupuncture at 2/100 Hz can improve chronic neuropathic pain by inhibiting the upregulation of P2X3 receptors in the dorsal root ganglion (DRG), modulating the JAK2/STAT3 signaling pathway, suppressing inflammatory responses in the spinal dorsal horn, and preventing abnormal synaptic remodeling.[19–21] Moreover, compared with a single frequency, 2/100 Hz performs better in alleviating mechanical and cold allodynia.[22] Although previous studies have demonstrated the efficacy of EA in the treatment of PHN, the outcome measures used were mostly NRS and VAS scores, which are somewhat subjective.[23,24]

In recent years, studies have found that neuropeptides and inflammatory factors play important roles in the pathogenesis of PHN.[25] Neuropeptide Y (NPY) exerts critical regulatory effects on neuropathic pain. After peripheral nerve injury, NPY activates Y1-Ins neurons in the dorsal horn of the spinal cord to inhibit abnormal pain signal transmission, thereby regulate pain.[26] Emerging evidence indicates that plasma NPY concentrations in patients with PHN may serve as a predictive biomarker for both pain severity and treatment resistance.[27] Substance P (SP) is a key mediator of nociceptive pathways. SP mediates nociceptive transmission from primary afferent neurons to the spinal dorsal horn via neurokinin 1 receptor (NK1R) activation, facilitating ascending signaling to the central nervous system.[28,29] SP levels are significantly elevated in chronic neuropathic pain states.[30] Its release is closely associated with the development of mechanical hyperalgesia and inflammatory pain.[28,31] Although previous studies have suggested a correlation between serum biomarkers and PHN, there are limitations such as lack of randomization and absence of intervention management.[25,27] Therefore, there is still a need for a well-powered, randomized controlled study to further explore the relationship between the two.

Many studies have demonstrated that serum biomarkers are not only directly associated with neuropathic pain but also exert a significant influence on inflammatory processes. NPY can reduce TNF-α production to alleviate tissue damage by inhibiting immune cells.[32] It can also induce the release of the anti-inflammatory factor IL-10 by activating the Y1R receptor.[33] SP can significantly upregulate the TNF-α expression by activating the neurokinin-1 receptor (NK-1R).[34] Therefore, serum biomarkers hold significant research value in investigating the mechanisms underlying acupuncture therapy for chronic inflammatory neuropathic pain. However, large-sample, quantitative RCT studies are still lacking to clarify the specific dynamic changes in serum biomarker levels in patients with PHN, which is essential for further investigating the mechanism of acupuncture. Therefore, we designed this study.

Given the substantial therapeutic potential of electroacupuncture in PHN and the limitations of previous research, this study is designed to (1) compare the efficacy of electroacupuncture combined with pharmacotherapy, sham acupuncture, and pharmacotherapy alone in patients with PHN through clinical outcomes, laboratory parameters, and quality of life scores. (2) Analyze the correlation between serum biomarkers and pain symptoms. (3) analyze whether serum biomarkers can serve as prognostic indicators for PHN.

Methods

Study Design

This study employs a randomized controlled trial design with an assessor-blinding approach. A total of 180 participants diagnosed with PHN are randomly allocated in a 1:1:1 ratio to the EA, SA, or WC groups. A 2-week run-in period was implemented between patient enrollment and allocation. Comparative analyses are conducted to evaluate pain symptom alleviation and changes in serum biomarker concentrations to elucidate the potential correlations between these variables. The trial is scheduled to commence in July 2025 and is anticipated to be completed by December 2026. The protocol is rigorously structured in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines. The SPIRIT checklist and trial flow diagram are presented in Table 1 and Figure 1, respectively.

Table 1 Timepoint for Recruitment, Interventions and Assessments

Study Period	**Baseline**	**Allocation**	**Intervention Period**				**Follow-Up Period**
Timepoint (week)	**−2**	**0**	**1**	**2**	**3**	**4**	**16**
Enrolment:							
Eligibility screen	•						
Informed consent	•						
Demographic characteristics	•						
Disease history of PHN	•						
PHN combination medication	•		•	•	•	•	•
Combined disease and medication history	•						
Randomization and allocation		•					
Interventions:							
(30mins × 3/week) EA			◄———	———	———	———►	
(30mins × 3/week) SA			◄———	———	———	———►	
WC			◄———	———	———	———►	
Assessments:							
NRS	•	•	•	•	•	•	•
Pain Episode Frequency		•	•	•	•	•	•
HAMA		•	•	•	•	•	•
HAMD		•	•	•	•	•	•
SF-36		•	•	•	•	•	•
NPY		•	•	•	•	•	•
SP		•	•	•	•	•	•
TNF-α		•	•	•	•	•	•
IL-10		•	•	•	•	•	•
Blinding assessment						•	
Safety assessment		•	•	•	•	•	•

Notes: •, required; ◄———►, required during this period.

Abbreviations: PHN, postherpetic neuralgia; EA, electroacupuncture; SA, sham acupuncture; WC, waiting-list; NRS, Numerical Rating Scale; HAMA, Hamilton Anxiety Scale; HAMD, Hamilton Depression Scale; SF-36, The Short-Form 36 Health Survey; NPY, Neuropeptide Y; SP, Substance P; TNF-α, Tumor Necrosis Factor-α; IL-10, Interleukin-10.

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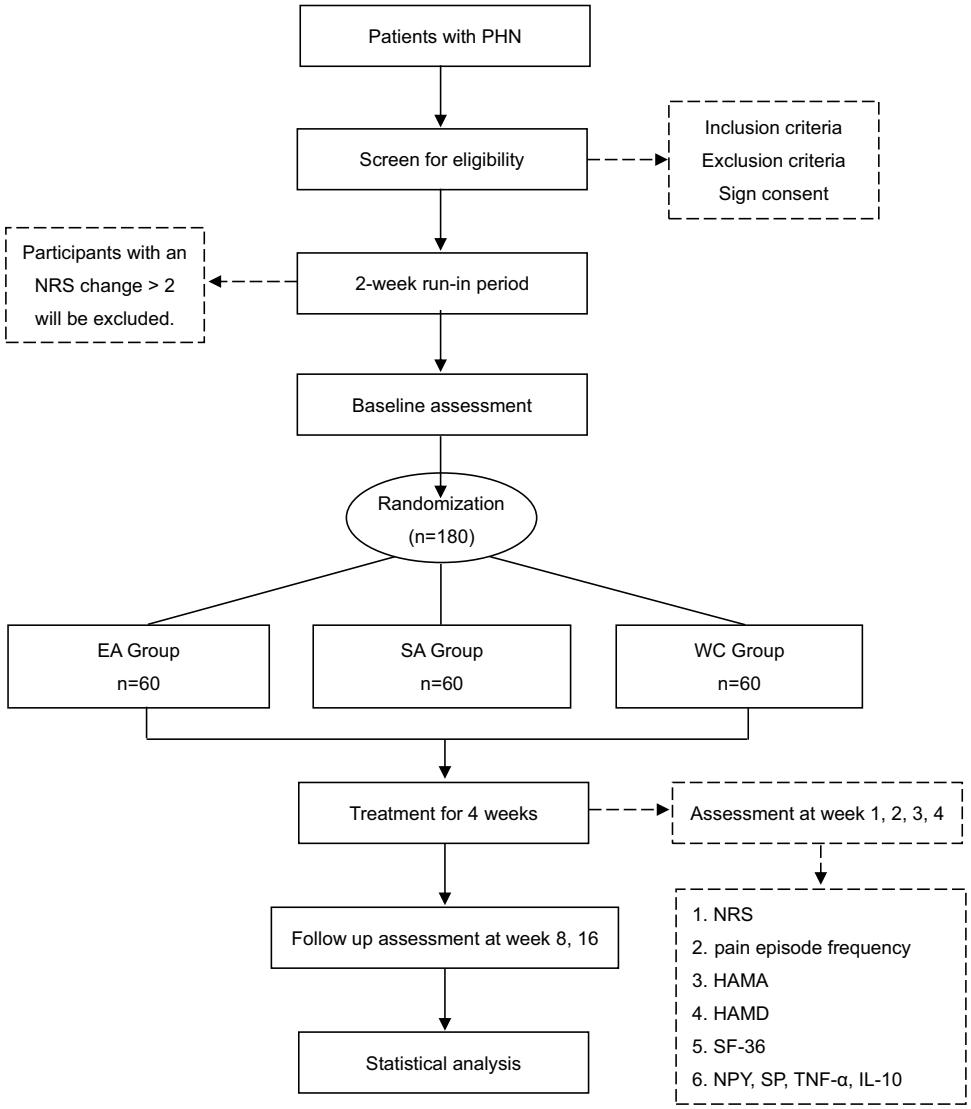

Figure 1 The trial design of the efficacy and safety of EA for PHN and the evaluation of biomarkers.
Abbreviations: PHN, postherpetic neuralgia; EA, electroacupuncture; SA, sham acupuncture; WC, waiting-list; NRS, Numerical Rating Scale; HAMA, Hamilton Anxiety Scale; HAMD, Hamilton Depression Scale; SF-36, The Short-Form 36 Health Survey; NPY, Neuropeptide Y; SP, Substance P; TNF-α, Tumor Necrosis Factor-α; IL-10, Interleukin-10.

Participants

Participants from the clinics of Acupuncture and Dermatology of the Third Affiliated Hospital of Zhejiang Chinese Medical University (main center), Hangzhou Third People's Hospital, and Changxing County Traditional Chinese Medicine Hospital will be enrolled in the study after meeting the following criteria:

Inclusion Criteria

1. Patients who meet the diagnostic criteria for PHN;[35]
2. Patients with a Numerical Rating Scale (NRS) score ≥ 4;
3. Patients aged between 20 and 80 years;
4. Patients voluntarily participate in the trial by signing the informed consent form.

Exclusion Criteria

1. Patients have a specific type of herpes zoster, such as disseminated herpes zoster, or HZ occurs in regions of the head, face, and viscera (cephalic or visceral PHN); These subtypes are excluded to ensure a homogenous patient population, as their underlying pathophysiology and response to treatment may differ from truncal PHN;
2. Patients who are pregnant or lactating;
3. Patients who have severe liver or kidney dysfunction, malignant tumors, or other serious diseases;
4. Patients who have hematologic diseases or coagulation disorders;
5. Patients who have mental illness or other cognitive impairments;
6. Patients who have received previous radiofrequency ablation treatment for PHN lesions;
7. Patients who persistent rupture or infection at the acupuncture site or skin allergy;
8. Patients who have participated in other clinical trials within the past 3 months.

Participant Withdrawal Criteria

Participants may be withdrawn from the trial under the following circumstances: At the investigators' discretion: 1) If complications or clinical deterioration necessitate prompt emergency interventions; 2) Due to inadequate adherence, where participants do not comply rigorously with the study protocol; 3) During the 2-week run-in period, if a participant's NRS score changes by more than 2 points from the baseline. Upon participant request: Individuals may voluntarily discontinue involvement at any point and for any reason.

Allocation Concealment and Randomization

This study is a prospective, randomized, double-blind, parallel-controlled, multicenter clinical trial conducted simultaneously at the Third Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou Third People's Hospital, and Changxing County Traditional Chinese Medicine Hospital. A multicenter stratified block randomization method is employed to ensure balance of baseline characteristics among the treatment groups.

To mitigate the key impact of participants' baseline NRS scores and PHN disease duration on the outcomes, these factors are set as stratification variables. The specific stratification criteria are as follows: baseline NRS scores are stratified into two levels—moderate pain (4–6 points) and severe pain (7–10 points); PHN disease duration is stratified into three levels—short term (3–6 months), medium term (6–9 months), and long term (greater than 9 months). Within each stratum, the random allocation sequence is generated using the SAS OnDemand for Academics cloud platform (https://welcome.oda.sas.com/). Participants within each stratum are ensured to be allocated to the EA group, SA group, and WC group in a 1:1:1 ratio.

In the pilot study, the standard deviations of the results in the three groups were: EA group (1.45–1.91), SA group (0.77–1.09), and WC group (0.79–1.93). Considering the subjectivity of the NRS score and the high variability of the data in the EA group, a block length of 4 is used to rebalance the group assignments more frequently and thus reduce the potential for imbalance due to random fluctuation. Given the sample size, the number of blocks is 45. Allocation concealment is implemented through the Sealed Envelope Method.

Blinding

In this study, therapists cannot be blinded due to direct contact with the participants, but evaluators, statisticians, and participants are blinded. The separation between therapists, evaluators, and participants is maintained. Final data will be analyzed by a specialized person who is not involved in the trial design.

To assess the effectiveness of blinding, the Bang Blinding Index[36] will be calculated. At the end of the 4-week treatment, participants will be asked: "Which treatment do you think you received? (a) Electroacupuncture, (b) Sham Acupuncture, or (c) I don't know". Blinding will be considered successful if the Bang Blinding Index is not significantly different from zero, indicating that the guess is no better than chance.

Interventions

All participants will undergo a 4-week treatment. Acupuncture will be performed thrice a week. This treatment cycle and frequency are determined based on previous clinical research and experience.[37]

Electroacupuncture (EA) Group

The acupoints selected are Ashi points (localized to herpetic lesion areas) and Jiaji points (EX-B2, ipsilateral to affected dermatomes), which are detailed in Table 2. Acupoint localization strictly followed WHO Standard Acupuncture Point Locations (2008) guidelines.[38] To ensure consistency, a detailed Standard Operating Procedure (SOP) for acupoint localization will be used across all centers. This involves identifying anatomical landmarks as per the WHO guidelines, followed by palpation to identify the most tender points (Ashi points) within the affected dermatome. For Jiaji points, localization will be confirmed using both anatomical measurements (0.5 cun lateral to the lower border of each spinous process) and palpation. After routine disinfection, a sham acupuncture patch device is placed at each acupoint. For each Ashi point, a pair of needles (0.25 × 40 mm, Hwato brand, Suzhou Medical Supplies Factory, China) are inserted horizontally to a depth of 15–20 mm. For EX-B2, the needles (0.30 × 50 mm, Hwato brand, Suzhou Medical Supplies Factory, China) are inserted perpendicularly to a depth of 40–45 mm. Participants in the EA group will undergo rotating manipulation to achieve the sensation of Deqi.[39] Electroacupuncture (Hans-100A, Nanjing Jisheng Medical Technology, China) is connected to the needles at each Ashi point and to the highest and lowest EX-B2 points, which is demonstrated in Figure 2. Parameters are set to dense-disperse wave mode (2/100 Hz) with intensity adjusted to patient tolerance, maintaining stimulation for 30 min.[40]

Sham Acupuncture (SA) Group

The Streitberger needle, a widely reported placebo needle device in acupuncture RCTs, is applied for sham intervention. Blinding assessments have predominantly demonstrated successful masking outcomes. This telescoping blunt-tip needle provides non-penetrating placebo stimulation through its retractable design. Its key advantage lies in evoking a skin-penetrating sensation akin to true needling through tissue compression, while avoiding actual dermal perforation to minimize specific therapeutic effects.

The acupoint prescription is identical to the EA group. After disinfection of the acupoints and placement of the sham acupuncture patch, the placebo needle is inserted without penetrating the skin. Following the perception of needle insertion reported by patients, the needle will be retracted by approximately 1 mm and connected to electroacupuncture apparatus without electrical stimulation activation, which is demonstrated in Figure 3.

Table 2 Introduction of Acupoints

Name	Ashi Point	Jiaji Point (EX-B2)
Location	Localizing to the pain points at herpetic lesion areas.	Located in the spinal region, on both sides below the spinous processes from the 1st thoracic vertebra to the 5th lumbar vertebra, 0.5 transverse finger width to the side from the posterior midline.
Function	Relieving localized pain.	Relieve pain in the areas corresponding to the infected nerve root segments and accelerate local nerve regeneration and repair.
Manipulation	Insert the needle according to the anatomical structure of the painful area. In the treatment of PHN of the trunk, the needle tip is inserted at a 15°angle to the skin surface, parallel to the course of the affected nerve, reaching a depth of 15–20 mm.	Insert the needle vertically to a depth of 40–45mm, and then perform the needling technique to induce the arrival of Deqi.

Abbreviation: PHN, postherpetic neuralgia.

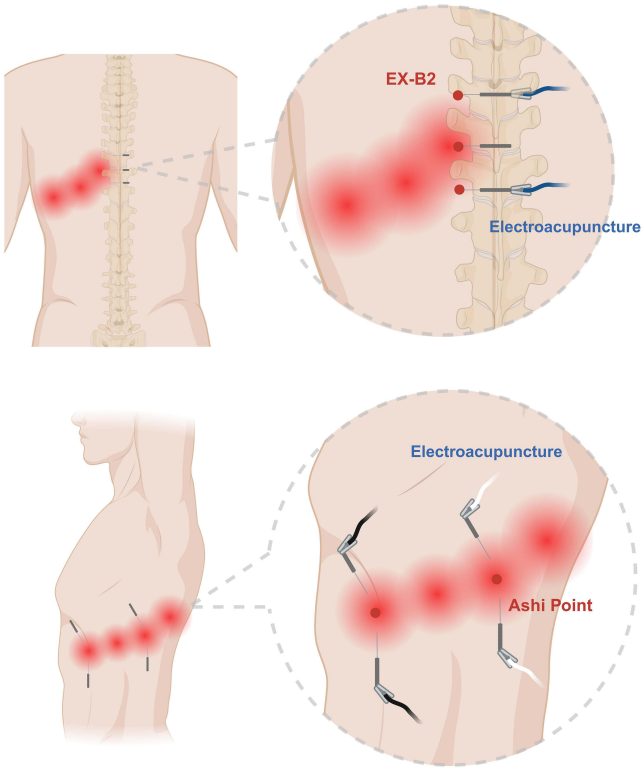

Figure 2 Illustration of the locations of EX-B2 and Ashi points and the method for electroacupuncture. The red circles denote areas of pain localization, while the dashed border delineates the magnified view of the corresponding anatomical region. The electroacupuncture needles are connected to leads, with homochromatic wires indicating paired electrodes.

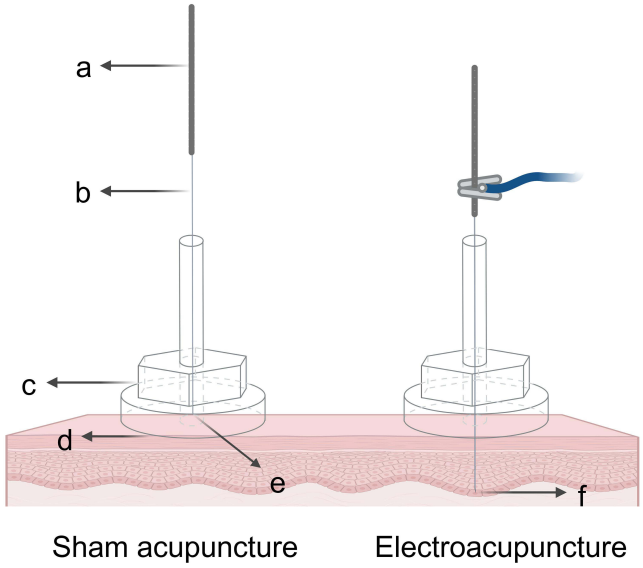

Figure 3 Illustration of sham acupuncture and electroacupuncture. The pink-colored area delineates the skin and subcutaneous tissue layers. a. Needle handle: Controls insertion/withdrawal; b. Needle body: Connect the needle handle and needle tip to conduct mechanical or electrical stimulation; c. Plastic cover: Protect and secure the needle body; d. Double-sided tape at the bottom: Secure the device and isolate the electrical stimulation; e. Blunt tip of the placebo needle: Simulate penetration without actual perforation; f. Needle tip: Penetrate the skin.

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Waiting-List Control (WC) Group

Participants are under clinical monitoring, which is carried out via outpatient follow-up with scale assessments and serum biomarker testing at each assessment node.

Medications

Most participants have already undergone medication treatment before recruitment. Since there are individual differences in participants' conditions and medication use, and considering the need for individualized treatment and ethical requirements, it is not feasible to apply the same medication plan to all participants after enrollment. Therefore, we maintain the original medication regimen for participants, and medications are not adjusted during the 4-week treatment period except in special circumstances.

Following participant allocation, all medications during the 2-week run-in period will be systematically documented. The recorded parameters included: medication name, clinical indication, dosage unit, administration frequency, route of administration, start and end dates of treatment. This comprehensive documentation ensured accurate tracking of concomitant medications throughout the study period.

To account for potential confounding effects of concomitant analgesic use, the daily dosage of all pain-related medications (eg, gabapentinoids, Pregabalin) will be recorded. To create a standardized metric for analysis, dosages for the major drug classes will be converted to standardized equivalents (eg, gabapentin equivalents for gabapentinoids). The cumulative standardized dose will be considered as a covariate in the statistical models to adjust for medication effects.

Concurrent Intervention and Emergency Management

During the study, participants must avoid additional interventions that could affect outcomes, such as other medications or physical therapies. If they receive combined treatments specifically for PHN, these must be carefully documented in CRFs. Participants with conditions like hypertension or diabetes can continue their standard treatments. All comorbidities and medications must be fully recorded in CRFs to ensure data integrity.

When pain is persistently severe, unrelieved, intolerable, and significantly impacts daily life, emergency adjustments to medications or other pain-relief measures may be made. Emergency measures should be recorded in the CRFs with the date, time, and dosage used. Adverse events (AEs) will be monitored and documented throughout the trial. The severity of AEs will be graded using a standardized tool, such as the Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Any serious adverse events (SAEs) will be reported to the principal investigator and the institutional review board (IRB) within 24 hours.

Outcomes and Measurements

The assessments will be conducted at baseline, the end of Weeks 1, 2, 3, 4, and follow-up in Weeks 8, 16. Based on previous studies, a 3-month follow-up is sufficient for the long-term efficacy assessment of electroacupuncture for PHN.[41]

Primary Outcome

Pain intensity is assessed using the NRS, an 11-point scale ranging from 0 ("no pain") to 10 ("intolerable pain"). This validated tool demonstrates rapid clinical utility and robust psychometric properties, including good reliability and validity for pain assessment.

Secondary Outcome

Secondary outcomes include four domains:

1. Pain episode frequency
   Daily documentation of pain episodes over 24-hour intervals to characterize symptom fluctuation patterns.
2. Psychological Status Assessment
   Hamilton Anxiety Scale (HAMA):[42] A 14-item clinician-administered tool evaluating anxiety severity across domains such as anxious mood, tension, and insomnia. Scores ≥14 indicate clinically significant anxiety. Hamilton Depression Scale (HAMD):[43] A 21-item instrument assessing core depressive symptoms spanning affective, cognitive, and somatic dimensions.

3. Quality of Life Evaluation
   The Short-Form 36 Health Survey (SF-36)[44] quantified the health-related quality of life across eight domains. This instrument has been extensively validated in chronic pain research.
4. Serum biomarkers
   1) NPY exacerbates PHN by modulating neural and immune responses; 2) SP contributes to PHN by promoting inflammation and pain signaling; 3) TNF-α induces neuroinflammation and nerve damage in herpes zoster, worsening PHN; 4) IL-10 alleviates PHN by inhibiting inflammatory responses.

Extraction of Serum Biomarkers

This study monitors serum concentration changes of NPY, SP, TNF-α, and IL-10 during treatment. Serum biomarkers will be screened for hemolysis prior to analysis to ensure quality control.

For NPY and SP, venous blood is collected in EDTA-Na2 tubes, left at room temperature for 1 hour, then centrifuged at 4°C, 1000 rpm for 15 minutes. The supernatant serum is carefully transferred to sterile tubes, avoiding hemolysis. Aliquots are stored at −80°C. SP ELISA Kit (E-EL-0067, AK21545, 48T, Elabscience Biotechnology Co., Ltd., China) and NPY ELISA Kit (E-EL-H1893, AK21545, 48T, Elabscience Biotechnology Co., Ltd., China) are used for quantitative analysis, with detection ranges of 78.13–5000 pg/mL for SP and 31.25–2000 pg/mL for NPY.

For TNF-α and IL-10, 10 mL fasting venous blood is collected before treatment, centrifuged at 3000 r/min for 10 minutes, and the upper plasma is stored at −80°C. Thawed samples are vortexed and used to measure TNF-α and IL-10 levels with TNF-α ELISA Kit (E-EL-H0109, AK21545, 48T, Elabscience Biotechnology Co., Ltd., China) and IL-10 ELISA Kit (E-EL-H6154, AK21545, 48T, Elabscience Biotechnology Co., Ltd., China), having detection ranges of 7.81–500 pg/mL for TNF-α and 1.56–100 pg/mL for IL-10. All procedures follow kit instructions to ensure sensitivity and consistency. Tests are conducted at the sampling hospital by blinded lab personnel.

The intra-assay and inter-assay coefficients of variation for both ELISA kits are less than 10%, which is in accordance with the acceptable coefficient of variation for this experiment. The replicate count is 3. For all the ELISA kits, standard wells, blank wells, and sample wells are set up separately. The final corrected values are the average optical density values of the standard and sample duplicates minus the optical density value of the blank well.

Sample Size Estimation

The sample size is estimated using the Hotelling Lawley Trace test via the website https://glimmpse.samplesizeshop.org/. Prior to the initiation of this study, we conducted a pilot study involving 45 patients with PHN. The inclusion and exclusion criteria, interventions, and assessment time points of the pilot study were consistent with those of the formal trial. The means and standard deviations of NRS scores for each group at different time points are presented in Table 3.

For the purpose of this study, the type I error (α) is set at 0.05, and the type II error (β) is set at 0.2 (power = 80%). The primary objective of the study is to compare mean differences between groups, and no adjustments to the means are required, so the Means Scale Factor is set to 1. The pilot study results showed an NRS difference of 2.5 points between the EA and WC groups (well above the Minimal Clinically Important Difference, MCID = 1 point). Even with a high

Table 3 The Means and Standard Deviations (NRS Score, Points) of Each Group in the Pilot Experiment

	Timepoints (at the End of Week)				
Group	**0**	**1**	**2**	**3**	**4**
EA group	6.27 ± 1.53	4.93 ± 1.69*	3.33 ± 1.45*	2.33 ± 1.74*	1.73 ± 1.91*
SA group	4.93 ± 0.77	5.07 ± 0.85	3.40 ± 0.95*	2.87 ± 1.09*	1.93 ± 1.00*
WC group	7.33 ± 0.79	6.07 ± 1.00*	4.87 ± 0.88*	4.13 ± 1.15*	3.87 ± 1.93*

Note: *Indicates $p < 0.05$ vs baseline (Week 0) by paired t-test.
Abbreviations: EA, electroacupuncture; SA, sham acupuncture; WC, waiting-list.

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degree of variability (SD ≈ 1.73), the effect size (Cohen's d ≈ 1.44) is still considered large, supporting the current sample size; thus, the Variability Scale Factor is set to 1.

Based on these parameters, the calculated total sample size is 117 participants. Accounting for a 20% dropout rate, the minimum required sample size is adjusted to 147, with 49 participants per group. Considering the high variability of the results in the EA group in the pilot study, a block length of 4 is used in the multicenter stratified block randomization method. To ensure that participants from the three centers are randomly and evenly assigned to the three trial groups and that the sample size is greater than 147, the number of blocks is set at 45, resulting in a final sample size of 180, with 60 people in each group.

Participant Recruitment

Individuals who meet the eligibility criteria for PHN will be recruited from the Department of Dermatology and Acupuncture outpatient clinic of the Third Affiliated Hospital of Zhejiang Chinese Medical University (main center), Hangzhou Third People's Hospital, and Changxing County Traditional Chinese Medicine Hospital. To ensure the effectiveness of blinding for participants, this trial will only recruit participants who have not previously received acupuncture treatment. The participants do not know each other. Prior to signing the informed consent form, each participant will receive a comprehensive explanation of the protocol. Investigator is responsible for obtaining informed consent from the participants and having them sign the consent form.

Data Analysis

Data analysis is performed using SPSS 26.0. Count data are presented as proportions, and measurement data as means ± standard deviations. Hypothesis testing is two-sided, with $p \leq 0.05$ indicating significance. A linear mixed-effects model will be used to assess the score changes in the NRS, HAMA, HAMD, SF-36 and pain episode frequency across treatments, including fixed effects for time, treatment, their interaction, and covariates such as age, sex, baseline NRS score, and disease duration. It also incorporates random intercepts and slopes for each patient to account for repeated-measures data dependency. Additionally, this model examines the correlation between the changes of NRS score and serum biomarkers, treating NRS variations as the dependent variable and biomarker changes in independent variables. The significance and sign of fixed-effect coefficients show the correlation direction, with individual differences considered in the analysis.

ROC curves are used to predict refractory PHN (defined as a reduction in NRS score of less than 30% from baseline after treatment) via serum biomarkers, with pain non-relief as the outcome and biomarker concentrations as predictors. The AUC (0–1 scale) will be calculated to assess predictive power.

A sensitivity analysis will be conducted to assess the impact of missing biomarker data (eg, due to hemolysis or other pre-analytical issues). Methods such as multiple imputation will be used to handle missing values and ensure the robustness of the findings and preserve statistical power.

Data Collection, Management, Monitoring and Auditing

All researchers must complete modular training on research protocols, ethical guidelines, and operational procedures, focusing on subject screening, informed consent documentation, and key data collection points. Training includes theory and scenario simulations, with only those passing the assessment eligible to participate. Result assessors receive SOP training, emphasizing case report form completion, consistency in efficacy evaluation, and adverse event determination. Quality control measures include cross-evaluation, blinded retesting, and a Kappa value ≥0.85 for inter-assessor consistency. Data input uses a dual-entry system with logical validation, and source data are uploaded via an EDC system. Key indicators undergo a three-tier verification process, and documents are stored using a "dual-backup" principle. Quarterly quality monitoring meetings use SPC methods to analyze quality metrics, with root cause analysis for deviations exceeding 2σ. A cross-departmental collaboration mechanism is established for CAPA development.

Adherence Improvement

To enhance participant compliance and minimize attrition rates, we intend to introduce two incentivizing measures: 1) Participants will receive acupuncture treatment and blood tests free of charge; 2) In cases where participants experience PHN during the 3-month follow-up period, they will have the option to undergo 10 extra complimentary acupuncture treatments. Moreover, prior to participant enrollment, the research team will deliver a thorough briefing on the study, encompassing details like its objectives, treatment protocols, visit timetables, evaluation criteria, participant advantages, and related aspects. This strategy will lay a strong groundwork for enhanced compliance.

Informed Consent

Researchers at each study center will provide patients with detailed information about the study's objective, potential risks, and expected benefits to ensure fully informed and voluntary participation. Written informed consent will be obtained from all participants prior to enrollment.

Confidentiality

The data collection and privacy protection plan follow full-process compliance and multi-layered protection principles, covering the entire data lifecycle. During ethical review and data authorization, the GDPR data minimization principle is applied, collecting only necessary information with informed consent and authorization. Identity protection uses triple anonymization (pseudonymization, generalization, and data masking), creating unique encrypted identifiers for participants to isolate original identity information from research data. Final data statistics are managed by designated personnel independent of the experimental design. This framework meets China's data governance requirements under relevant laws and references international privacy-preserving technologies.

Ethical Approval and Trial Registration

According to the Opinions on Deepening the Reform of the Review and Approval System to Encourage Innovation in Drugs and Medical Devices issued by the General Office of the Communist Party of China Central Committee (https://www.forestry.gov.cn/main/4815/20171008/1033684.html), this study obtained ethical approval from the institutional review board (IRB) of the leading center, and the IRBs of participating centers accepted this approval without requiring additional review.

This trial follows the principles of the Declaration of Helsinki. The Institutional Ethical Review Board of the Third Affiliated Hospital of Zhejiang Chinese Medical University has approved the trial (ZSLL-KY-2025-034-01, 1 July, 2025). Before enrollment, the investigators will fully inform the participants of the study's objectives, research items, benefits, and potential drawbacks. Participants will retain the right to decide whether to join the trial and must sign an informed consent form before being included in the study. Strict privacy protection measures will be maintained throughout the research process, and all personal and medical information will remain confidential. This trial protocol is registered on ClinicalTrials.gov (NCT06990854, 3 June, 2025).

Discussion

Review studies have found that more than half of patients with PHN may experience recurrence or persistent non-remission.[45,46] Long-term pain can significantly impact both the physical and psychological aspects of patients. Electroacupuncture is highly effective, safe, and affordable, with very few side effects.[47] It is particularly well-suited for elderly patients or those who cannot tolerate the side effects of medications. Therefore, it is of great value to improve effective acupuncture treatment protocols as complementary therapies based on existing pharmacological treatments and to evaluate the prognosis of patients with PHN.

The primary outcome measure of this trial is the score on the NRS scale, which has become the gold standard for pain assessment since the introduction of pain since the introduction of pain as the "fifth vital sign" by the American Pain Society in the 1990s. Despite its limitations, it remains the basis for primary outcome measures in clinical trials for chronic pain treatment and is recommended by regulatory authorities as a core measurement tool.[48] Studies have found that the correlation between the NRS and the PROMIS T-score is greater than that of the VAS, indicating that the

correlation between the NRS and pain intensity items (r = 0.71) is significantly higher than that of the Visual Analog Scale (VAS).[49] The NRS scale is highly subjective, and its scores can be influenced by patients' negative emotions, such as anxiety and depression, as well as individual pain tolerance. Therefore, we also assessed the anxiety and depression status of participants. The HAMA and HAMD scales have demonstrated high correlations with other standardized scales in multiple studies, indicating good concurrent validity, and they can be used to assess comorbidities.[50,51] The SF-36 scale covers eight health dimensions and can comprehensively reflect patients' health-related quality of life.[52]

Current studies have demonstrated that serum biomarkers have prognostic value in certain diseases. In patients with traumatic brain injury (TBI), elevated serum levels of substance P are associated with poor prognosis.[53] NPY levels may serve as a prognostic biomarker for both stroke and electrical storm.[54,55] If a correlation exists between decreased levels of NPY or SP and a reduction in NRS scores, it could potentially replace subjective scales for assessing pain severity and monitoring progress in PHN. This might also provide a more objective outcome measure for future PHN research, thereby reducing the influence of subjective factors on trial results. Based on the current research status, we will analyze whether there is a correlation between the changes in patients' pain scores and the concentrations of various serum biomarkers throughout the experimental period using linear mixed-effects models. The ROC curve will be used to evaluate whether the concentrations of these serum biomarkers are correlated with the incidence of refractory PHN and to determine whether these serum biomarkers can serve as prognostic indicators for PHN. The optimal cutoff values for biomarkers, such as X pg/mL for NPY, as determined by ROC curves—along with their corresponding sensitivity and specificity—can be used to identify patients at high risk for PHN. Early multidisciplinary intervention (eg, pharmacotherapy combined with electroacupuncture and other physical therapies) is recommended for these patients to lower the incidence of refractory PHN.

An ideal sham acupuncture control should meet three basic conditions: (1) the placebo acupuncture has no or almost no specific therapeutic effect; (2) acupuncture is applied to non-therapeutic sites; (3) participants cannot perceive the difference between placebo and therapeutic acupuncture. However, due to the complexity of acupuncture manipulation and the diversity of therapeutic effects, it is not easy to fully meet the above requirements. The stimulation of the sham acupuncture needle is obvious to patients with PHN and pain sensitization. It provides a certain amount of stimulation, and the location of the PHN is clear. Using acupoints in other parts may arouse the suspicion of participants in actual operation, affecting their compliance. For the above reasons, we will use a small-stimulating flat needle to perform placebo acupuncture at the same acupoints as the acupuncture group and not apply further pressure after contacting the patient's skin to produce only an extremely brief stimulation for the patient as much as possible to ensure the rationality of the sham acupuncture control in this trial.

In traditional Chinese medicine, ZAP is considered to be caused by a deficiency of the body's healthy energy and the external penetration of damp-heat-toxin, and it is called "Snake Herpes". The end of the herpes is the snake head, and its tail end near the spine is a snake tail. Therefore, in this trial, the Jiaji and Ashi points with obvious pain at the snake head or snake body are selected as the therapeutic points to eliminate residual pathogenic factors, promote the flow of collaterals, and relieve pain. The electroacupuncture parameters in this trial are selected as the 2/100 Hz sparse-dense wave according to existing research findings. The single-treatment duration and treatment frequency are selected based on previous studies and current clinical practice, with each session lasting 30 min and three sessions per week. After a 3-month follow-up after the 4-week treatment period, we will analyze the overall efficacy of this treatment regimen for patients with PHN using linear mixed-effects models and evaluate whether it can serve as a supplementary and alternative treatment option for patients with PHN.

Limitations

This study design has several limitations. First, this preliminary trial aims to assess the value of serum biomarkers in evaluating the condition and prognosis of PHN. As an initial study, the results may only reveal a correlation between biomarkers and pain symptoms, rather than a quantitative relationship between the two. Therefore, the results of this trial should be interpreted with caution when considering conducting further large-scale studies. Second, due to the nature of acupuncture manipulation, it is impossible to blind the acupuncturist. To mitigate this, independent, blinded evaluators who are not involved in treatment delivery will conduct all outcome assessments, reducing the risk of measurement bias.

Furthermore, an intent-to-treat analysis will be employed to minimize bias arising from participant attrition. Third, patients with PHN may experience pain sensitization. Compared with patients with other diseases, a blunt needle may cause a certain amount of stimulation in these patients. Therefore, no further pressure is applied after the sham needle contacts the skin, in order to produce only an extremely brief stimulation as much as possible, and a Waiting-list control group is set up as a control. Fourth, the sham acupuncture protocol, which specifies "no further pressure is applied after the sham needle contacts the skin", lacks a precise quantitative criterion (eg, a specific pressure range). While this design aims to minimize stimulation, the absence of quantitative measurement makes it difficult to standardize the minimal pressure applied across practitioners and centers, representing a potential source of variability.

Conclusions

This multicenter, sham-controlled, randomized RCT assesses electroacupuncture's efficacy and safety for PHN. It is the first RCT for PHN using serum biomarkers as outcomes, exploring their value in assessing PHN severity and predicting refractory PHN occurrence, attempting to provide new insights for exploring objective indicators of PHN. However, the exclusion of patients with cephalic/visceral PHN or those with prior acupuncture experience may limit the generalizability of our findings. Future studies should aim to include these populations to validate the efficacy of EA across a broader spectrum of PHN presentations.

If the trial results are positive, it will provide a basis for further expanding into larger sample-sized real-world studies, exploring the positive concentration range and sensitivity of serum biomarkers for PHN, and providing objective quantitative indicators for evaluating the progression of PHN. During the treatment process, serum biomarkers can be utilized to assess the prognosis of patients with PHN, enabling timely escalation of therapeutic strategies and reducing the incidence of refractory PHN.

Trial Status

This study is scheduled to commence in July 2025 and is expected to be completed by December 2026. As of the writing of this manuscript, participant recruitment has not yet begun. Three research centers will collaboratively conduct participant recruitment, intervention delivery, follow-up assessments, and data collection.

Abbreviations

EA, Electroacupuncture; PHN, Postherpetic Neuralgia; NRS, Numerical Rating Scale; HAMA, Hamilton Anxiety Scale; HAMD, Hamilton Depression Scale; SF-36, The Short-Form 36 Health Survey; NPY, Neuropeptide Y; SP, Substance P; TNF-α, Tumor Necrosis Factor-α; IL-10, Interleukin-10; ROC, Receiver Operating Characteristic; AUC, Area Under the Curve; CRFs, Case Report Forms; SPIRIT, Standard Protocol Items: Recommendations for Interventional Trials; WHO, World Health Organization; WC, Waiting-list Control; SA, Sham Acupuncture; PROMIS, Patient-Reported Outcomes Measurement Information System; VAS, Visual Analog Scale; TBI, Traumatic Brain Injury; DRG, Dorsal Root Ganglion.

Data Sharing Statement

The data presented in this study are available on request from Dexiong Han, Email han_0213@163.com.

Ethics Approval and Consent to Participate

The study will be conducted according to the guidelines of the Declaration of Helsinki and ethics approval (ZSLL-KY-2025-034-01, 1 July, 2025) has been obtained from the Institutional Ethical Review Board of the Third Affiliated Hospital of Zhejiang Chinese Medical University. Before registration, all participants read and sign the written consent form. A copy of the signed consent form is given to the participant.

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

Qintao Yu and Xinru Wang are co-first authors for this study. The authors report no conflicts of interest in this work.

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