Jiangsu Province Hospital of Chinese Medicine

Affiliated Hospital of Nanjing University of Chinese Medicine

Clinical Study Protocol

Analgesic Effect of Electroacupuncture on Postherpetic Neuralgia: a Multicenter Randomized Controlled Trial

eTrack study number 2020NL-103-02

Abbreviated Title AEEPN

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Trial registration Clinicaltrials.gov identifier: NCT04560361

Version date Amendment 4.0 Final: April 15, 2021

PROTOCOL REVISION HISTORY

Version Number	Version Date	Summary of Revisions Made
Amendment 1.0	June 16, 2020	Draft version for GPC review
Amendment 2.0	July 3, 2020	Draft version reviewed by Ethics Committee
Amendment 3.0	August 4, 2020	Trial version after review (corrections and additions)
Amendment 4.0	April 15, 2021	Final Version: Update clinical sub center information; add a secondary outcome (Zoster Brief Pain Inventory); correction of minor typos throughout

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Declaration of Interests

The study director of the AEEPN trial and the principal investigators of other 7 clinical centers have no financial or other conflict of interest. The research results of this study are owned by primary sponsors, and all secondary sponsors will be signed in order of contribution.

Confidentiality Statement

The clinical scientific research data, technical information and other information provided in this document is strictly confidential and is available for review to the sponsor, researchers, Ethics Committees, investigators, investigation review committees, and other government regulatory agencies. Without the written authorization of the protocol developing investigator, no disclosure, notification, or transfer is allowed.

CONTENTS

1. Background

Postherpetic neuralgia (PHN) is the most common complication of herpes zoster (HZ) and it is a kind of severe and intractable pain. According to meta-analysis data, the annual incidence of this disease is 3.9-42.0/100,000 people[1]. The annual incidence of HZ is 3‰-5‰, about 5%-30% of patients with HZ have PHN, and 30%-50% of PHN patients have experienced persistent pain for more than 1 year[2], of which middle-aged and elderly people are the main population of PHN. Clinical manifestations of the disease for patients suffering from nerve distribution of sudden or persistent burning, tingling, jumping pain or knife cutting pain, many pain allergies or pain abnormalities, such as wind, light touch can produce severe pain, often affect diet and sleep.

Due to prolonged severe pain, patients often have mental symptoms such as depression and irritability. In the area of skin damage, scars, pigmentation or pigment shedding left after the skin lesion can be seen. Although the occurrence and prognosis of this disease are related to many factors, the body's own immune function status has a direct impact. For patients with strong immunity, even without medicine, they can contain varicella-zoster virus through their own strong immunity and heal themselves quickly. For people with low immunity, high work pressure, staying up late, sick, overworked, or older patients with basic systemic diseases, the incidence of PHN is extremely high, and severe cases often have recurring attacks. Even the pain lasts for months or years, which seriously affects the patient's quality of life, and even leads to depression of the patient, seriously affecting their living ability and social activities, and increasing the burden on individuals and society.

For patients with PHN, antiviral and analgesic treatments are often used clinically to regulate immune function and nourish nerves. Because the varicella-zoster virus has considerable nerve and skin toxicity, when the subcutaneous nerves are destroyed by the virus for a long time, although some antiepileptic drugs (such as gabapentin, pregabalin), tricyclic antidepressants (such as nortriptyline), opioids, 5% lidocaine

patch, etc., as well as nerve block therapy can relieve the patient's pain to a certain extent, but may cause serious side effects, and the treatment effect is not good. Pain is prone to recurrence after the drug is stopped, making PHN become a pain problem in the medical field and a potential killer of the health of middle-aged and elderly people. Therefore, finding a treatment method that can effectively relieve the pain of patients with PHN without pharmacological side effects has become the common demand of today's society and the majority of pain patients, and has strong clinical research significance.

According to clinical experience and related literature reports, electroacupuncture has a certain analgesic effect on PHN. According to Chinese National Knowledge Infrastructure (CNKI) literature reports, Therapies such as blood pricking, cupping, ozone, acupoint embedding, moxibustion, acupuncture bloodletting, and fire needling have a certain therapeutic effect on PHN. There is no high-quality clinical randomized controlled study specifically aimed at the analgesic effect of electroacupuncture in the treatment of PHN. A correlation study retrieved in the National Center of Biotechnology Information (NCBI) in the United States reported that the effectiveness of electroacupuncture at Jiaji points combined with moxibustion and intermediate frequency treatment on PHN[3], and Tongji Medical College of Huazhong University of Science and Technology reported that electroacupuncture can improve the heat sensitivity and mechanical sensitivity of rats with PHN[4]. However, there is no report on the clinical randomized controlled (RCT) study of the analgesic effect of electroacupuncture on PHN.

In view of the high epidemiological incidence of PHN, the severity and stubbornness of pain, the disease is insensitive to many drugs, and the existence of drug resistance and many drug side effects, to bring great pain and distress to patients, so the treatment of PHN has become a world problem. However, the clinical randomized controlled study related to the analgesic effect of electroacupuncture on PHN has not been reported in the literature so far. Therefore, our research group initiated this clinical trial, mainly

on Ashi point, combined with the distal acupoints Zhigou and Yanglingquan, to evaluate whether electroacupuncture can effectively relieve the pain of patients with PHN, and to provide a strong basis for clarifying the treatment of PHN by electroacupuncture.

2. Study Objectives

The objective of this study is to examine the analgesic effect and safety of electroacupuncture and sham electroacupuncture for the treatment of PHN.

3. Methodology

3.1 Trial design

The Analgesic Effect of Electroacupuncture on Postherpetic Neuralgia (AEEPN) study is a multicenter, prospective, parallel-arm, randomized, participant-blinded, sham electroacupuncture-controlled clinical trial of an estimated 448 patients with PHN, which follows the Declaration of Helsinki and the Quality Management Practices for Clinical Trials of Medical Devices. The study duration (as shown in Figure 1) is about 10 weeks, which includes a washout period (7 days or more), a screening observation period (3 to 7 days), a treatment period (4 weeks), and a follow-up period (1 month). AEEPN is conducted at 7 hospitals in China and the ethics committee of each hospital approved the study protocol.

3.2 Randomization

Eligible patients are randomly allocated in a ratio of 1:1 to the EA or SEA group by a central randomization system (Clinical Research Data Collection and Management System of Jiangsu Province Hospital of Chinese Medicine). Multi-center stratified variable block randomization is used, and the block size of each center is randomly set to 4, 6, and 8. Considering that the number of patients in each stratum fluctuates due to block variation, 21 stratums are preset at random and take the first 7 groups with the number of patients equal to 64 as the final grouping. The randomization sequence is

generated and validated by an independent statistician using R software, and then imported into EDC's central randomization system and kept by an administrator who do not participate in this trial. The central randomization system has set strict personnel permissions, and no one has right to view the randomization scheme except the highest-level system administrator. After participants meet all the inclusion criteria and complete the baseline assessment, an acupuncturist will log in to the central randomization system to apply for random numbers which will be displayed then, and the patients will receive the corresponding treatment. The Clinical Research Coordinators (CRCs) will be responsible for enrolling participants, obtaining informed consent, and CRF recording.

3.3 Blinding

Patients and CRCs (i.e., outcome assessors, data recorders, data entry clerks and statistical analysts) are blinded to the group assignment. Due to the nature of the intervention, acupuncturists are not be blinded to the treatment.

3.4 Sample size

According to previous studies, it is anticipated that a difference in primary outcome (NRS-11) between EA group and SEA group is 1.2 and the combined standard deviation of the two groups is 3.5. To achieve 90% statistical power and control the type I error rate below 0.05, we calculated by PASS 15 that a sample of 448 participants (224 participants in each group) will be required to detect a two-sided significant difference between the two groups and compensate for a dropout rate of 20%. All participants are equally distributed among 7 clinical centers, and 64 participants per center will be recruited.

4. Subjects

4.1 Diagnostic criteria

Guidelines for the management of herpes zoster based on the European consensus Part 1: diagnosis (under the guidance of the European Dermatology Forum (EDF) and the European Academy of Dermatology and Venereology (EADV), 2017)[5], and the 2016 edition of the guidelines and specifications of the Chinese expert consensus on the diagnosis and treatment of postherpetic neuralgia: have a clear history of acute HZ and the pain persists for more than 90 days after the onset of erythematous macules and rash.

The auxiliary indications for PHN:

- The lesions are usually accompanied by paroxysmal, persistent or evoked pain, sensory abnormalities and hyperalgesia, and have the characteristics of distribution according to innervation area;
- The lesions may be accompanied by manifestations of autonomic nervous dysfunction such as hyperhidrosis;
- Local skin can be seen with residual scars or pigmentation;
- Patient's ability of daily living changes, that may be accompanied by sleep disorders, anxiety, low mood and depression.

4.2 Eligibility criteria

- Meet the diagnostic criteria for PHN;
- Men or women between 45 and 75 years;
- Diagnosed with moderate or higher pain during the screening observation period (daily pain scores of 11-point numeric rating scale (NRS-11) were collected during the observation period, and the average pain score $\geq$4) ;
- Did not participate in other ongoing clinical studies;
- Volunteer to participate in the AEEPN trial and sign the informed consent form

(ICF).

4.3 Exclusion criteria

- patients who are currently receiving, or have received more than one "permitted concomitant medications" or any "prohibited concomitant medications and treatments" for the treatment of PHN at least 14 days before the screening observation period, and are unwilling to undergo a washout period (≥7 days), or patients with serious safety issues during the washout period or observation period;
- Patients who are expected to receive any new prescription drug or other treatment for PHN after the start of the trial;
- Patients with serious uncontrolled medical conditions, such as cardiovascular, lung, liver, kidney, gastrointestinal tract, metabolism, endocrine, nervous system, respiratory system, urogenital system and other serious diseases, or systemic organ dysfunction, malignant tumor, hematologic disease such as bleeding tendency or coagulation dysfunction, serious mental illness such as depression or schizophrenia Symptoms, hepatitis B antigen or hepatitis C antibody positive known state or history of immune dysfunction, history of HIV infection, etc.;
- Patients with severe pain unrelated to PHN, such as after surgery for clinical major diseases;
- Patients with PHN who have received nerve intervention or other neurosurgical treatment, such as selective nerve damage, percutaneous radiofrequency thermocoagulation or pulsed nerve modulation technology, etc.;
- Patients with some special types of herpes zoster, such as those with meninges, cornea, conjunctiva, ear involvement, visceral herpes zoster, generalized herpes zoster;
- Patients with skin ulceration, new herpes, or skin infection;
- Patients with cardiac pacemaker, metal allergy or severe fear of needle;
- Patients who are unable to give full informed consent or cannot cooperate with pain

scale assessment due to mental, mental, linguistic or behavioral disorders;

- Patients who have poor compliance or are prone to fall off due to other reasons, such as the current residence is not in the city where the recruitment hospital is located, or the working environment changes frequently;
- Pregnant and lactating women

4.4 Subject termination

- Those who cannot tolerate acupuncture, have serious adverse events during the treatment, and should stop the clinical trial of this case according to the doctor's judgment;
- During the research period, the subject has serious complications or other serious diseases and needs emergency measures; or has other diseases that affect the observation of the test, and the clinical trial should be stopped according to the doctor's judgment;
- During the clinical trial, the subject is unwilling to continue the clinical trial for various reasons, and actively asks the doctor in charge to withdraw from the clinical trial.

4.5 Subject dropping and handling

Criteria for Subject dropping: subjects who have received informed consent and screened qualified to enter the randomized trial, who fail to complete the course of treatment and observation period specified in this program for some reason, are regarded as dropped cases.

Disposal of subjects dropping:

- When the subject falls off, the person in charge of the project will contact the subject as much as possible, ask the reason, record the details, and complete the evaluation project as much as possible by means of door-to-door visits, follow-up appointments, telephone calls, and WeChat.

- If the test case is withdrawn due to needle allergy or fainting or other adverse reactions, and treatment is ineffective, the person in charge of the project will take corresponding measures based on the actual conditions of the subjects.
- Relevant test data are properly kept for the dropped cases and kept in files for subsequent statistics of the full analysis set. There is no need to re-recruit subjects to fill the number of dropped cases.

4.6 Subject elimination

- Due to the patient's concealment of the condition or other conditions, cases that did not meet the inclusion criteria and met the exclusion criteria were found after inclusion.
- After being included, they refused to participate in the trial and have not yet recorded any clinical data.

Before the statistical analysis of the data, the statistician and the main researcher shall discuss and judge whether the case should be eliminated.

5. Interventions

5.1 Lifestyle education

All participants will receive lifestyle interventions as basic treatment: advocate reasonable diet for patients, promote healthy diet knowledge of low-salt, low-fat and low-sugar; identify patients' concerns, help patients relieve stress factors and reduce avoidance behavior, establish a positive doctor-patient relationship; review patients' drug dosage, quality of life, daily activity ability, anxiety and depression assessments, provide healthy lifestyle education.

Electroacupuncture therapy program is developed by the consensus reached by acupuncture experts based on previous studies of electroacupuncture for PHN. This study will use Hwato brand disposable acupuncture needles (size: 0.30 × 40 mm), placebo blunt needles (size: 0.40×13 mm), insulating adhesive pads (Chinese patent

number: ZL 2020 2 1980069.2), and SDZ-V electroacupuncture apparatuses.

5.2 Electroacupuncture (EA) group

Points selection: ipsilateral Zhigou (SJ6), Yanglingquan (GB34), and Ashi points.

Location: Refer to the National Standard of the People's Republic of China "Acupoint Name and Location" (GB/T 12346-2006) for acupoint location.

Operation method: Participants take the appropriate position on the treatment bed according to the location of PHN. After routine skin disinfection, the sterile insulating adhesive pads are placed on ipsilateral Zhigou, Yanglingquan and Ashi points. Then acupuncture needles are inserted vertically into the skin of Zhigou and Yanglingquan through the pads approximately 15 to 20 mm, and performs slight, equal manipulations of twirling and lifting to reach the sensation of deqi (known as soreness, numbness, distention, heaviness or other sensations, which is considered to indicate effective acupuncture). Besides, acupuncture needles are inserted obliquely (at an angle of 30 to 45 degrees) into the skin of Ashi points through the pads approximately 10 mm, and point the needle towards the painful area of PHN. The paired poles of electroacupuncture apparatus are connected to the needle handles at ipsilateral Zhigou and Yanglingquan, and for Ashi points, the paired poles are connected to the head and tail acupoints of the long axis of the painful area. The waveform of electroacupuncture stimulation is a continuous wave with a frequency of 2 Hz and a current intensity of 1-5 mA (causing mild tremor of the skin around the acupoints without pain), and continue the electroacupuncture treatment for 30 minutes.

Frequency and duration of treatment: All patients will receive electroacupuncture treatment once per day, 5 times a week for 4 consecutive weeks (20 treatments in total).

5.3 Sham electroacupuncture (SEA) group

Participants randomly assigned to the SEA group will received sham electroacupuncture by using placebo blunt needles at the same acupoints. After

disinfecting the skin and placing the sterile insulating adhesive pads on ipsilateral Zhigou, Yanglingquan and Ashi points, placebo blunt needles are inserted through the pads and reach the insulating adhesive layer, causing the participants to feel the needle resistance (a sensation of needle insertion). Other procedures, electrode placements, parameter of electroacupuncture apparatus and treatment settings are the same as in the EA group, but with no skin penetration or electricity output.

6. Concomitant Medications

6.1 Permitted concomitant medications

During the first visit, the medication usage of the participants in the last 2 weeks will be inquired in detail and recorded, including drug name (or other therapy name), indications, dosage unit, frequency of administration, route of administration, and start and end time of medication.

Participants will be allowed to take only one of the following medications to treat PHN if they take a stable dose level for PHN at least 14 days before the screening period:

- any anticonvulsant drugs (e.g., pregabalin, gabapentin, oxcarbazepine, carbamazepine);
- any one of serotonin-norepinephrine reuptake inhibitors (SNRIs) (venlafaxine, duloxetine, milnacipran);
- any TCAs (e.g., amitriptyline, nortriptyline, clomipramine, doxepin, desipramine);
- any opioid analgesics (e.g., tramadol, codeine, morphine, oxycodone, methadone);
- any one of oral Non-steroidal anti-inflammatory drugs (NSAIDs) (e.g., ibuprofen, aceclofenac, celecoxib, nimesulide, meloxicam, diclofenac, ketotifen, naproxen).

Afterwards, the participants should maintain the medication regimen during the entire study period unless there are safety issues during the observation period. If the participant wants to adjust the medication regimen, he or she can apply to his or her doctor, who can adjust the medication plan after the specific condition has been

assessed.

Participants will be allowed to take a stable dose of the following drugs for the treatment of underlying diseases throughout the study:

- benzodiazepines, non-benzodiazepines (e.g., eszopiclone) or related drugs for insomnia;
- stable dose of diuretics, calcium antagonists or related drugs for the treatment of hypertension;
- the selected 5-serotonin reuptake inhibitor for depression (e.g., sertraline, fluoxetine);
- β agonists or anticholinergic drugs for chronic obstructive pulmonary disease;
- oral aspirin for cardioprotection;
- hypolipidemic drugs;
- vitamin D, calcium supplements, or related drugs for the prevention of osteoporosis;
- other drugs not included above and not related to the treatment of PHN.

6.2 Prohibited concomitant medications

The prohibited concomitant medications for the AEEPN trial are as follows:

- any topical medication for PHN, including 5% lidocaine patch, lidocaine ointment, capsaicin patch, NSAIDs and any other topical drug preparations for the treatment of PHN;
- monoamine oxidase inhibitors or any other antidepressants not included in the permitted concomitant medications;
- steroids;
- mexiletine;
- lamotrigine;
- ibuprofen and codeine phosphate tablets;
- alpha-lipoic acid;
- evening primrose oil;

- any skeletal muscle relaxant (e.g., botulinum toxin, baclofen);
- any antipsychotics or neuroleptic medications;
- any other medication for pain relief not included above.
- during the study period, any neuromodulation techniques (e.g., nerve pulse radiofrequency, nerve electrical stimulation), nerve block, and other forms of analgesic therapy that may confuse the evaluation of PHN is prohibited.

6.3 Rescue medication

Participants will be allowed to take oral paracetamol/acetaminophen (up to 2 grams per day, as needed) as rescue medication for unacceptable pain. The use of rescue medication must be promptly recorded in the CRF and entered into the EDC system, and all participants are discouraged from receiving any prohibited medications or treatments throughout the trial, if received, they are asked to document all.

7. Outcomes measures

7.1 General record items

Hospital code, case random number, abbreviation of subject's name, start date of trial.

7.2.1 Biological information

Demographic characteristics: gender, age, height, weight, medical history, marriage, education

History of PHN: course of disease, location of onset, TCM syndrome, medication and treatment for PHN in the past 14 days

Basic diseases: medication and treatment for basic diseases in the past 14 days

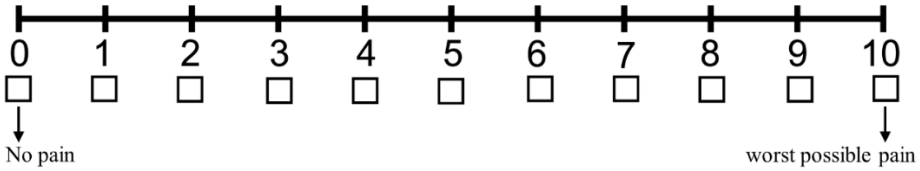
Observation time point: Collect the above data before enrollment

7.2.2 Outcomes

7.2.2.1 primary outcome

11-point numeric rating scale (NRS-11)[6-8]: Use a scale of 0-10 to represent different degrees of pain: 0 means no pain; 10 means severe pain.

The grading standard of pain degree is: 0: no pain; 1-3: mild pain; 4-6: moderate pain; 7-10: severe pain.



Time Frame: Change from Baseline at 4 weeks

7.2.2.2 Secondary Outcomes

7.2.2.2.1 11-point numeric rating scale (NRS-11)

Time Frame: Change from Baseline at 1 day, 3 days, 1 week, 2 weeks, 3 weeks and 4 weeks, one-month follow-up after treatment

7.2.2.2.2 Visual analogue scale (VAS)[8,9]

A horizontal line 10cm long (or 100mm), one end of the horizontal line indicates no pain (0); the other end indicates the most severe pain imaginable (10); the middle part indicates different degrees of pain. Ask the subjects to draw a vertical line mark at the place closest to their pain level to quantify the intensity of their pain.

Time Frame: Change from Baseline at 1 day, 3 days, 1 week, 2 weeks, 3 weeks and 4 weeks, one-month follow-up after treatment

7.2.2.2.3 Verbal rating scale (VRS)[7]

According to the grading method used to assess the degree of pain in the subject, the evaluator divided the degree of pain in the subject from no pain to severe pain, which

is relatively simple and has a good correlation with NRS. VRS was scored with "no pain" = 0, "mild pain" = 1, "moderate pain" = 2, and "severe pain" = 3.

- Level 0: No pain.
- Level I (mild): Pain, but tolerable, can live a normal life, sleep is not disturbed.
- Level II (moderate): Pain is obvious, intolerable, painkillers are required, and sleep is disturbed.
- Level III (severe): The pain is severe and unbearable, analgesics must be used, sleep is severely disturbed, and it may be accompanied by autonomic disorders or passive posture.

Time Frame: Change from Baseline at 1 day, 3 days, 1 week, 2 weeks, 3 weeks and 4 weeks, one-month follow-up after treatment

7.2.2.2.4 Mechanical pain threshold (MPT)[10-13]

In order for the subject to focus on the sensory test, the test should be in a quiet room. After exposing the test site (select the middle position of the PHN, try to ensure that the test position is basically unchanged at subsequent time points; avoid scars and injury sites), the researcher should ask the subject to close their eyes or look away, using 20 hand-helds The Von frey filament (starting from the 2.83 specification) is applied vertically on the skin surface until the filament is bent into a 90 degree or "C" shape and remains in place for about 1.5 s. The subject indicated whether the Von frey filament caused pain by answering "yes" or "no". If the subject answers "No", use a larger diameter filament to increase the intensity application until the subject responds. After the subject answered "yes", the descending stimulus sequence was used, and the smaller diameter filament was used to reduce the intensity of the stimulation until the subject answered "no". Alternate between ascending and descending order until 5 deflection points are recorded. The final mechanical pain threshold is the geometric mean of these 5 points.

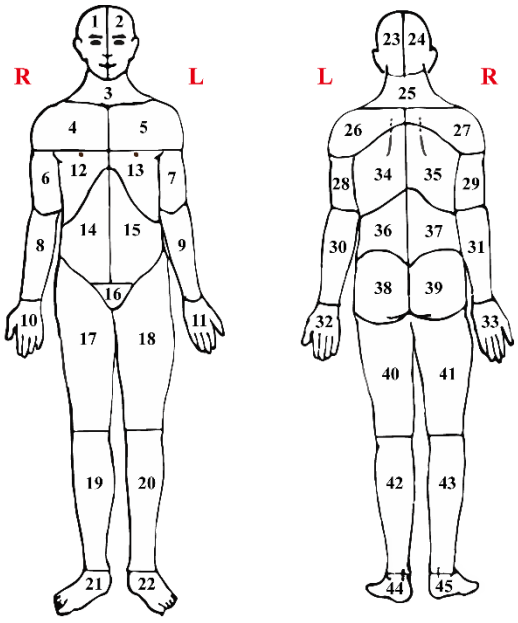
Time Frame: Change from Baseline at 1 day, 3 days, 1 week, 2 weeks, 3 weeks and 4 weeks, one-month follow-up after treatment

7.2.2.2.5 Pain area of PHN (PAP)[14,15]

Refer to the scoring method of the 45 body areas rating scale.

PHN pain area = the patient's body surface area (BSA, m^2) * "pain area code" as a percentage of body surface * "PHN area" as a percentage of pain area (assessed by the investigator)

45 Body Areas Rating Scale (BARS-45)



Body surface area (BSA)

$BSA\ (m^2) = \sqrt{Ht\ (cm) * Wt\ (kg)\ /3600}$

Pain area code	Percentage of body surface area
25, 26, 27	0.50%
4, 5, 16	1.00%
3, 8, 9, 10, 11, 30, 31, 32, 33	1.50%
1, 2, 21, 22, 23, 24, 44, 45	1.75%
6, 7, 12, 13, 28, 29, 36, 37	2.00%
38, 39	2.50%
14, 15	3.00%
19, 20, 42, 43	3.50%
34, 35	4.00%
17, 18, 40, 41	4.75%

Time Frame: Change from Baseline at 1 day, 3 days, 1 week, 2 weeks, 3 weeks and 4 weeks, one-month follow-up after treatment

7.2.2.2.6 Average number of pain episodes (ANPE)[16] (Within 24 hours)

- Painless: 0 times
- Intermittent pain: 1-50 times (optional 1-2, 3-5, 6-10, 11-50)
- Persistent pain: >50 times

Time Frame: Change from Baseline at 1 day, 3 days, 1 week, 2 weeks, 3 weeks and 4 weeks, one-month follow-up after treatment

7.2.2.2.7 Average duration of each pain episode (ADEPE)

Duration range: 0 minutes (no pain) -24 hours (persistent pain)

Time Frame: Change from Baseline at 1 day, 3 days, 1 week, 2 weeks, 3 weeks and 4 weeks, one-month follow-up after treatment

7.2.2.2.8 Short form of McGill pain questionnaire 2 (SF-MPQ-2)[17-21]

It includes four dimensions: persistent pain, paroxysmal pain, neuropathic pain, and the influence on mood, with a total of 22 items (See appendix 1).

Time Frame: Change from Baseline at 4 weeks, one-month follow-up after treatment

7.2.2.2.9 Zoster brief pain inventory (ZBPI)[22] (See appendix 2)

Time Frame: Change from Baseline at 4 weeks, one-month follow-up after treatment

7.2.2.2.10 Depression, anxiety and positive outlook scale (DAPOS)[23] (See appendix 3)

A reliable and brief scale that specifically evaluates the mood of patients with pain, including depression, anxiety, and positive influence, with a total of 11 items. Each item is scored 1-5, 1 point means never happening, 5 points means always happening.

Time Frame: Change from Baseline at 4 weeks, one-month follow-up after treatment

7.2.2.2.11 Patient global impression of change (PGIC)[24]

Clinical overall impression scale, to assess whether the patient's clinical condition has improved or declined. Score 1-5, in order of obvious improvement, slight improvement, no change, slight aggravation, and obvious aggravation.

Time Frame: Change from Baseline at 4 weeks, one-month follow-up after treatment

7.2.2.2.12 Safety of electroacupuncture (SEA)

Evaluation is performed before and after each treatment. Contents include broken needles, fainting needles, unbearable acupuncture pain (VAS $\geqslant$ 8 points), local hematomas, infections and abscesses; other discomforts after acupuncture (after acupuncture with a duration of 1 hour or more after the needle stick) Pain, nausea, vomiting, palpitations, dizziness, headache, anorexia and insomnia) symptoms, average severity and average duration; and other unforeseen adverse events.

This study requires patients to report adverse reactions at any time, and doctors timely record the name, frequency and duration of adverse reactions.

7.2.2.2.13 Use of concomitant medications

The percentage of patients using concomitant medications and the changes in dosage

and frequency of concomitant medications (including rescue medication) is analyzed after the completion of the trial.

8. Safety assessment standard

8.1 Observation of adverse events

Adverse events are any unexpected symptoms, signs, or health conditions during the entire clinical study period (including washout period, observation period, routine treatment period, follow-up period, a total of 10 weeks), and may not have a causal relationship with the treatment in this study. Health conditions or diseases that existed before the start of this study can only be considered as an adverse event if they deteriorate further after starting the treatment of this study. Abnormal laboratory test values or test results can only be considered adverse events (AE) when they cause clinical symptoms or signs, are considered clinically significant or require treatment.

Use non-inductive questions at each visit during the study period to discover adverse events from patients. Adverse events may also be reported by the patient during or between visits or discovered through physical examination, laboratory examination or other methods. All adverse events must be recorded on the adverse events page of the CRF, and the following information about the adverse events must be provided at the same time:

- Severity (mild, moderate, severe).
- The relationship with the research treatment (definitely related, very likely related, possibly related, possibly unrelated, definitely unrelated).
- Duration (start and end dates or whether they still exist at the time of the last inspection).
- Whether it is a serious adverse event (SAE). A serious adverse event (SAE) is defined as an adverse event leading to any of the following outcomes: 1) leading to death. 2) Fatal or life-threatening. 3) Lead to permanent or significant loss of

function or disability. 4) The patient needs to be hospitalized or the existing hospitalization time is extended, unless the hospitalization is due to: ① Conventional treatment or monitoring of research indications has nothing to do with any deterioration of physical condition; The disease undergoes elective or pre-planned treatment, and the disease has not deteriorated after the application of the research treatment; ③In the outpatient and emergency department, the event did not meet the criteria for serious adverse events mentioned above, and did not lead to hospitalization; ④Social reasons And containment, and the patient’s general condition has not deteriorated. 5) Lead to congenital malformations or birth defects. 6) Other important medical events, that is, the event causes harm to the patient or may require medical or surgical intervention to prevent the occurrence of any one of the results listed in the above definition. Unlike conventional safety assessments, SAE requires continuous monitoring and special reporting requirements.

- All adverse events need to be dealt with correctly. Treatment methods may include one or more of the following methods: no measures are taken (that is, only further observation); study treatment adjustment/temporary interruption; permanent suspension of study treatment due to the adverse event; addition of combined drug treatment; non-drug treatment ; Allow the patient to be hospitalized or extend the patient's hospital stay. The measures taken to deal with adverse events shall be recorded on the adverse events page of CRF. Once an adverse event is found, follow-up until it is resolved or until it is determined that it is permanent, and at each follow-up (if necessary, the frequency of follow-up can be increased) changes in the severity of the adverse event, suspicious relationship with the treatment of this study, and the need The intervention means and results are evaluated.

8.2 Standards for judging the severity of adverse events

- Mild: The subject can tolerate it, does not affect the treatment, does not require special treatment, and has no effect on the subject's recovery.

- Moderate: The subjects are unbearable and need to withdraw the drug to suspend the test or do special treatment, which has a direct impact on the subjects' recovery.
- Severe: Endangering the life of the subject, causing death or disability, requiring immediate withdrawal or emergency treatment.

8.3 Treatment of adverse events

8.3.1 Observe and record

Researchers should ask patients to truthfully report the changes in their condition after acupuncture and avoid induced questions.

Any adverse reaction during the test should be filled in the "Adverse Event Form", followed up and investigated, and the treatment process and results should be recorded in detail until the laboratory examination returns to normal and the symptoms and signs disappear. Follow-up and follow-up methods can choose hospitalization, outpatient clinic, home visit, telephone, communication, etc. according to the severity of adverse reactions.

8.3.2 Medical treatment

When an adverse reaction is discovered, the researcher decides on diagnosis and treatment measures based on the condition and decides whether to suspend the observation. In the event of a serious adverse event, the study immediately took necessary measures to protect the safety of the subjects.

8.3.3 Report

For all adverse events that occurred during the clinical study period (including washout period, observation period, routine treatment period, and follow-up period, a total of at least 10 weeks), the investigator must truthfully fill in the "Adverse Events/Adverse Reaction Record Form" and include it on the report Sign and date. If a serious adverse event (SAE) occurs, it will be handled as usual, regardless of whether it is related to the treatment of this study, it must be reported to the head of the PHN clinical trial group

of Jiangsu Provincial Hospital of Traditional Chinese Medicine within 24 hours of the investigator's knowledge (contact/Tel: Jianhua Sun /13914722816, Email: 377201634@qq.com), and report to the ethics committee; if the enrolled patient is pregnant, it is also regarded as a major event, and the adverse event/adverse reaction record form must be filled in, and the investigator is informed Report to the person in charge of the PHN clinical trial group of Jiangsu Provincial Hospital of Traditional Chinese Medicine within hours (contact person/telephone: Jianhua Sun/13914722816, email: 377201634@qq.com), and report to the ethics committee at the same time.

9. Quality control and assurance of the study

9.1 Clinical quality control measures

Establish standard operating procedures and quality control procedures for experimental observation indicators. The test results must be printed on a computer, and the data should be traceable.

9.2 Pre-clinical trial training

In order to ensure the smooth progress of the research, the research team must hold a special clinical training meeting to conduct unified training for clinical researchers before the official launch of the clinical trial.

Carry out key training on the project implementation plan and various standard operation procedures (Standard Operation Procedure, SOP), so that each clinical researcher (including acupuncture operators, scale evaluators, research nurses, quality controllers and other related research Personnel) To be familiar with the research process and specific test implementation rules to improve the consistency of internal observations by researchers and the consistency between observers, and to ensure the reliability of clinical research conclusions.

Sign the investigator's statement and establish indicator observation and quality control SOPs in the participating hospitals.

9.3 Measures to improve subject compliance

In order to obtain better compliance, make the final summary analysis not less than 80% of the total number of cases entered into the trial, adopt the following measures to improve patient compliance: adhere to the principle of voluntariness, sign patient informed consent; from medical treatment Improve and maintain good patient compliance in terms of quality, treatment environment, medical expenses, etc., to encourage patients to adhere to treatment as much as possible during the study period; pay attention to establishing a good doctor-patient relationship, and explain in detail various examinations, treatments and re-examinations for included cases To obtain the patient's consent and cooperation for the purpose and necessity; record their contact information in detail for follow-up.

9.4 Quality control and quality assurance system

Operators in charge of acupuncture treatment in each center must have an acupuncturist qualification certificate and independently undertake clinical treatment for more than 2 years. Scale assessors and other investigators participating in the trial should perform their respective duties, strictly follow the clinical trial protocol, and adopt standard operating procedures to ensure the implementation of the clinical trial quality control and quality assurance system.

10. Data collection, management, monitoring and auditing

The data collection and analysis, quality assurance, trial conduct and implementation for this study will follow Good Clinical Practice (GCP) guidelines43. Before the AEEPN trial is officially initiated, the research group will hold a specialized clinical training meeting to conduct unified interpretation and training of all clinical researchers on the study implementation scheme, standard operation procedure (SOP), CRF filling, EDC system use and electronic data entry, so that researchers in each clinical center (including acupuncturists, outcome assessors, data recorders, data entry clerks, research

nurses, quality controllers and other related researchers) will be familiar with the study protocol and SOP, thereby the internal observation consistency of researchers will be improved.

All CRFs for each participant will be filled in timely by researchers in each clinical center, including assessment scales, questionnaires, treatment compliance, concomitant medication and rescue medication use, AE, etc.. Any evidence-based correction of CRF, only lines can be drawn. The marginal note modified data will be signed and dated by the researcher, and the original records shall not be erased or overwritten. All original documents and CRFs will be stored in the clinical study office. Besides, all data will be accurately double-entered into EDC system and the electronic CRF are identical to paper CRF. Once the data entry is completed, the database will automatically perform consistency checks, missing value checks, value range and logic checks. If any inconsistencies or missing data are found, the data will be re-checked and corrected based on the original documents and CRFs. And the contents, time and operators of all operations will be recorded by the EDC system to ensure the accuracy, completeness and traceability of the research data entry. When 50% of the participants' data is entered into the EDC system, we will perform an interim analysis on the primary outcome, whichever comes first. This will be performed by an independent statistician and will inform us whether the intervention has been proved to be effective (beyond reasonable doubt). Subsequently, we will decide whether (if necessary) to modify the study or terminate it prematurely. When all data is entered in the EDC system, 10% of the eCRF will be randomly selected for manual inspection, and the database will be locked and sent to the statisticians for further statistical analysis after all data inspection is completed and updated. Finally, we will submit the end of trial notification and final report to the Ethics Committees of 7 clinical centers, the Sponsor and ClinicalTrials.gov.

11. Statistical Analysis

11.1 Choice of analysis data set

Full analysis set: refers to the ideal subject set that is as close as possible to the principle of intentional analysis (the main analysis should include all randomized subjects). This data set is composed of all randomized subjects with the smallest sum It is obtained after a reasonable method is eliminated. Missing data of withdrawn participants is imputed using the multiple imputation method. The number of subjects who evaluated the efficacy at the end point of each group remained the same as that at the beginning of the trial.

Per Protocol Set: In line with the experimental treatment plan, the main variables can be measured, the baseline variables are not missing, and there is no major violation of the experimental plan.

Security set: All subjects who received at least one treatment after randomization.

The main variables were analyzed using the full analysis set and the conforming plan set; the demographics, other baseline characteristics, and other curative effect index analysis were all using the conforming plan set.

11.2 statistical software

SAS 9.4 and graphpad were used for statistical analysis

11.3 Content of statistical analysis

The actual number of subjects in the two groups, shedding and elimination cases, demographic and other baseline characteristics, compliance, observation index analysis and safety analysis.

11.4 Statistical analysis of population

Randomized population: all randomized subjects constitute a randomized population.

According to the ITT principle, all randomized subjects will be statistically analyzed.

11.5 Statistical analysis method

The description of the enumeration data will use the number of cases and percentages, and the comparison between groups will use chi-square test, Fisher's exact probability method, Wilcoxon rank sum test, CMH χ^2 test, and WLS covariance. The description of the measurement data will be carried out using the mean ± standard deviation, median, maximum, and minimum value. Quantitative data conform to a normal distribution with t test (test for homogeneity of variance between groups, with 0.05 as the test level, uneven variance The Satterthwaite method was used for the corrected t test), the Wilcoxon rank sum test and the Wilcoxon signed rank sum test were used for non-normal distribution. The hypothesis test uses a two-sided test uniformly, and the test statistics and the corresponding P value are given. $P<0.05$ is considered statistically significant, and $P<0.01$ is considered highly statistically significant.

12. Ethical considerations

Ethical review: This study will follow the relevant regulations of the World Medical Congress "Declaration of Helsinki". Before the start of the study, the clinical study was carried out after the ethics committee approved the trial protocol. If this protocol is revised during the implementation of the clinical trial, it will be submitted to the ethics committee for approval before implementation.

Benefits and risks: The subjects and the society will benefit from this research, including the pain of the subjects will be improved, and the subjects can get the research-related inspection fees and registration fees for free during the research period. Obtain good medical services during the period. At the same time, this study may help more patients in the international community recognize the analgesic effect of electroacupuncture on PHN patients, so as to help other patients with the same disease get rid of pain as soon as possible. Subjects are at risk of possible adverse events due

to acupuncture during the experiment, such as fainting needles, broken needles, local infections or subcutaneous hematomas, etc. Researchers will take corresponding diagnosis and treatment measures according to the condition, and suspend observation when necessary to protect Subject safety.

Recruitment of subjects: Recruiting subjects announcements, WeChat public account tweets, etc., release relevant information → sign up for interested persons → read research introduction → subject screening → selection of qualified persons → sign informed consent → random subjects Grouping → baseline evaluation → electroacupuncture intervention→collecting observation indicators. Please refer to the attachment for the recruitment notice and research brief, and submit it to the ethics committee for review.

Medical treatment and protection of subjects: The investigator is responsible for the medical treatment of the subjects, ensuring that the subjects receive appropriate treatment in the event of adverse events during the trial.

Subject's privacy protection: The subject's personal privacy and data will be protected during the research process, and the subject's personal information will not be disclosed. Only the researchers participating in the clinical trial may have access to the subject's personal medical records. Data processing will adopt the method of "data anonymity", omit the information that can identify the individual of the subject, and will publish it publicly regardless of whether the research results are positive or negative.

Informed consent process: Before each subject is selected for this study, the investigator will give the subject or his agent a complete and comprehensive introduction to the details of the study, including the purpose of the trial, trial procedures, possible benefits and Risks, subjects' rights and obligations, etc., to enable subjects to fully understand and have sufficient time to consider, and to give their consent after satisfactory answers to all questions raised, and to sign written informed consent, and let subjects know that they have The right to withdraw from this study at

any time, and the informed consent will be retained as a clinical study document for future reference. When each patient signs the informed consent form, the doctor will leave his contact number to the patient so that the patient can contact the doctor at any time when his condition changes.

13. Abbreviations

AEEPN: Analgesic Effect of Electroacupuncture on Postherpetic Neuralgia; PHN: Postherpetic Neuralgia; HZ: Herpes Zoster; Chinese National Knowledge Infrastructure: CNKI; National Center of Biotechnology Information: NCBI; RCT: Randomized Controlled Trials; European Dermatology Forum: EDF; European Academy of Dermatology and Venereology: EADV; CRF: Case Report Form; EDC: Electronic Data Capture; NRS-11: 11-point Numeric Rating Scale; ICF: Informed Consent Form; EA: Electroacupuncture; SEA: Sham electroacupuncture acupuncture; VAS: Visual Analogue Scale; VRS: Verbal Rating Scale; MPT: Mechanical Pain Threshold; PAP: Pain Area of PHN; ANPE: Average Number of Pain Episodes; ADEPE: Average Duration of Each Pain Episode; SF-MPQ-2: Short Form of McGill Pain Questionnaire 2; ZBPI: Zoster Brief Pain Inventory; DAPOS: Depression, Anxiety and Positive Outlook Scale; PGIC: Patient Global Impression of Change; SEA: Safety of Electroacupuncture; AE: Adverse Events; CRCs: Clinical Research Coordinators; GCP: Good Clinical Practice; SOP: Standard Operation Procedure; ITT: Intention-To-Treat.

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Appendix 1

Short-form McGill Pain Questionnaire 2 (SF-MPQ-2)

1. Throbbing pain	None	0	1	2	3	4	5	6	7	8	9	10	worst possible
2. Shooting pain	None	0	1	2	3	4	5	6	7	8	9	10	worst possible
3. Stabbing pain	None	0	1	2	3	4	5	6	7	8	9	10	worst possible
4. Sharp pain	None	0	1	2	3	4	5	6	7	8	9	10	worst possible
5. Cramping pain	None	0	1	2	3	4	5	6	7	8	9	10	worst possible
6. Gnawing pain	None	0	1	2	3	4	5	6	7	8	9	10	worst possible
7. Hot-burning pain	None	0	1	2	3	4	5	6	7	8	9	10	worst possible
8. Aching pain	None	0	1	2	3	4	5	6	7	8	9	10	worst possible
9. Heavy pain	None	0	1	2	3	4	5	6	7	8	9	10	worst possible
10. Tender	None	0	1	2	3	4	5	6	7	8	9	10	worst possible
11. Splitting pain	None	0	1	2	3	4	5	6	7	8	9	10	worst possible
12. Tiring-exhausting	None	0	1	2	3	4	5	6	7	8	9	10	worst possible
13. Sickening	None	0	1	2	3	4	5	6	7	8	9	10	worst possible
14. Fearful	None	0	1	2	3	4	5	6	7	8	9	10	worst possible
15. Punishing-cruel	None	0	1	2	3	4	5	6	7	8	9	10	worst possible
16. Electric-shock pain	None	0	1	2	3	4	5	6	7	8	9	10	worst possible
17. Cold-freezing pain	None	0	1	2	3	4	5	6	7	8	9	10	worst possible
18. Piercing	None	0	1	2	3	4	5	6	7	8	9	10	worst possible
19. Pain caused by light touch	None	0	1	2	3	4	5	6	7	8	9	10	worst possible
20. Itching	None	0	1	2	3	4	5	6	7	8	9	10	worst possible
21. Tingling or ‘pins and needles’	None	0	1	2	3	4	5	6	7	8	9	10	worst possible
22. Numbness	None	0	1	2	3	4	5	6	7	8	9	10	worst possible

Appendix 2

Zoster brief pain inventory (ZBPI)

Pain Items	Interference Items
Worst pain in last 24 hours	General activity
Least pain in last 24 hours	Mood
Pain on average	Walking ability
Pain right now	Normal work (including housework)
	Relations with other people
	Sleep
	Enjoyment of life
Are you receiving any treatments or medications for your shingles pain?	
1.Yes 2.No	
In the last 24 hours, how much relief have these treatments or medications provided for your shingles pain? Please circle the one percentage that most shows how much relief you have received.	
0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100% No Relief Complete Relief	

Appendix 3

The Depression, Anxiety and Positive Outlook Scale (DAPOS)

We would like to know how you have been feeling in the last few weeks. Please circle a number for each statement indicating how often you feel that way, where 1, almost never and 5, almost all the time

		Almost never				Almost all the time
1	I feel like a failure	1	2	3	4	5
2	I get a frightened feeling, as if something awful is about to happen	1	2	3	4	5
3	I feel guilty	1	2	3	4	5
4	I can laugh and see the funny side of things	1	2	3	4	5
5	I am disappointed in myself	1	2	3	4	5
6	I get a frightened feeling, like butterflies in the stomach	1	2	3	4	5
7	I feel cheerful	1	2	3	4	5
8	I blame myself constantly	1	2	3	4	5
9	I get a sudden feeling of panic	1	2	3	4	5
10	I look forward with enjoyment to things	1	2	3	4	5
11	I think about harming myself	1	2	3	4	5