

# Efficacy and safety of the extracorporeal shock wave therapy in patients with postherpetic neuralgia: study protocol of a randomized controlled trial

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## Study protocol

**Keywords:** extracorporeal shockwave therapy (ESWT), postherpetic neuralgia (PHN), neuropathic pain

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# Abstract

**Background:** Postherpetic neuralgia (PHN) is one of the most common chronic neuropathic pain, which seriously affected the quality of the life due to the severity of pain and the poor response to the current treatment. The main management strategies of PHN include medication therapy and invasive interventional therapy. However, there are lots of side effects. It is meaningful to find another effective and safe treatment for PHN.

**Methods:** A single-center, randomized, single-blind clinical trial will be held. A total of 98 participants will be randomly divided into control group and experimental group in a 1:1 ratio. Patients in control group will receive conventional treatment including medication therapy and invasive interventional therapy. The experimental group will be treated with extracorporeal shockwave therapy (ESWT) in addition to conventional therapy. The primary outcome is visual analogue scale (VAS), secondary outcome contains 36-item short-form health survey (SF-36), self-rating anxiety Scale (SAS), self-rating depression scale (SDS) and Pittsburgh sleep quality index (PSQI). Assessors who are blinded to the randomization will collect data during the intervention period at baseline, 1 weeks, 4 weeks, and 12 weeks in this study. The plasma levels of TNF- $\alpha$  and IL-6 in patients will be detected before and after ESWT to explore part of the biochemical mechanism of ESWT for the treatment of PHN.

**Discussion:** This randomized controlled trial will be held to evaluate the actual effectiveness and safety of ESWT in patients with PHN, and thus provide clinical evidences for its application in the PHN management and explore the potential mechanism of this treatment.

**Trial registration:** [www.ChiCTR.org.cn](http://www.ChiCTR.org.cn), identifier: ChiCTR1900025828. Registered on 10th September 2019.

## Background

Postherpetic neuralgia (PHN) is one of the most common chronic neuropathic pain, which is defined as a kind of neuropathic pain (NP) that persists 3 months or more after recovering from shingles (1). PHN occurred in nearly 20% of patients with herpes zoster, and the risk increases with age, most sharply between 50 and 79 years (2, 3). Patients with PHN may suffer from constant burning, itchy, sharp or lightning pain, and some may experience allodynia or hyperalgesia, which seriously affected the quality of life due to severity of pain and the poor response to current treatment (4).

The main pain management strategies of PHN include medication therapy and invasive interventional therapy. The first-line drugs include gabapentin, pregabalin, 5% lidocaine patch and antidepressants (3). Although medication therapy is effective, a number of side effects (such as constipation, nausea and vomiting) often limit their practical use. When medication therapy cannot effectively relieve patients' pain or adverse reactions are intolerable, invasive interventional therapy could be considered, including nerve block, pulsed radiofrequency therapy (radiofrequency regulation and radiofrequency thermocoagulation), transcutaneous electrical nerve stimulation (TENS) and spinal cord stimulation (5). However, invasive

interventional therapy still has risks of infection, bleeding and nerve injury. Therefore, it is an urgent problem to find an effective and safe treatment for PHN.

Extracorporeal shockwave therapy (ESWT) is a new technique which induces single-impulse transient acoustic wave by electromagnetic, electrohydraulic and piezoelectric device (6). The probe needs to be focused on the painful area during therapeutic process, with the energy and frequency of shockwave adjusting according to the patients' reaction. The application of ESWT is gradually being noticed because of it is non-invasive characteristic and low rate of complications compared with other treatments. It was indicated that ESWT has potential efficacy in neuropathic pain such as Morton's Neuroma, trigeminal neuralgia and diabetic foot ulcers in some studies(7–11). However, there exists no randomized controlled trial to confirm the efficacy and safety of ESWT in patients with PHN and explore the potential mechanism. Hence, this randomized controlled trial will be held to evaluate the actual effectiveness and safety of ESWT in patients with PHN, and thus provide clinical evidences for its application in the PHN management.

## Methods

### Study design

This single-center, randomized, single-blind clinical trial was approved by the ethics committee of West China Hospital of Sichuan University (Version 2.0 of this protocol was approved on 30th December 2019, reference 2019[814]) and has been prospectively registered at Chictr.org.cn (ChiCTR1900025828) on 10th September 2019. It will be conducted in Department of Pain management, West China Hospital, Chengdu, China from February 2020 to December 2020. The trial flowchart is shown in Fig. 1. Additional file 1 is the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist. The schedule of enrollment, interventions, and assessments follows the SPIRIT Figure (Fig. 2).

A total of 98 participants will be randomly divided into two groups: control group and experimental group. Assessors who are blinded to the randomization will collect data during the intervention period at baseline, 1 weeks, 4 weeks, and 12 weeks in this study. The plasma levels of TNF- $\alpha$  and IL-6 in patients will be detected before and after ESWT to explore part of the biochemical mechanism of ESWT for the treatment of PHN.

### Selection of the participants

Patients diagnosed with PHN according to the European consensus-based (S2k) Guideline on the Management of Herpes Zoster will be informed of this trial (12). After a brief introduction about the trial, patients could decide whether they will participate in this study. Then detailed information will be acquired to assess the eligibility according to following criteria (Table 1). All of the participants must sign the informed consent before treatment. Two physicians in department of pain management will enroll participants and obtain the informed consent.

Table 1  
Eligibility criteria.

Inclusion criteria	Exclusion criteria
■ Diagnosed with PHN	■ Allergic to coupling agent
■ VAS $\geq$ 4 points	■ History of tumor
■ Age $\geq$ 18 years	■ Liver or kidney dysfunction
■ Describe symptoms objectively	■ History of tumor
■ Did not received ESWT before	■ History of thrombosis
■ Did not participate in other clinical trials within 3 months	■ Disturbance coagulation function using anticoagulants
	■ With cardiac pacemaker
	■ Infection in the pain area
	■ Pregnant or puerperal patients
	■ With fracture or severe osteoporosis
	■ Any mental disorder
	■ Cannot be followed up on schedule
Abbreviations: PHN, postherpetic neuralgia; VAS, visual analogue scale; ESWT, extracorporeal shockwave therapy.	

### Sample size

The sample size was estimated based on the effect from a previous study which used effective rates as primary outcome (experimental group= 96%; control group = 77%). we used power analysis software (G\*power 3.1.9.4) with the superiority test (one-tailed test with alpha = 0.05 and beta = 0.2). It was estimated that a sample size of 78 participants (39 participants per group). Considering potential drop out rate of 20%, a total of 98 participants will be enrolled in this study.

### Patient and Public Involvement

There were no funds or time allocated for PPI so we were unable to involve patients. We have invited patients to help us develop our dissemination strategy.

### Randomization and blinding

Patients will be randomly divided into control group or experimental group in a 1:1 ratio according to random numbers generated by EXCEL table. Sealed opaque envelopes were used for allocation concealment. A researcher will generate the allocation sequence, and another researcher will assign

participants to interventions. The assessors and statisticians were blinded to randomization and did not participate in the treatment.

## **Interventions**

### ***Control group***

Patients in control group will receive conventional treatment including medication therapy and invasive interventional therapy.

#### *Medication therapy*

##### 1. Anticonvulsion medicine

Gabapentin (A daily dosage of 0.3g on the first day, 0.6g on the second day and 0.9g on the third day. Then 0.9g/d was maintained and the dosage could be adjusted according to patient's reaction)

Pregabalin (Starting dose of 75mg twice a day and adjust the dosage according to the actual situation of the patients)

##### 2. Opioid analgesics

Oxycodone and acetaminophen tablets (One tablet three times a day and adjust the dosage according to pain intensity)

##### 3. Neural nutrients

Mecobalamin (0.5mg three times a day).

#### *Invasive interventional therapy*

Low dose Computed Tomography (CT) guided pulsed radiofrequency regulation (according to the patient's condition) will be administered.

### ***Experimental group***

The experimental group will be treated with ESWT in addition to conventional therapy. The patients could be in prone, lateral, or seated position depending on the painful area. ESWT will be performed with radial extracorporeal shockwave generator (MASTERPULS MP100; Storz Medical AG, Tagerwilen, Switzerland) and all treatments should be performed by the same therapist who is formally trained. After applying the ultrasonographic coupling agent to the skin of treated area, the patients will receive 5000-7000 pulses every session by a R15 probe (radius of 15 mm) at a frequency of 10 Hz, with energy gradually increasing from 1 to 4 bar depending on patients' reaction. The therapist will move the probe in transverse or longitudinal directions along the nerve. The procedure was performed every 3-5 days and 3-5 sessions constitute a therapeutic course.

## Outcome measure

### General conditions

Age, gender, Body Mass Index (BMI), previous history, duration of PHN, painful segment, medication use, previous treatment will be obtained at baseline.

### *Primary outcome*

The visual analogue scale (VAS) will be used to access pain intensity at baseline, 1 weeks, 4 weeks, and 12 weeks after treatment in this study. VAS comprises of a horizontal line which is 10 centimeters long with terminal descriptors of 0 = no pain and 10 cm = worst imaginable pain(13). The participants marked the position on the line according to their degree of pain and the VAS score was determined by measuring the distance from 0 to the marked point.

### *Secondary outcome*

Secondary outcome as follows will be collected at baseline, 1 weeks, 4 weeks, and 12 weeks after treatment.

1. The quality of life will be accessed by 36-Item Short-Form Health Survey (SF-36) which measures three aspects of health including functional ability, wellbeing and overall health(14).
2. Anxiety and depression are common mental disorders in patients with chronic pain(15). The psychological state of patients will be measured by Self-Rating Anxiety Scale (SAS) and Self-Rating Depression Scale (SDS).
3. Pittsburgh sleep quality index (PSQI) will be used for accessing the sleep quality, which includes 19 questions and seven components (perceived sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, sleep medications and daytime dysfunction)(16).
4. Mechanical withdrawal threshold will be tested using Von-Frey hairs (Aesthesiometer, Somedic, Sweden) according to the methods by Moharić M et al.(17), which presents level of peripheral sensitization.
5. The plasma levels of TNF- $\alpha$  and IL-6 in patients will be detected before and after ESWT to explore part of the biochemical mechanism of ESWT for the treatment of PHN.

## Safety evaluation

Adverse reactions will be recorded including petechiae and swelling of the skin, allergy, fever, paresthesia, pain aggravated, tissue edema and other adverse effect related to ESWT. At the same time, incidence of adverse reactions will be analyzed as a measurement of safety. Serious adverse events refer to events that prolong hospitalization time, cause disability, affect ability to work or endanger life in clinical trials. Once serious adverse events have occurred, treatment should be suspended immediately and remedy

actions should be taken appropriately and freely in time. The serious adverse events will be reported to the ethical committees and relevant responsible units to determine whether to stop the research.

### **Data management and statistical analysis**

All original data will be stored in case report form (CRF) and any personal information will be protected. The study supervisor has access to the trial dataset and make the final decision to terminate the trial. Audits of the trial will be performed bimonthly. Data analysis will be performed by SPSS software (version 22; SPSS Inc, Chicago, IL, USA). Continuous data will be presented as mean  $\pm$  standard deviation while categorical variables will be reported as numbers or percentages. The basic characteristics of participants will be described and compared by student's t-test to ensure comparability. All statistical analysis followed the principle of intent-to-treat analysis. The difference in treatment effect between the two groups will be evaluated by one-way ANOVA while using the repeated-measures analysis of variance (RM- ANOVA) to analyze the changes over time in the group. The duration of PHN and painful segment, as potential factors, will be assessed using the logistic regression. All tests were single-sided, and  $p \leq 0.05$  was considered statistically significant.

### **Discussion**

As a common disease of the elderly, PHN seriously affects patients' quality of life and mental health. Despite multiple therapies for PHN, there still lack of effective and safe treatment recommended. The aim of this randomized controlled trial is to ensure the efficacy and safety of ESWT in patients with PHN and explore the potential mechanism of this treatment.

It was shown that persistent inflammation, oxidative stress-mediated injury and cytokines activation play an important role in the pathological mechanism of neuropathic pain (7). TNF- $\alpha$ , IL-1, IL-6, IL-17 might be the main pro-inflammatory cytokines in neuropathic pain in some studies(18). As far as we can surmise, the mechanism of ESWT for PHN might be related to immune regulation and analgesic effect. In a recent study, ESWT may reduce the plasma levels of TNF- $\alpha$  and IL-6, which has an effect of anti-inflammatory (19). Meanwhile, decreased substance P levels after ESWT may produce analgesic effects(20). Hopefully, the results of our study will confirm the effect of ESWT for patients with PHN and provide clinical evidence. Besides, ESWT could be recommended as an effective and safe therapy for PHN if our hypothesis is verified.

However, there are still some limitations in our study. First of all, it is a single-center clinical trial, which might influence the recruitment of participates. Secondly, this clinical trial is single-blind because it is difficult to ensure double-blind considering the therapeutic properties of ESWT, which might cause bias from patients. Another limitation is that our trial follows up for 3 months after the treatment, extended follow-up might be needed to demonstrate the benefits of ESWT in further studies.

### **Trial Status**

The protocol version is 2.0 (issue date: 29 October 2019). Recruitment began in February 2020 and will probably be completed at the end of May 2020.

## **Abbreviations**

PHN: postherpetic neuralgia; NP: neuropathic pain; TENS: transcutaneous electrical nerve stimulation; ESWT: extracorporeal shockwave therapy; CT: computed tomography; BMI: body mass index; VAS: visual analogue scale; SF-36: 36-item short-form health survey; SAS: self-rating anxiety Scale; SDS: self-rating depression scale; PSQI: Pittsburgh sleep quality index; CRF: case report form ; RM- ANOVA: repeated-measures analysis of variance.

## **Declarations**

### **Ethics approval and consent to participate**

The study was approved by the ethics committee of West China Hospital of Sichuan University (Version 2.0 of this protocol was approved on 30th December 2019, reference 2019[814]) and has been prospectively registered at Chictr.org.cn (ChiCTR1900025828). Informed consent will be written from all participants.

### **Consent for publication**

Not applicable.

### **Availability of data and materials**

Not applicable.

### **Competing Interest**

The authors declare that they have no conflicts of Interest.

### **Funding**

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### **Author contributions**

LC, RHZ designed this randomized controlled trial and wrote the protocol. YL is the leader and supervisor of the project. PLY and LY contributed equally to the design of the study, with emphasis on the statistical

analysis and sample size analyses, critical revision of the manuscript and final approval of the study. LC will perform ESWT in treatments. FGS and YW will collect the data. ZRH will perform the statistical analysis. All authors have read and approved the final manuscript.

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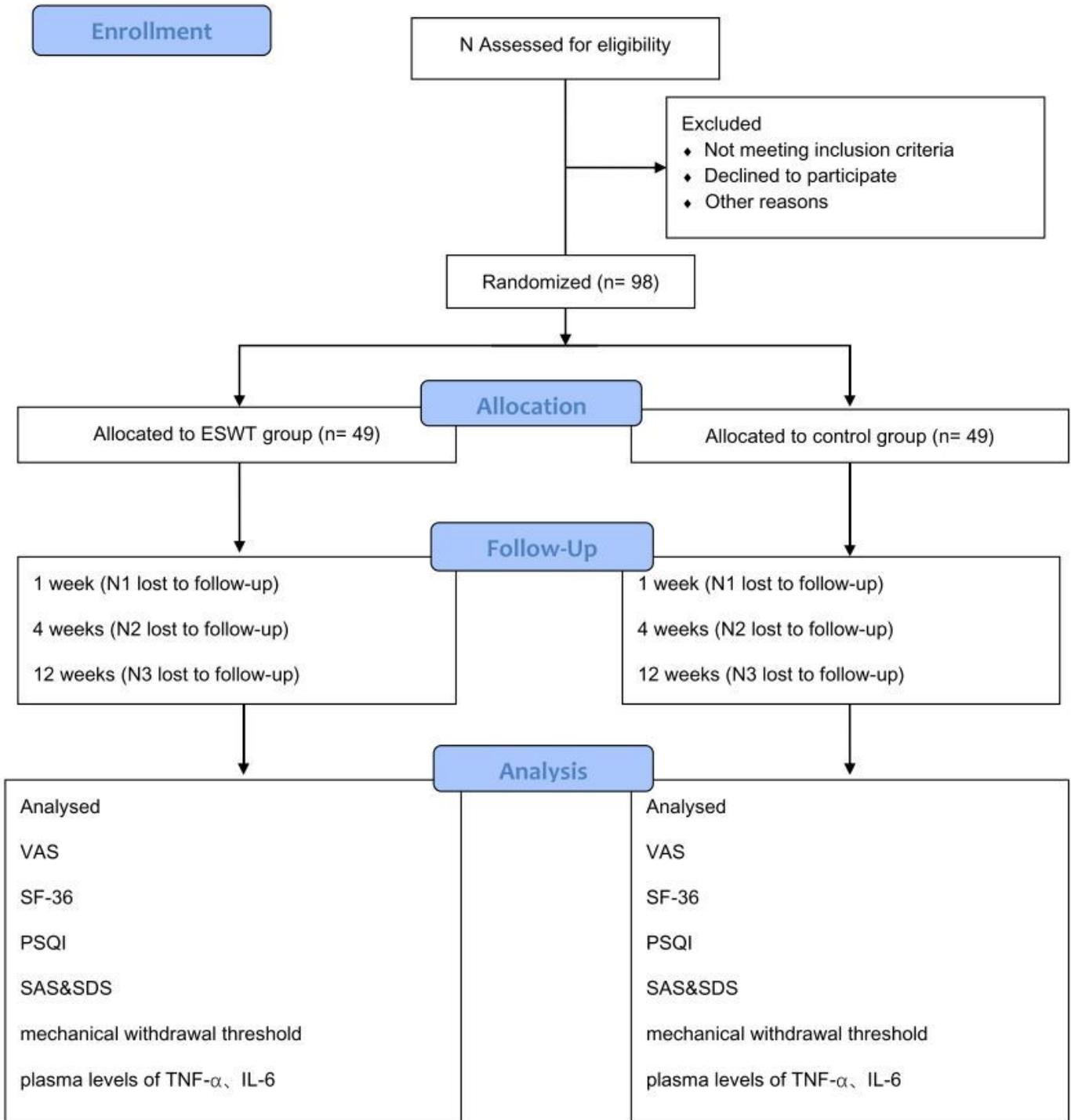
None.

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## Figures



**Figure 1**

CONSORT Flow Diagram. ESWT, extracorporeal shockwave therapy; VAS, visual analogue scale; SF-36, 36-item short-form health survey; SAS, self-rating anxiety Scale; SDS, self-rating depression scale; PSQI, Pittsburgh sleep quality index.

	Enrolment	Allocation	Intervention	Post-intervention		
TIMEPOINT**	Admission	Allocation	Hospitalization	1 week	4 weeks	12 weeks
<b>ENROLMENT:</b>						
Eligibility screen	X					
Informed consent	X					
Demographic characteristics	X					
Allocation		X				
<b>INTERVENTIONS:</b>						
ESWT+ conventional treatment			X			
conventional treatment			X			
<b>ASSESSMENTS:</b>						
VAS	X			X	X	X
SF-36	X			X	X	X
SAS	X			X	X	X
SDS	X			X	X	X
PSQI	X			X	X	X
Mechanical withdrawal threshold	X			X	X	X
plasma levels of TNF- $\alpha$ , IL-6	X			X	X	X

**Figure 2**

Recommendation for Interventional Trials (SPIRIT) schedule of enrollment, interventions and assessments. ESWT, extracorporeal shockwave therapy; VAS, visual analogue scale; SF-36, 36-item short-form health survey; SAS, self-rating anxiety Scale; SDS, self-rating depression scale; PSQI, Pittsburgh sleep quality index.

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SPIRITchecklist.docx](#)