

# Acupuncture for diabetic peripheral neuropathy: study protocol for a randomized, placebo-controlled, single-blinded trial

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## Study protocol

**Keywords:** Manual acupuncture, Sham acupuncture, Diabetic peripheral neuropathy, Randomized controlled trial, Protocol

**Posted Date:** June 10th, 2020

**DOI:** <https://doi.org/10.21203/rs.3.rs-18355/v1>

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**Version of Record:** A version of this preprint was published on October 26th, 2020. See the published version at <https://doi.org/10.1186/s13063-020-04811-3>.

# Abstract

## Background

Diabetic peripheral neuropathy (DPN) is the most common chronic complication of diabetes mellitus that has a considerable impact on quality of life, but there are few effective therapeutic strategies. The aim of this trial is to determine the efficacy and safety of manual acupuncture (MA) versus sham acupuncture (SA) for DPN.

## Methods/design:

This is a study protocol for a randomized, two-arm, single centre, clinical trial. A total of 118 patients with DPN will be recruited and randomly assigned to the MA group or the SA group in a 1:1 ratio. All patients will receive 24 sessions over 12 weeks. Participants will complete the trial by visiting the research centre at month 6 for a follow-up assessment. The primary outcome is the peroneal motor nerve conduction velocity (peroneal MNCV) at week 12 compared with baseline. Secondary outcomes include the peroneal motor nerve action potential amplitude (peroneal MNAP) and latent period (peroneal MNLP), the sural sensory nerve conduction velocity (sural SNCV), action potential amplitude (sural SNAP) and latent period (sural SNLP), fasting plasma glucose (FPG), 2-hour postprandial blood glucose (2hPG), glycated hemoglobin (HbA1c) at week 12 compared with baseline, the Michigan Neuropathy Screening Instrument (MNSI) score and Diabetes Specific Quality of Life scale (DSQL) at week 12 and month 6 compared with baseline. Safety is assessed during the whole trial. Masking effectiveness is assessed by patients.

## Discussion

This trial may provide high-quality evidence for evaluating the efficacy and safety of MA treatment for DPN compared with SA treatment. The results of this study will be published in peer-reviewed journals.

## Trial registration:

Chinese Clinical Trials Registry, ID: ChiCTR1800020444. First registered on 29 December 2018 - Retrospectively registered, <http://www.chictr.org.cn/showproj.aspx?Proj=31063>

## Background

DPN is the commonest cause of neuropathy worldwide, and its prevalence increases with the duration of diabetes [1]. Approximately 50% of patients with diabetes will develop peripheral neuropathy [1,2,3]. DPN is symmetric and predominantly sensory, starting distally and gradually spreading proximally in a glove-and-stockings distribution [1]. DPN is associated with the development of foot problems and is one of the leading causes of [amputations](#) and the development of foot ulcers. DPN is frequently underreported and

undertreated and can lead to an increased risk for **morbidity** and mortality and decreased quality of life[1,2]. Once symptoms appear, there are few effective therapeutic strategies [4]. Whilst neuropathic pain and paresthesia can be palliated by anti-convulsants, tricyclic antidepressant drugs or serotonin-noradrenalin re-uptake inhibitors [5], pharmacologic management of decreased sensation is generally ineffective. Therefore, more and more patients have turned to seek nonpharmacological treatments. Multiple complementary and alternative medicine therapies such as acupuncture and yoga show efficacy in the treatment of painful peripheral neuropathy [6]. A pilot RCT has demonstrated the practicality and feasibility of acupuncture as an additional treatment for people with DPN. The treatment was well tolerated with no appreciable side effects [7]. Acupuncture may effectively ameliorate selected DPN symptoms—such as aching pain, burning pain, prickling sensation, numbness, allodynia in American Indian patients [8]. Reviews concerning acupuncture for peripheral neuropathy (PN) have found that, despite the majority of studies reporting positive results, a reliable statement of effectiveness is not possible due to methodological limitations [9-12]. A recent meta-analysis of acupuncture for DPN indicates acupuncture for DPN appears to improve symptoms [13]. However, the application of acupuncture varies greatly, and the quality of included studies was generally low. Available studies have varying methodologies and different outcome measures. Further, suitably powered studies using appropriate DPN outcome measures are required [13].

Therefore, we have designed a study with a 6-month observation period to explore its effectiveness and safety.

## Methods

### Study design

This randomized, participant-blind, sham controlled trial will be conducted at Longhua hospital affiliated to Shanghai University of Traditional Chinese Medicine in China. The protocol for this trial is reported based on the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 Checklist: defining standard protocol items for clinical trials (Additional file 1). The study has been approved by the Ethics Committee of Longhua hospital (the Approved No. of the Ethics Committee is 2016LCSY028) and was registered on the Chinese Clinical Trial Registry (ChiCTR) platform on 29 December 2018. (Registration number: ChiCTR1800020444). A flow diagram of the trial is shown in Fig. 1.

### Patient recruitment

Patients meeting the DPN diagnostic criteria will be recruited from the endocrinology departments of Longhua Hospital affiliated to Shanghai University of Traditional Chinese Medicine in Shanghai, China. Recruitment posters will be posted in the hospital and also be uploaded to social Internet media (WeChat) from October 2016 to December 2021. All patients will be required to provide written informed consent (Additional file 2) before randomization.

## **Inclusion criteria**

1. Aged 18–75years (either sex);
2. Clinically Confirmed diagnosis of diabetic peripheral neuropathy; symmetric and predominantly sensory, starting from the lower limbs distally and gradually spreading proximally in a glove-and-stocking distribution;
3. Ability to understand study procedures and willingness to comply with them for the entire length of the study;
4. Written informed consent

## **Exclusion criteria**

1. PN caused by conditions other than diabetes (e.g., alcohol abuse, chemotherapy, hereditary causes, chronic inflammatory or idiopathic PN, and others);
2. Psychiatric illnesses other than mild depression;
3. severe or unstable cardiovascular, liver, kidney, respiratory or hematological disorders;
4. Acupuncture treatment in the last 3 months;
5. Pregnant or breast-feeding women;
6. Research unit personnel directly related to the study and their immediate family members;
7. Incapacity in giving informed consent or in following the study instructions due to language disturbances, serious cognitive deficits, or lack of time;
8. Current participation in other clinical trials.

## **Randomization and allocation concealment**

All eligible patients will be randomly assigned to the A group or SA group in a 1:1 ratio. The blocked randomization sequence will be computer-generated with the EXCEL software by an independent statistician, who is not involved in the implementation and statistical analysis of the trial. The randomization will be stratified by the number of limbs affected by DPN (i.e., both only the lower limbs and four limbs) and with a random block size of 6 and 4. The allocation was placed inside sequentially ordered sealed opaque envelopes, opened only after enrolment. The treatment allocation was revealed to the acupuncturists out of sight of the patients to ensure blinding. To reduce the risk of observer bias, the acupuncture practitioners were discouraged from discussing the treatments or previous results with the patients. The random allocation sequence and the opaque sealed envelopes will be kept separately by two specific researchers. The clinical research coordinator will be responsible for enrolling patients, obtaining informed consent and requesting randomization.

## **Masking**

Due to the nature of acupuncture, masking of acupuncturists is quite difficult to achieve. Patients, outcome assessors, and statisticians who perform the statistical analyses will be blinded to group

assignment. Participant's allocated intervention will be not revealed until the statistical analysis is completed.

## **Interventions**

Treatment will be performed by licensed acupuncturists who have at least five years of experience in acupuncture. All the acupuncturists will be trained how to locate acupoints, puncture, and manipulate needles before the trials. Single-use sterile disposable acupuncture needles (length: 25-40mm, diameter: 0.25mm; Jiajian, Wuxi China) will be used. Both the MA and SA treatments will consist of 24 sessions of 40-min duration over 12 weeks (two sessions per week). Acupuncture will be discontinued if the patients suffer from any serious adverse events (AEs).

### **Manual acupuncture**

Patients allocated to the MA group will take treatment with needles inserted at the prespecified acupuncture points. The protocol including obligatory and additional acupoints was developed from the clinical experience of acupuncture experts. The obligatory acupoints included Zhongwan(RN12), and bilateral Weiwanshu(EX-B3), bilateral Ganshu(BL18), bilateral Pishu(BL20), bilateral Shenshu (BL23) bilateral Zusanli (ST36), bilateral Yanglingquan(GB34), bilateral Sanyinjiao(SP6), bilateral Taixi(KI3), and Bafeng(EX-LE10) . The additional acupoints Baxie(EX-UE9) will be added when patients' symptoms appear not only in the lower limbs but also in the upper limbs. All acupoints are localized according to the WHO Standard Acupuncture Locations and exhibited in Table 1 and Fig. 2. After skin disinfection, 25mm or 40mm-length acupuncture needles were inserted approximately 10-20 mm into the skin according to acupoint, then manipulations of twirling, lifting, and thrusting will be performed on all needles for at least 10s to reach De qi (a compositional sensation including soreness, numbness, distention, and heaviness), which is believed to be an essential component for acupuncture efficacy. Firstly, RN12, ST36, GB34, SP6, KI3, EX-LE10, EX-UE9 will be punctured when patients lie supine, then, EX-B3, BL18, BL20 and BL23 will be punctured when patients lie prone, the needles will be retained in each acupoints for 20min.

### **Sham acupuncture**

Patients in the SA group received sham acupuncture. After skin disinfection, sterile adhesive pads were placed on the same acupoints with the MA group, then the 25mm-length blunt tipped placebo needle were inserted through the adhesive pads to the surface of the skin, but no skin penetration, without needle manipulation for De qi.

Although it is difficult to set an eligible placebo control, using a blunt tipped needle which does not penetrate patient's skin is the most commonly used approach for administering sham treatments among acupuncture trials on the basis of a literature review [14,15]. And this study will exclude those received acupuncture treatment in the last 3 months. This population can most probably distinguish SA from MA. The same control, no skin penetration at acupoints, was adopted and is successful to mask patients with

DPN [7]. Furthermore, all patients will be asked to guess which treatment they have received to test the patient-blinding effects at week 12.

## Concurrent Treatments

Participants will receive routine health care as provided to all other patients with DPN. These treatments include glucose control, antihypertensive therapies, dyslipidemia control, analgesic and neurotrophic treatments, if necessary. All information regarding the use of medications (including date of administration, and types and dosage) will be recorded. This contribute to improving adherence.

Table 1 Locations of acupoints

Acupoints	Locations
Zhongwan( <i>RN12</i> )	On the anterior midline, 4 cun <sup>a</sup> above the umbilicus
Weiwanxiashu( <i>EX-B3</i> )	at the same level as the inferior border of the spinous process of the 8th thoracic vertebra (T8), 1.5 cun lateral to the posterior median line
Ganshu( <i>BL18</i> )	at the same level as the inferior border of the spinous process of the 9th thoracic vertebra (T9), 1.5 cun lateral to the posterior median line
Pishu( <i>BL20</i> )	at the same level as the inferior border of the spinous process of the 11th thoracic vertebra (T11), 1.5 cun lateral to the posterior median line
Shenshu ( <i>BL23</i> )	at the same level as the inferior border of the spinous process of the 2nd lumbar vertebra (L2), 1.5 cun lateral to the posterior median line
Zusanli ( <i>ST36</i> )	3 cun directly below Dubi ( <i>ST35</i> ), and one finger-breadth lateral to the anterior border of the tibia
Yanglingquan( <i>GB34</i> )	in the depression anterior and distal to the head of the fibula
Sanyinjiao( <i>SP6</i> )	3 cun superior to the prominence of the medial malleolus, posterior to the medial border of the tibia,
Taixi( <i>KI3</i> )	in the depression between the prominence of the medial malleolus and the calcaneal tendon
Bafeng( <i>EX-LE10</i> )	on the dorsum of the foot, between the first and fifth toes at the junction of the red and white skin posterior to the margin of the web; 4 points on each foot, 8 in total
Baxie( <i>EX-UE9</i> )	at the dorsum of the hand between the first and fifth fingers, proximal to the web margins between the five fingers at the junction of the red and white skin, 4 points on each hand, 8 in total

<sup>a</sup>1 cun ( $\approx 20\text{mm}$ ) is defined as the width of the interphalangeal joint of patient's thumb

## Follow-up

After the 12-week treatment, all participants will enter an additional 3 months follow-up period. During this time, they will receive routine health care as provided to all other patients with DPN. However, acupuncture treatment are not permitted during follow-up.

## **Outcomes**

### **Primary endpoint**

The primary endpoint is the difference of the 12-week measurement minus baseline of the peroneal motor nerve conduction velocity (peroneal MNCV).

### **Key secondary endpoints**

Secondary endpoints are the differences of the 12-week measurement minus baseline of the peroneal motor nerve action potential amplitude (peroneal MNAP) and latent period(peroneal MNLP), the sural sensory nerve conduction velocity (sural SNCV), action potential amplitude (sural SNAP) and latent period(sural SNLP).

Additional secondary endpoints include glycated hemoglobin (HbA1c), fasting plasma glucose(FPG), 2-hour postprandial blood glucose (2hPG), Body mass index(BMI) blood pressure(BP), at week 12 compared with baseline, the Michigan Neuropathy Screening Instrument (MNSI) score at week 12 and month 6 compared with baseline.

### **Quality of life (QoL)**

Disease-specific QoL will be assessed at baseline and at weeks 12, month 6 after randomization using Diabetes Specific Quality of Life scale (DSQL) which consists of four domains: interference (12 items); psychology (8 items); social relations (4 items); and treatment (3 items). Each item is measured with a 5-point Likert scale ranging from "not at all" to "extremely." Higher scores indicate a worse QoL.

### **Patients' global assessment of DPN**

Patients' global assessment of DPN is evaluated on a 5-point Likert scale at week 12. Patients are asked to respond to the following question: 'Considering all the ways your DPN affects you, how are you doing today?' 1=very poor; 2= poor; 3=fair; 4= good; and 5=very good.

### **Blinding assessment**

To test the patient-blinding effects, all patients will be asked to guess their group assignment allocation within 2min after the last treatment session in week 12 as following: "which group do you think you are in?: A. traditional acupuncture; B. modified acupuncture; or C. not sure".

### **Credibility and expectancy**

Credibility and expectancy of patients will be assessed using the Credibility/Expectancy Questionnaire before the first treatment.

### **Adverse events**

AEs data will document the occurrence, duration, and severity of adverse reactions (symptoms and signs), and how the event was resolved (or not) during the treatment. Based on their potential association with the acupuncture needling procedure, AEs will be categorized by acupuncturists and related specialists as treatment-related or not within 24h of occurrence. Common treatment-related AEs include local subcutaneous hematoma, itching at the sites of needle insertion, continuous post-needling pain, dizziness, and so on. All participants will receive routine blood test, liver function (alanine transaminase and aspartate transaminase), and kidney function tests (serum creatinine and blood urea nitrogen). These tests will be performed twice after randomization and at the end of the 12-week treatment period. Serious adverse events are reported to Medical Ethics Committee and treat the participants with relevant conventional therapy or hospitalization if necessary (the participant's allocated intervention will be revealed).

### **Assessment of safety**

The patients are asked to assess the safety of the treatment after 12 weeks' treatment, in terms of 4 grades: safe, relatively safe, unsafe, and very unsafe.

### **Sensation during the treatment**

The patients are asked about their sensation during the treatment at every visit as following: "what sensation do you feel during the treatment? A. soreness; B. distention; C. pain; D. no feeling; E. else, please specify\_\_\_."

### **Usage of medication**

Medication Usage Log: The participants are given a printed log to record their daily intake of medications prescribed on a symptom-contingent (i.e., as per necessary, prn) basis. We measure the outcomes at week 12.

The schedule of enrolment, interventions, and assessments are presented in Fig. 3.

### **Data collection, management and monitoring**

All researchers including acupuncturists, outcome assessors, and statisticians will receive training regarding data management. The Case Report Form (CRF) will be first completed and then double entered into the Electronic Data Capture (EDC) system electronically by two independent investigators to ensure the accuracy of the data.

All research documents, including both the paper files and electronic documents, will be preserved for at least five years after publication. If reviewers or readers have any questions regarding our published data, they can contact the corresponding author for access to the original data or visit ResMan (<http://www.medresman.org/uc/project/projectadd.aspx>). The private information of patients—including name, telephone number, and ID number will be anonymous to ensure participant confidentiality.

The safety of the study will be monitored by a Data and Safety Monitoring Board (DSMB) of the clinical evaluation center of Longhua hospital, affiliated Shanghai university of TCM, which consists of independent clinical experts and statisticians with access to unblinded data. The DSMB is independent from the sponsor, the competing interests and the investigational site and will review the performance and safety of the trial per six months.

The criteria for unblinding and discontinuing allocated interventions for a given trial participant experiencing serious acupuncture-related AEs (if any), which have been described previously. The DSMB will reveal a participant's allocated intervention, and make the final decision to terminate the trial.

## **Statistical methods**

### **Sample size**

Based on the results of a previous study, a sample size of 49 participants per group was estimated to provide 80% power to detect a between-group difference of 2.4m/s of the conduction velocity improvement of the common peroneal nerve, assuming a 2-sided significance level of 5%. To compensate for a 17% loss to follow-up, the sample size was increased to 59 participants in each group.

### **Statistical analysis**

The statistical analysis will be performed by an independent statistician who is not aware of the group allocation. SPSS 21.0 statistical software (IBM SPSS Statistics, New York, USA), will be used for data analysis. The level of significance will be established at  $\alpha < 0.05$  with a two-sided test. Continuous data will be represented as the mean  $\pm$  standard deviation or median (range), whereas categorical data will be represented by percentage. All efficacy analyses will be performed using the intent-to-treat (ITT) approach. For the ITT analysis, the population will consist of all patients who have been randomized. Missing data will be imputed using the last observation carried forward (LOCF) method. Continuous variables will be compared using a Student's t-test or Wilcoxon rank-sum test as appropriate. Categorical variables will be compared using Fisher's exact test or Wilcoxon rank-sum test as appropriate.

### **Ethics and dissemination**

The study protocol follows the principles of the Declaration of Helsinki and was approved by the Medical Ethics Committee of Long-Hua Hospital affiliated to Shanghai University of Traditional Chinese Medicine on 7 July 2016 (Approval No. 2016LCSY028). The study was registered with Chinese Clinical Trial Registry, ChiCTR1800020444. The results will be disseminated through peer-reviewed publications, a

master's thesis, or conference presentations. The data will be anonymized prior to publication to prevent identification of individual participants.

## Discussion

DPN impacts patients' QoL and causes a financial burden for society. This trial will evaluate the efficacy of MA versus SA in improving the symptoms of DPN.

This trial meets the methodological demand of adequate randomization and allocation concealment, blinding of patients, outcome assessors, and statisticians. The amount of acupuncture is intensive, which is similar to clinical practice in China. Needles will be stimulated manually for at least 10s at each acupoint and retained in place for 20min. There will be 2 treatment sessions per week in the 12-week treatment phase, giving a total of 24 sessions. A suitable control group is critical for a well-designed clinical trial. On the basis of literature review, using a blunt tipped needle which does not penetrate patient's skin is the most commonly used approach for administering sham treatments among acupuncture trials [14,15]. Patients who have received acupuncture treatment in the last 3months and can distinguish SA from MA will not be included. The same control, no skin penetration at acupoints, was adopted and is successful to mask patients with DPN [7]. Furthermore, all patients will be asked to guess which treatment they have received to test the patient-blinding effects at week 12.

The limitation of our trial is the acupuncturists are not blinded for the nature of intervention. At the end of this trial, we hope the results will provide more reliable evidence and clarify the value of acupuncture as a treatment for DPN.

### Trial status

This trial is currently recruiting patients. This is version 2.0 of the protocol, dated June 6th, 2016. Recruitment began on 10 October 2016. Recruitment is anticipated to end on 31 December 2021.

### Additional files

Additional file 1: Completed Standard Protocol Items: Recommendation for Interventional Trials (SPIRIT) 2013 Checklist: items addressed in this clinical trial protocol. (DOC 137 kb)

Additional file 2: informed consent

## Abbreviations

AEs: Adverse events; BMI: Body mass index; BP: blood pressure; CRF: Case report form; DPN: Diabetic peripheral neuropathy; DSMB: Data and Safety Monitoring Board; DSQL: Diabetes Specific Quality of Life scale; FPG: fasting plasma glucose; HbA1c: glycated hemoglobin; 2hPG: 2-hour postprandial blood glucose; ITT: Intent-to-treat; MA: Manual acupuncture; MNAP: Motor nerve action potential amplitude; MNCV: Motor nerve conduction velocity; MNLP: motor nerve action potential latent period; MNSI:

Michigan Neuropathy Screening Instrument; PN: Peripheral neuropathy; QoL: Quality of life; SA: sham acupuncture; SNAP: sensory nerve action potential amplitude; SNCV: sensory nerve conduction velocity; SNLP: sensory nerve action potential latent period.

## **Declarations**

### **Acknowledgements**

### **Funding**

This study was supported by the Three-Year development plan project for Traditional Chinese Medicine of Shanghai Municipal Health Commission (grant numbers ZY (2018-2020)-CCCX-1006. The funding play no role in study design, collection, management, analysis, interpretation of data, writing of the report, or the decision to submit the report for publication.

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

All the individual participant data collected during the trial after deidentification will be available for anyone who wishes to access the data immediately following publication in accordance with FAIR principles.

### **Authors' contributions**

HPD, XYS, HY, HT, and JP participated in the conception and design of this trial. HPD, LZ , YS and JP were responsible for planning the draft and revising the manuscript. JP and XYS are monitors of this study. KC is responsible for randomization and allocation concealment. HY and HT are responsible for the recruitment of patients and obtain informed consent. HPD, TTZ and YS are responsible for the treatment of patients. YS and PRL are responsible for collecting the data. All authors have read the manuscript and approved the publication of this protocol.

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

The study is approved by the Medical Ethics Committee of Long-Hua Hospital affiliated to Shanghai University of Traditional Chinese Medicine, (Approval No. 2016LCSY028) and registered with Chinese Clinical Trial Registry, ChiCTR1800020444. Written informed consent will be obtained from all patients prior to their enrolment in the study.

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## Competing interests

The authors declare that they have no competing interests.

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## Figures

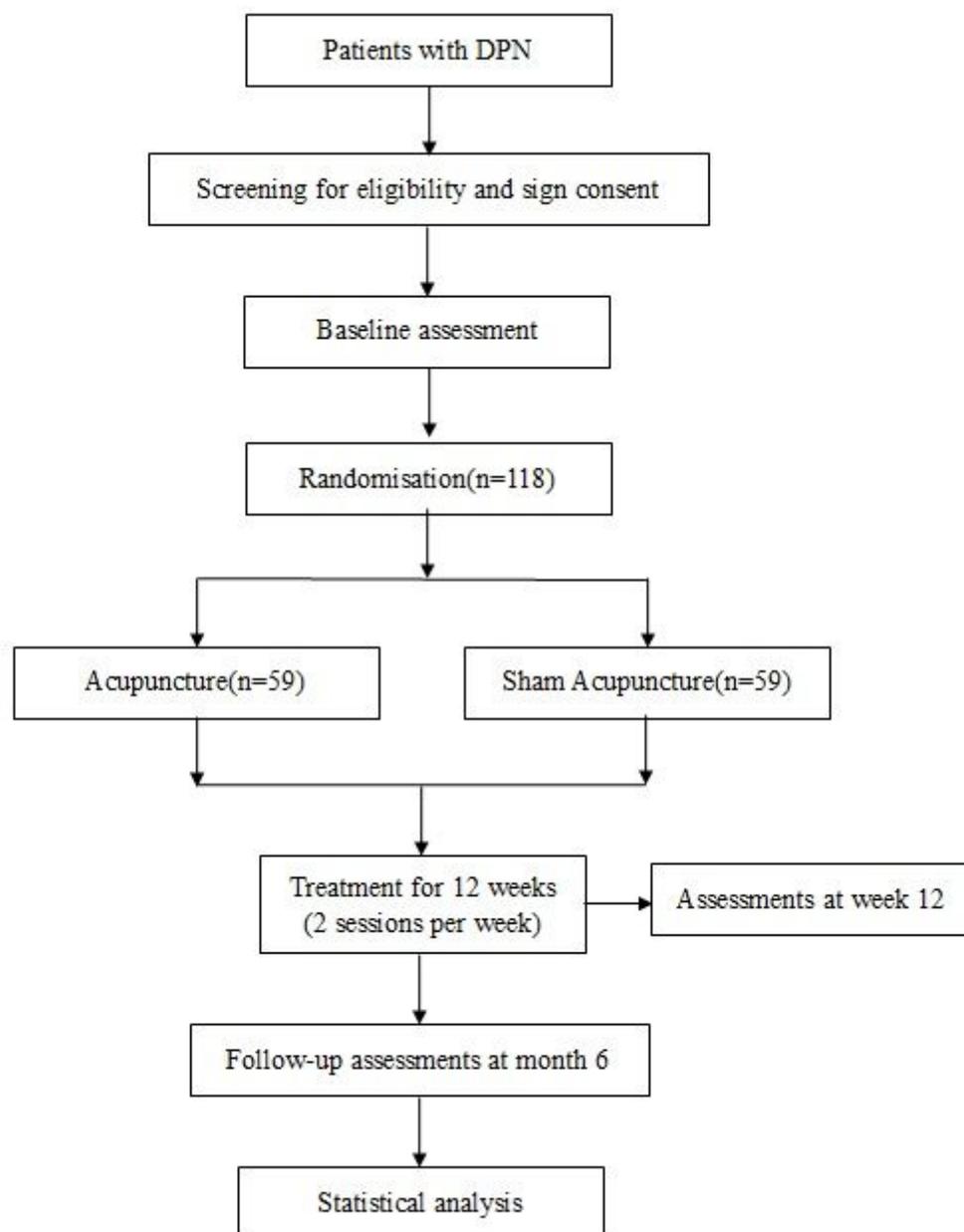


Figure 1

Flow diagram

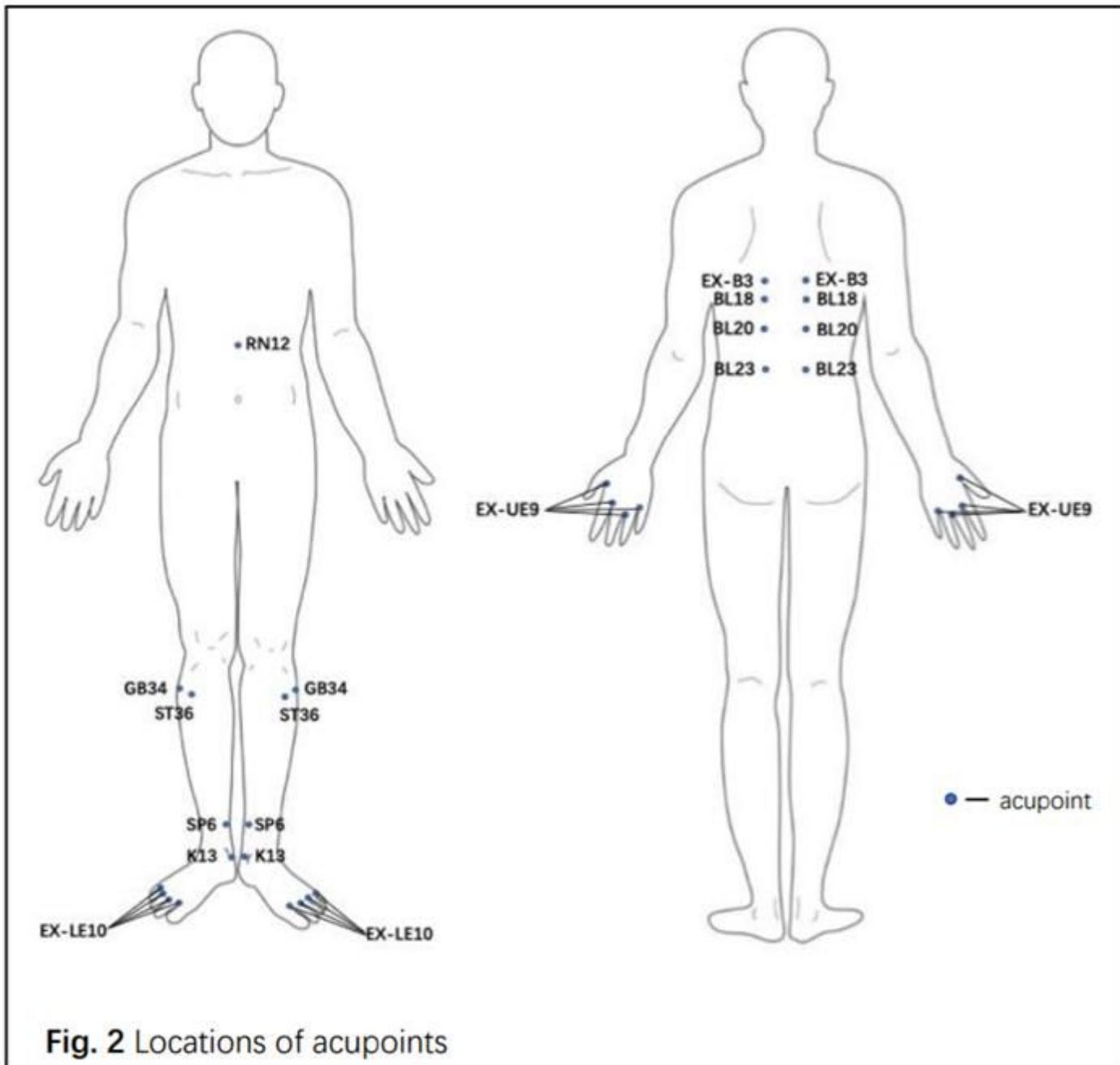


Figure 2

Locations of acupoints

TIMEPOINT	STUDY PERIOD				
	Enrolment	Allocation	Treatment period		Follow-up period
	-1 week	0	1-11 week	12 week	6 month
<b>ENROLMENT:</b>					
Eligibility screen	X				
Informed consent	X				
Allocation		X			
Credibility and expectancy		X			
<b>INTERVENTIONS:</b>					
Acupuncture group			X	X	
Sham Acupuncture group			X	X	
<b>ASSESSMENTS:</b>					
peroneal MNCV, MNAP, MNLP	X			X	
sural SNCV, SNAP, SNLP	X			X	
MNSI	X			X	X
DSQL	X			X	X
HbA1c	X			X	
FPG	X			X	
2hPG	X			X	
BMI	X			X	
BP	X			X	
Routine blood test	X			X	
Liver function test	X			X	
Kidney function test	X			X	
Usage of medication	X			X	
Sensation during the treatment			X	X	
Adverse events			X	X	
Blinding assessment				X	
Patients' global assessment				X	
Assessment of safety				X	

**Figure 3**

The schedule of enrolment, interventions, and assessments

## Supplementary Files

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

- [supplement1.pdf](#)
- [supplement2.pdf](#)