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Efficacy of electro-acupuncture versus sham acupuncture for diabetic peripheral neuropathy: study protocol for a three-armed randomised controlled trial

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ABSTRACT

Introduction Specific treatment for diabetic peripheral neuropathy (DPN) is still lacking, and acupuncture may relieve the symptoms. We intend to investigate the efficacy and safety of electro-acupuncture (EA) in alleviating symptoms associated with DPN in diabetes.

Methods and analysis This multicentre, three-armed, participant- and assessor-blind, randomised, sham-controlled trial will recruit 240 eligible participants from four hospitals in China and will randomly assign (1:1:1) them to EA, sham acupuncture (SA) or usual care (UC) group. Participants in the EA and SA groups willl receive either 24-session EA or SA treatment over 8 weeks, followed by an 8-week follow-up period, while participants in the UC group will be followed up for 16 weeks. The primary outcome of this trial is the change in DPN symptoms from baseline to week 8, as rated by using the Total Symptom Score. The scale assesses four symptoms: pain, burning, paraesthesia and numbness, by evaluating the frequency and severity of each. All results will be analysed with the intention-to-treat population.

Ethics and dissemination The protocol has been approved by the Ethics Committee of the Beijing University of Chinese Medicine (Identifier: 2022BZYLL0509). Every participant will be informed of detailed information about the study before signing informed consent. The results of this trial will be published in a peer-reviewed journal.

Trial registration number ChiCTR2200061408.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The sham acupuncture group performing non-acupoint areas and non-penetrating the skin compared with the usual care (UC) group, allowing for a more accurate estimate and a clearer observation of the disease's natural course and the placebo effect.
⇒ Blind assessment will be conducted to avoid bias from subjective interference insofar as possible and expectation will be evaluated regarding needling treatment for promoting the reliability and validity of the trial.
⇒ A limitation is that participants in the UC group and acupuncturists cannot be blinded.
⇒ Second, our study includes an 8-week follow-up period post-treatment, which does not involve the assessment of longer-term outcomes.
⇒ Finally, our study only includes participants with a Total Symptom Score of 5 or higher, which may limit the generalisability of the results to those with milder symptoms.

INTRODUCTION

The International Diabetes Federation estimates that there are at least 425 million diabetics worldwide.[1] One of the major chronic complications of diabetes is diabetic peripheral neuropathy (DPN), which affects up to 50% of individuals with either type 1 or type 2 diabetes.[2–5] At present, DPN can be divided into two clinical types: typical distal symmetric polyneuropathy and atypical DPN. Since distal symmetric polyneuropathy is the most common type of diabetic nerve damage, accounting for approximately 75% of DPN cases,[6–8] distal symmetric polyneuropathy also referred to as DPN.[9] Prolonged hyperglycaemia will damage nerve fibres in diabetics, manifesting in symmetrical sensory impairment, numbness, pain and diminished or absent tendon reflexes in distal limbs.[3 6 9–11] DPN is also associated with increased risks of foot ulcers, lower extremity amputation and a greater risk of falling due to gait instability.[8 12] Besides, individuals with DPN tend to have a higher risk of all-cause and cardiovascular death than diabetics without peripheral neuropathy.[13]

Regretfully, disease-modifying treatment implemented for DPN remains suboptimal. Pharmacotherapy is the main modality for palliating neuropathic pain and paraesthesia, whereas it is still unsatisfactory[14] due to side effects such as dry mouth, dizziness, nausea

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and somnolence,[15–17] which will lead to poor compliance with treatment. In addition, some medications may further exacerbate the renal impairment already caused by diabetes.[18] Intensive glucose control and lifestyle changes are crucial for individuals with diabetes to intervene early and prevent the progression of neuropathy.[9 19] However, glucose control can only marginally affect DPN progression in type 2 diabetes.[2 12]

Previous studies indicated electro-acupuncture (EA) may relieve neuropathic symptoms.[20 21] It is proven effective in relieving the pain of DPN.[20–22] However, it is difficult to draw meaningful conclusions based on available acupuncture trials in DPN as studies often have flawed study designs, such as the high risk of bias and small sample size.[23 24] Therefore, we aimed to evaluate the efficacy and safety of EA in alleviating symptoms associated with DPN by means of randomised controlled trial design.

METHODS AND ANALYSIS

Study design

This is a three-armed, participant- and assessor-blind, randomised, sham-controlled study that will be conducted at the Second Hospital of Hunan University of Chinese Medicine, Shenzhen Traditional Chinese Medicine Hospital, Shanxi Provincial Acupuncture and Moxibustion Hospital, and Shanxi Provincial Hospital of Traditional Chinese Medicine. We planned to recruit patients through posters displayed in hospitals and online, and the flow chart of our trial was shown in figure 1. The recruitment commenced on 20 October 2022 and is expected to continue until 20 October 2024.

Patient and public involvement

Patients or the public are not involved in the design, conduct, report or dissemination of our research.

Inclusion and exclusion criteria

All participants will be diagnosed by specialist physicians. Participants will be eligible if they: (1) are aged between 18 and 75 years; (2) have been diagnosed with diabetes mellitus; (3) have DPN with associated symptoms for more than 6 months; (4) with Total Symptom Score (TSS) for DPN ≥5; (5) have no history of taking medication for DPN within 1 month; (6) didn't experience acupuncture treatment in the past 3 months; (7) did not participate in other ongoing clinical studies and (8) signed the informed consent to participate in the study voluntarily.

Participants will be excluded if they meet any one of the following exclusion criteria: (1) with glycosylated haemoglobin >10%; (2) have installed cardiac pacemaker; (3) are currently pregnant, lactating or preparing for pregnancy; (4) have malignancy, severe cardiovascular disease, infectious disease or liver and kidney insufficiency; (5)

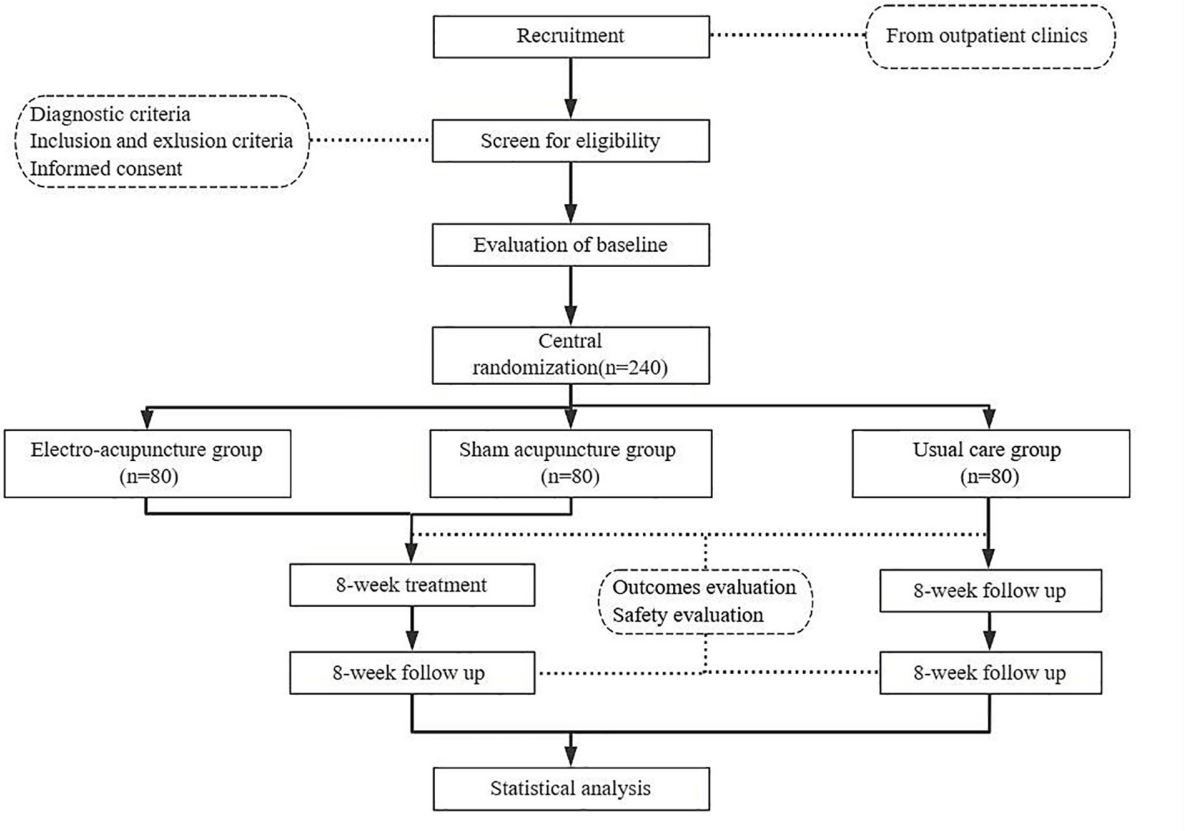

Figure 1 Trial flow chart of or the selection of study participants, including the process of enrolment, allocation, follow-up and analysis.

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other factors may affect nervous system diseases, such as vitamin B_{12} deficiency, undergoing chemotherapy, cervical and lumbar spine disease, hereditary neuropathy or alcoholism; (6) have a history of cerebral haemorrhage, hereditary bleeding disorders or are using anticoagulant drugs such as warfarin; (7) are suffering from foot ulcers or gangrene and (8) experience cognitive impairment, aphasia or mental disorders that hinder cooperation with study.

Randomisation and allocation concealment

Participants will be randomly assigned in a 1:1:1 ratio to receive EA, sham acupuncture (SA) or usual care (UC). Randomisation will be done in permuted blocks and stratified by centre. After obtaining consent, eligible participants will be randomised through a central randomisation system. The random sequence was generated using PROC PLAN in SAS, V.9.4 (SAS Institute).

Interventions regimen

All participants will maintain their original basal glucose-lowering therapy. Detailed medication administration must be collected at baseline, and any adjustment for dose or medication will be recorded accordingly.

EA group

Both EA and SA treatments consist of 24 sessions across 8 weeks, with three sessions each week, and will be performed by licensed acupuncturists with at least 2 years of clinical experience. Participants in the EA group will receive stimulation at bilateral Zusanli (ST36), Sanyinjiao (SP6), Yinlingquan (SP9), Xuanzhong (GB39), Zulinqi (GB41), Taichong (LR3) and Qiduan (EX-LE12). Additionally, bilateral acupoints at Hegu (LI4) and Quchi (LI11) will be used if participants have symptoms in the upper extremities. After sterilising, the acupuncturists will attach sterile adhesive foam pads to the acupoints except for EX-LE12, then use needles to pierce through the adhesive foam pads into the body. The needles will be lifted, thrust and twisted evenly after insertion to induce the sensation of deqi. Electronic acupuncture apparatus (Hwato, SDZ-V, Suzhou Medical Appliance) will be attached to the two pairs of needles longitudinally for each side of ST36 and GB39, SP6 and SP9. Participants with upper extremity symptoms additionally attached one pair of apparatus per side of LI4 and LI11. The EA stimulation will last 20 min with a dilatational wave of 2/100 Hz and a current intensity of 0.1–1 mA depending on the participant's comfort level with three sessions a week (ideally every other day) over a period of 8 weeks. The location of the acupoints[25] was shown in figure 2, as well as the angle and depth of needle insertion are listed in table 1.

SA group

Participants in the SA group will receive SA at bilateral sham ST36, sham SP6 and sham LR3. Sham ST36 is located one proportional bone (skeletal) cun (B-cun, 1 B-cun approximately equals to 1.5 cm) horizontally outside of ST36; sham SP6 is located one B-cun horizontally outside of SP6; sham LR3 is located half B-cun anterior to LR3. Blunt-tipped needles (0.30×25 mm) will be inserted through the adhesive foam pads but will not penetrate the skin (figure 3). No manipulation will be conducted. The electronic acupuncture apparatus will be attached to the needles longitudinally at each side of sham ST36 and sham SP6. The electronic acupuncture apparatus in the SA group will show the same working power indicator and sound without actual current output when switched on. The location of non-acupuncture points is shown in figure 2.

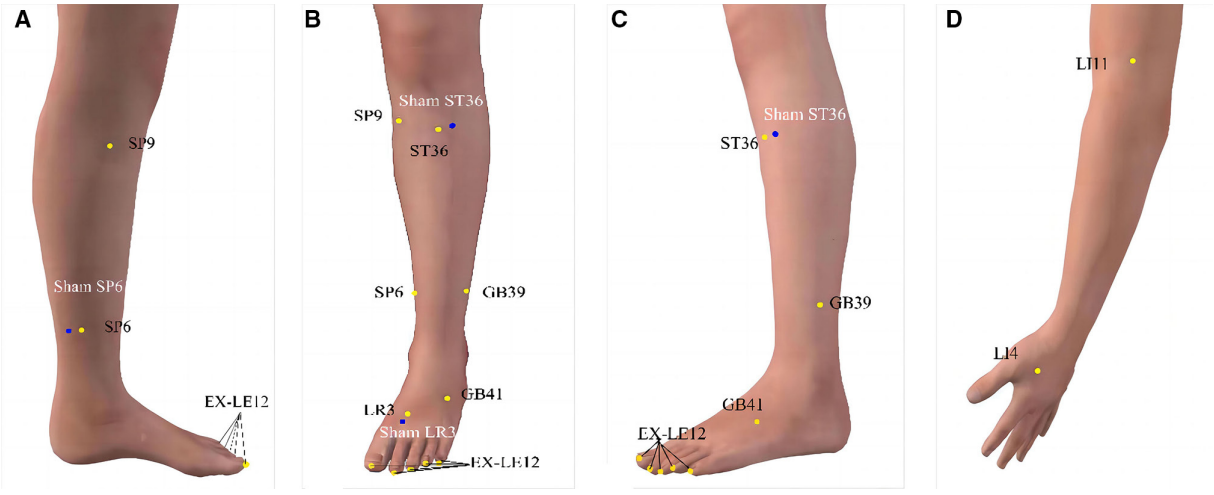

Figure 2 Location of acupoints and non-acupuncture points. Yellow dots: location of acupoints in the electro-acupuncture group; blue dots: location of non-acupuncture points in the sham acupuncture group. (Note: This figure is modified based on www.3Dbody.com). (A) Medial aspect view of the lower extremity; (B) anterior aspect view of the lower extremity; (C) lateral aspect view of the lower extremity; (D) view of the upper extremity.

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Table 1 Location, angle and depth of the operation of acupoints in the electro-acupuncture group

Acupoints	Location, angle and depth of the operation
ST36	On the anterior side of the leg, on the line connecting the depression lateral in the patellar ligament with the depression at the centre of the front surface of the ankle joint between the tendons of extensor hallucis longus and extensor digitorum longus, 3 B-cun inferior to the patellar ligament; pierced vertically 1–2 B-cun with needles of 0.25×50 mm size.
GB39	On the anterior to the fibula, 3 B-cun above the prominence of the lateral malleolus; pierced vertically 0.5–1 B-cun with needles of 0.25×40 mm size.
SP6	On the posterior to the medial border of the tibia, 3 B-cun above the prominence of the medial malleolus; pierced vertically 1–1.5 B-cun with needles of 0.25×50 mm size.
SP9	On the inner aspect of the tibia, in the depression between the inferior border of the medial border of the tibia and the medial condyle of the tibia; pierced vertically 1–1.5 B-cun with needles of 0.25×50 mm size.
GB41	On the dorsum of the foot, on the anterior to the union of the bases of the fourth and fifth metatarsal bones, in the depression of the lateral aspect of the fifth extensor digitorum longus tendon; pierced vertically 0.5–0.8 B-cun with needles of 0.25×40 mm size
LR3	On the dorsum of the foot, between the first and second metatarsal bones, in the anterior depression of two bones union, the dorsalis pedis artery can be palpated; pierced upward oblique pricking 0.5–1 B-cun with needles of 0.25×40 mm size
EX-LE12	On the middle of the tip of the ten feet toes; pierced vertically 0.1–0.2 B-cun with needles of 0.25×40 mm size
LI4	On the dorsum of the hand, in the depression of the second metacarpal bone midpoint off to the radial side; pierced vertically 0.5–1 B-cun with needles of 0.25×40 mm size
LI11	On the lateral aspect of the elbow, on the lateral side of the elbow, at the line midpoint of the lateral depression of the biceps brachii tendon and the lateral epicondyle of the humerus; pierced vertically 1–1.5 B-cun with needles of 0.25×50 mm size

All the above locations of acupoints are referenced to WHO Standard Acupuncture Point Locations in the Western Pacific Region.
B-cun, proportional bone cun.

UC group

Participants in the UC group will be provided with disease counselling and follow-up evaluation for 16 weeks. Participants will not be restricted from accessing their physicians for neuro-nutrition and other related treatments as prescribed by their physicians. Detailed records will be kept. After the trial, they will receive the 24-session EA treatment mentioned above as compensation.

All participants in the three groups are allowed to use rescue medication as prescribed by the doctors to alleviate symptoms if they become unbearable. The name, dosage and time of administration of the medication will be documented.

Blinding

Participants in the EA and SA groups will be blinded to treatment allocation, while those in the UC group will not be blinded. Participants will be treated separately to prevent communication. The efficacy evaluation is assessed by outcome assessors who are blinded to treatment allocation. Additionally, all individuals involved in the study, excluding the acupuncturists, are kept unaware of the group allocations. The data analysts are also blinded to the allocation of this trial.

Sample size

The primary outcome is the difference in TSS compared with baseline at 8 weeks. Based on previous studies, the mean TSS after 8 weeks of acupuncture was 4.95, with an SD of 3.55.[26] Multiple corrections will be conducted to compare the outcomes of the EA group with the SA group and the EA group with the UC group using a significance level of α=0.025 (two-sided). To detect the minimum clinically significant difference of 1.83,[27] a sample size of 72 participants will be needed in each group based on the sample size calculation of one-way analysis of variance (ANOVA) F-tests, which would provide a power of 80%. Assuming 10% dropouts, 240 participants should be recruited.

Endpoints and outcome measures

Primary outcome

The primary outcome of this trial is the change in DPN symptoms from baseline to week 8, as rated by using the TSS.[27 28] TSS is a validated scale that quantitatively assesses four symptoms: pain, burning, paraesthesia and numbness.[29] Each symptom is rated in terms of frequency and severity, with a total score ranging from 0 to 14.64.[30]

Secondary outcomes

The secondary outcomes of this study include the following indicators:

- Symptom reduction: The score change in the TSS at weeks 4, 12 and 16 compared with baseline.
- Responder rate for TSS: The proportion of responders at weeks 4, 8, 12 and 16, a responder is defined as a participant with a 50% or more reduction in TSS.[31]

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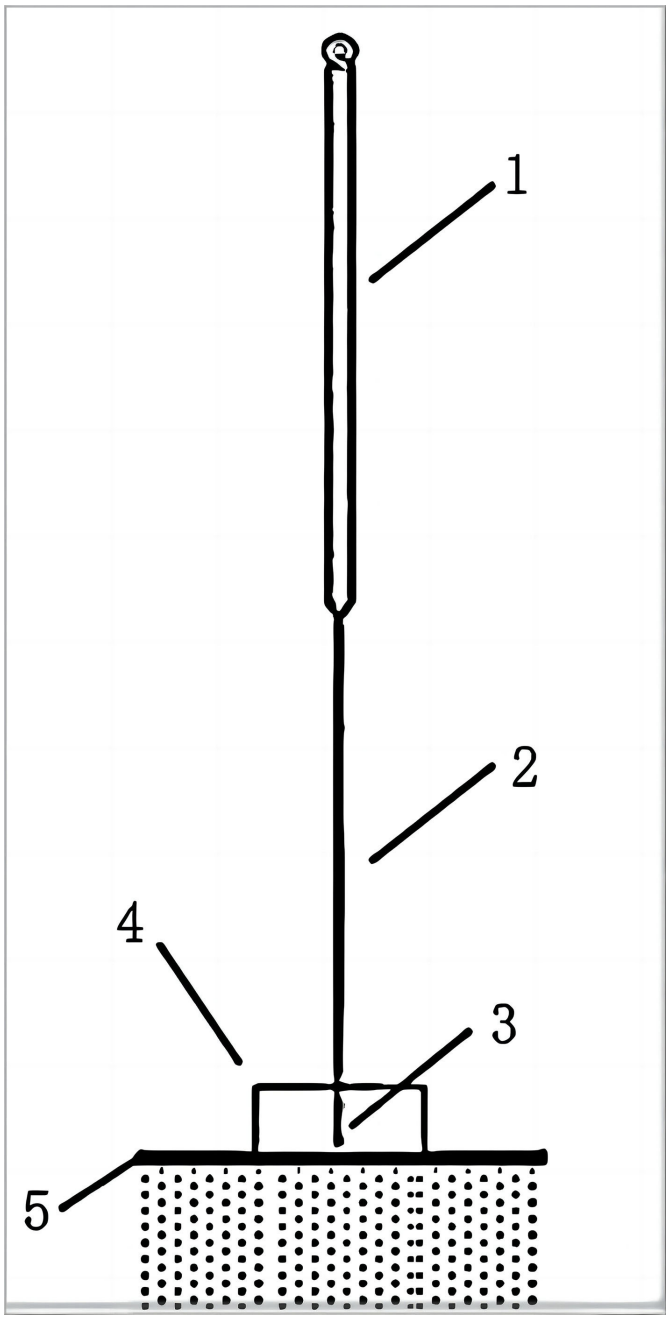

Figure 3 The piercing diagram of the sham acupuncture
Note: 1+2+3: blunt needle: 1—needle handle, 2—needle body, 3—the blunt tip of the needle; 4—base unit; 5—skin.

- Pain: The changes in the Numeric Rating Scale for Pain Intensity (NRS) at weeks 4, 8, 12 and 16. NRS is an 11-point scale mark to depict the pain level score, ranging from no pain (0) to the most severe pain (10). Participants will retain the score that best represents their level of pain.[32] This assessment will only be conducted on participants who report pain symptoms.
- Quality of life: Changes in overall health and quality of daily life, measured using the 12-item Short Form Health Survey (SF-12, a scale about overall health and quality of daily life)[33] at weeks 4, 8, 12 and 16.
- Nerve conduction studies: The nerve conduction studies (NCS) will be conducted at week 8 to assess changes from baseline. We will measure the nerve conduction velocity (m/s) and the wave amplitude (μV). NCS will only be performed among participants enrolled in the Second Hospital of Hunan University of Chinese Medicine.

Expectancy and blinding assessment

Participants' expectations regarding the effect of acupuncture will be rated at baseline. The blinding assessment will be performed within 5 min of the end of the last treatment session, participants in the EA and SA groups will be asked to guess their group allocation. The Bang's Blinding Index will be used to evaluate the success of blinding.[34] Both expectation and blinding assessments will be performed in the EA and SA groups only.

Safety evaluation

Adverse events (AEs) monitoring and recording will be done throughout the trial, regardless of whether the AEs are related to acupuncture. Whether these events are treatment-related will be determined by the endocrinologists and acupuncturists.

Data collection

The data collection for the participants' baseline, treatment and follow-up periods will be done using the electronic data capture (EDC) system. In principle, the entire process is completed on the EDC system, except in particular circumstances, such as the disconnection of the internet, where alternate paper versions of the documents will be used, and the corresponding entry into the EDC system will be completed in time. The study schedule for data collection is shown in table 2.

Quality control

All trial personnel at each hospital are required to receive training in study methods, EA and SA administration and efficacy assessment to ensure standard operating procedures. We will establish a two-tier monitoring system, with the first level monitoring the completion of cases by the subcentre, and the second level being the project team, responsible for the overall system data monitoring and quality control. To ensure clinical records and laboratory sheets will be traceable, the timeliness and completeness of data must be collected in the EDC system. If any network problems occur, the study investigator must promptly document them in the medical record form and input them into the EDC system afterwards. Evaluation of outcomes will be performed independently by personnel not involved in the treatment of participants. The database will be password-protected, and only the principal investigator has the right to assess the final data set. Data acquisition, excluding private participant information, will be available to the principal investigator upon reasonable request.

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Table 2 Study schedule

Time points	Week 0	Week 4	Week 8	Week 12	Week 16
Enrolment					
Eligibility screen	√				
Informed consent	√				
Allocation	√				
Demography characteristics	√				
Medical history	√				
Intervention					
Electro-acupuncture		√	√		
Sham acupuncture		√	√		
Usual care					
Assessments					
TSS	√	√	√	√	√
NRS	√	√	√	√	√
SF-12	√	√	√	√	√
NCS	√		√		
Fasting blood glucose	√		√		
HbA_{1c}	√		√		
Expectancy assessment*	√				
Blinding assessment*			√		
Adverse events		√	√	√	√

*Only for participants in electro-acupuncture and sham acupuncture groups.
HbA_{1c}, haemoglobin A1c; NCS, nerve conduction studies; NRS, Numeric Rating Scale for Pain Intensity; SF-12, 12-item Short Form Health Survey; TSS, Total Symptom Score.

Statistical analysis

All analyses will be based on the intention-to-treat principle, where every participant who has been under randomisation is considered to the part of the intention-to-treat population. For the primary outcome, a linear mixed model will be used to estimate the change in TSS from baseline after 8 weeks of treatment between the EA and SA groups, as well as the EA and UC groups. Primary endpoint will be controlled for type I error by using a two-sided α=0.025, a Bonferroni adjustment, to adjust for multiple comparisons. The linear mixed model will include baseline TSS as a covariate, with group, time, the interaction between group and time, and study centre as fixed effects, and participant as a random effect. Generalised linear mixed models will be assessed for response rates between groups at weeks 4, 8, 12 and 16, as well as the proportion of participants who used rescue medication. Reduction in TSS from baseline at weeks 4, 12 and 16, along with change in NRS, NCS and SF-12 from baseline, will be compared between groups using repeated measures ANOVA or non-parametric tests. The evaluation of acupuncture expectancy involves describing baseline differences between groups. AEs will be compared across the three groups using the χ^2 test or Fisher's exact test. Furthermore, sensitivity analysis will be conducted by excluding participants who used rescue medication. For missing values, multiple imputation will be used as it is effective in handling error variance and provides unbiased estimates.[35] The results of secondary outcomes will be interpreted as exploratory. No predefined subgroup analyses are planned. The statistical analysis plan of this trial will be finalised in advance of data analysis, and analyses will be performed using SAS V.9.4 (SAS Institute).

ETHICS AND DISSEMINATION

The protocol has been approved by the Ethics Committee of Beijing University of Chinese Medicine (2022BZYLL0509) and obtained the approval of the ethics committees of every study site. This trial will adhere to the guidelines outlined in the Declaration of Helsinki and the International Conference on Harmonisation E6 Guideline on good clinical practice. Participants will receive detailed information about the trial and informed written consent will be required. The trial results will be published in a peer-reviewed journal.

DISCUSSION

DPN is considered one of the most common prolonged complications of diabetes, with a prevalence of 60%–90% among participants with diabetes,[36] which not only

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impacts the quality of health of people seriously but also brings a huge economic burden to society.[9 37] Available studies suggest that the pathological mechanism of DPN may be related to a variety of physiological factors, including oxidative stress, mitochondrial dysfunction, inflammation and altered gene regulation.[38 39] Unfortunately, despite DPN being long-recognised, there is still a lack of effective specific treatment for DPN to date, clinical treatment is mostly focused on managing symptoms such as pain and other indicators. Based on previous research findings, EA may relieve the symptoms of DPN by anting inflammation with multitargets,[40–44] modulating oxidative stress[45 46] and improving neurological and vascular function.[47–49] However, preceding studies of EA for DPN based on inadequate sample size, deficiencies in placebo needling design and limited reports of AEs did not suggest definitively that EA is effective and safe for DPN.

We hope to deliver high-quality evidence on the efficacy and safety of clinical EA in participants with DPN and have therefore initiated this multicentre, three-armed, randomised, controlled trial. We have designed a superficial stimulation performing non-acupoint areas and non-penetrating the skin as a sham control to eliminate the placebo effect as much as possible, allowing a better estimation of the specific effect of EA compared with the SA group. In the UC group, participants will be allowed to receive counselling related to health education, facilitating better observation of the natural course of the disease and allowing for a better estimation of the placebo effect compared with the SA group. We will also evaluate blinding to avoid bias from subjective interference insofar as possible, and to evaluate participants regarding needling expectancy, contributing to the reliability and validity of the trial. In addition, this study is the multicentre trial with the largest sample size to date, which will further ensure that the results are extensive and real-world.

There are several limitations to this study. Blinding of acupuncturists cannot be achieved due to the unique nature of acupuncture procedures in this trial. Additionally, the lack of treatment related to acupuncture in the UC group leads to the inability to blind participants in this group, probably causing potential performance bias. However, we have taken efforts to mitigate these limitations to obtain more reliable evidence regarding the efficacy of EA for the treatment of DPN. For example, we will offer compensatory treatment free of charge for the UC group to ensure compliance. Furthermore, since the outcome assessors of the DPN are also unaware of group assignments, it is unlikely that the results will be significantly biased. We acknowledge that for the purpose of blinding the participants in the EA and SA groups, the use of base units in the EA group might reduce appropriate stimulation,[50] so we chose EA stimulation to compensate for it. We expect that the results of this study will contribute meaningful insights into the potential therapeutic benefits of this approach and seek greater scope for future clinical research in this area.

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Contributors SY proposed and initiated the study and made revisions to the manuscript; RZ drafted and revised the manuscript; ZX participated in the designing, drafting and revising the manuscript; HZ is responsible for statistical analysis plan and revised the manuscript; QD, WL, JM, YZ, XF, WZ, XW, LL, JC, TZ, CH, XH and LJ helped to refine the design of this trial. The final manuscript was reviewed and approved by all authors.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Consent obtained directly from patient(s).

Provenance and peer review Not commissioned; externally peer reviewed.

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