Electrophysiologically verified effects of acupuncture on diabetic peripheral neuropathy in type 2 diabetes: The randomized, partially double-blinded, controlled ACUDIN trial

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Abstract
Background: Acupuncture is commonly used in Traditional Chinese Medicine for treatment of diabetic peripheral neuropathy (DPN), but data from randomized controlled trials are rare.

Methods: This randomized, placebo-controlled, partially double-blinded clinical trial randomly assigned adults with confirmed type 2 diabetes-induced DPN to receive 10 sessions of needle acupuncture, laser acupuncture, or placebo laser acupuncture for 10 consecutive weeks. Treatment was provided at bilateral acupoints Ex-LE-10 (Bafeng), Ex-LE-12 (Qiduan), and ST-34 (Lianqiu).

Neurological assessments, including nerve conduction studies (NCS) of sural and tibial nerves, were performed at baseline and weeks 6 and 15. Primary outcome was delta of sural sensory nerve action potential (SNAP). Secondary outcomes included further NCS values, clinical scores, and patient-reported outcome measures (PROMs).

Results: Of 180 participants, 172 completed the study. Sural SNAP and sural and tibial nerve conduction velocities improved significantly after 10 treatments when comparing needle acupuncture to placebo. Needle acupuncture showed earlier onset of action than laser acupuncture. PROMs showed larger improvements following needle and laser acupuncture than placebo, reaching significant differences for hyperesthesia and cramps following needle acupuncture and for heat sensation following laser acupuncture.

Conclusions: Classical needle acupuncture had significant effects on DPN. Improvement in NCS values presumably indicates structural neuroregeneration following acupuncture.

Keywords
acupuncture, diabetic peripheral neuropathy, laser acupuncture, nerve conduction studies, randomized controlled trial

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1 | INTRODUCTION

Diabetic peripheral neuropathy (DPN) is a common complication of type 1 and type 2 diabetes mellitus. Duration of diabetes and hyperglycemia are major risk factors; however, rigorous glycemic control has shown to be insufficient to prevent DPN in type 2 diabetes. Metabolic sequelae directly affect neuronal tissues and the vasa nervorum, causing changes in nerve microvasculature with reduced nerve perfusion and endoneurial hypoxia. Several pathomechanisms contribute to peripheral nerve injury in DPN, including oxidative stress, mitochondrial dysfunction, inflammation, and altered gene regulation. Recent research focuses on endoplasmic reticulum stress (ERS) and mediated cell apoptosis in the pathophysiology of DPN.

DPN typically presents as a chronic, symmetrically distributed stocking glove, length-dependent sensorimotor polyneuropathy. Sensory clinical manifestations include neuropathic pain, paresthesia, hyperesthesia, or hypoesthesia. Motor symptoms occur less frequently. DPN is associated with increased risks of foot ulcers, Charcot arthropathy, and lower extremity amputation and a greater risk of falling due to gait insecurity. Overall, DPN causes elevated healthcare costs. Pharmacologic treatment is limited to palliating neuropathic pain and paresthesia, whereas neuronal degeneration remains unaffected.

During the last decades, acupuncture was empirically applied for treatment of DPN, yielding positive reports. The aim of the ACUDIN (ACUpuncture and laser acupuncture for treatment of DIabetic peripheral Neuropathy) trial was to quantify the effect of acupuncture on DPN in NCS and on patient-reported outcome measures (PROMs) and clinical variables compared with placebo.

The definition of adequate control interventions for a double-blind study design has, despite many efforts, remained a methodological challenge in acupuncture trials. Sham needling performed away from acupuncture points or shallow needling elicits unspecific physiological responses on skin penetration and cannot be regarded as an inactive placebo intervention. To date, there are no international standards regarding direct placebo procedures for the evaluation of acupuncture effects in a double-blind study.

Therefore, we chose an indirect control for the ACUDIN trial, using laser acupuncture as a second treatment intervention. Laserneedle is a particular type of laser acupuncture that has previously been shown to be equally effective as needle acupuncture and is suitable for placebo treatment, preventing any nonspecific physiological activation by deactivated laser irradiation. This can be completely concealed from the patient. Laser acupuncture has been previously evaluated as valid control for classifying the effect of acupuncture needling. Therefore, we included laser acupuncture as a second verum treatment and placebo intervention in a double-blind procedure in the ACUDIN trial. Particulars are detailed in the previously published trial protocol.

2 | METHODS

The prospective, randomized, partially double-blinded, placebo-controlled, three-armed, single-center ACUDIN study was conducted between January 2012 and August 2018 at the HanseMerkur Center for Traditional Chinese Medicine at the University Medical Center Hamburg-Eppendorf, Germany (German Clinical Trial Registry No. DRKS00008562, https://www.drks.de/drks_web/navigate.do?navigationId=trial.HTML&TRIAL_ID=DRKS00008562). Hypotheses were previously established. The study protocol was approved by the Ethics Committee of the Chamber of Physicians Hamburg, Germany (No. PV3518, 13 Jul 2011). Written informed consent was obtained from all patients. The study was carried out in accordance with the Declaration of Helsinki.

Figure 1 shows the ACUDIN study flowchart.

3 | PARTICIPANTS

Participants were primarily recruited from regional outpatient centers. Additionally, 113 individuals (42% of a
total of 272 potential participants) were recruited from the community by poster advertisements. Only patients with a confirmed history of type 2 diabetes and DPN including abnormal electrophysiological findings were assessed for eligibility. Patients were eligible if they were aged $\geq 18$ years; presented with diabetes for $\geq 1$ year; had a symptomatic symmetrical length-dependent sensorimotor DPN at the lower extremities, and showed abnormal results in NCS, sural sensory nerve action potential (SNAP) <10 $\mu$V, sural sensory nerve conduction velocity (SNCV) <42 m/s, tibial motor nerve conduction velocity (MNCV) <40 m/s, and tibial motor nerve action potential (MNAP) <8 mV. Exclusion criteria were neuropathies caused by other conditions, including alcohol abuse, chemotherapy, hereditary causes, and chronic inflammatory or idiopathic neuropathies; history of epilepsy; coagulopathies with prothrombin time < 40%; local bone fractures; local bacterial infections or skin lesions; analgesic or drug abuse; psychiatric illnesses; acupuncture in the last 3 months; pregnancy or breastfeeding; and incapacity or failure in giving informed consent. Current medications remained unchanged. Participants were offered 10 verum treatments free of charge after completion of the study if they were randomized to placebo.
Patients were randomly assigned to receive either classical needle acupuncture, verum laser acupuncture, or placebo laser acupuncture with a parallel 1:1:1 allocation ratio using random four-digit numbers generated with Microsoft Office Excel 2007 (Microsoft Cooperation, Redmond, WA, USA). Allocation concealment was implemented by envelope lottery using opaque sealed envelopes containing the assigned information. Randomization was performed by study nurse 1 who was later exclusively involved in the process of verum laser and placebo laser acupuncture as described later. Randomization was unstratified and well balanced. Patients of all groups were informed that they would receive either verum or placebo treatment. Needle acupuncture was performed in single-blind mode, and verum laser and placebo laser acupuncture were performed in a double-blind procedure. For patient blinding, acupuncture situs and laser device were shielded from the patient. For caregiver blinding, the acupuncturist fixed the laser needles at the acupuncture points but did not operate the laser device before leaving the room. Study nurse 1 entered the room and operated the laser device according to the randomization schedule. Thus, study nurse 1 was the only person who had knowledge about patients’ allocation to verum or placebo laser. Neurologists and statisticians were blinded to patients’ group allocation. Neurological assessments were conducted at a separate neurological practice. Patients agreed not to disclose treatment information to the neurologist. For data transfer and processing, pseudonym codes were used in order to mask patient identity and treatment groups from outcome assessors and statisticians. Data were matched only after completion of statistical analysis.

All participants received 10 identical treatment sessions weekly for 10 consecutive weeks. Needle acupuncture was performed with sterile disposable stainless-steel needles 0.2 × 15 mm for Ex-LE-10 and Ex-LE-12, and 0.3 × 30 mm for ST-34, both manufactured by Wujiang City Cloud & Dragon Medical Devise Co. Ltd, China. After skin disinfection, needles were inserted perpendicularly to a depth of 0.2-0.3 cm at Qiduan, 0.8-1.2 cm at Bafeng, and 1.5-2.0 cm at Lianqiu. Depth varied with the thickness of the skin and subcutaneous tissues at the site of the acupuncture points. Needles remained in place for 20 minutes. They were then removed by a staff member not involved in further study procedures and disposed in puncture-resistant containers. Verum laser acupuncture was performed with two Laserneedle devices (European patent PCT/DE 102006008774.7) using multichannel semiconductor laser diodes for simultaneous acupoint stimulation. Activated diodes emitted a wavelength of 685 nm in continuous mode. Each channel provided an optical power of 35 mW. Power density was 2.3 kJ/cm² per channel with a spot diameter of 500 μm. After local disinfection, laser needles were placed at an angle of 90° directly on the skin. With activation, laser radiation was emitted for 20 minutes, then deactivated automatically; laser needles were removed by a staff member not involved in further procedures. Placebo laser acupuncture was performed under identical conditions, but manipulating an invalid point on the laser device touch screen meant no laser light was emitted.

Acupuncturists are members of one registered German physicians society for acupuncture. They have completed a standardized training course, undertaken formal accreditation by examination, a period of supervised medical experience for administering interventions, and have been trained for the implementation of laser acupuncture.

Clinical assessments including NCS of bilateral sural and tibial nerves were performed by independently trained neurologists at baseline, following five treatment sessions at weeks 6 and 15. Primary endpoint was the change of SNAP from baseline to week 15 compared with placebo. Key secondary endpoints were changes of SNCV, MNCV, and MNAP compared with placebo. NCS were performed bilaterally with standard orthodromic needle recording methods for the sural nerve and standard orthodromic surface electrode recording methods for the tibial nerve with Neuropack-Sigma, MEB-9400, EMG/NCV/EP-System (Nihon-Khoden, Japan). Values of nerve conduction velocities were adjusted for the effect of skin temperature.

Additional secondary outcomes included clinical findings and PROMs. Clinical assessments included Achilles

5 | INTERVENTIONS

The ACUDIN treatment concept was developed by acupuncturists based on Traditional Chinese Medicine meridian theory and previously tested in a study for neuropathy of unknown cause. The bilateral acupuncture point selection consisted of two multiple local points, Ex-LE-10 (Bafeng) and Ex-LE-12 (Qiduan), and ST-34 (Lianqiu) with a total of 20 needles. According to Chinese medicine theory, Bafeng enhances the peripheral blood flow, Qiduan promotes local activation of Qi, and Lianqiu improves the Qi flow through meridians and Luo channels. This concept was standardized for all patients owing to a relatively even effect on local meridians caused by DPN.
and patellar tendon reflexes, gait qualities, sensory qualities, for example, pain and temperature perception and pallesthesia, and DPN-related symptoms; neuropathic pain, numbness, burning and tingling sensations, muscle weakness, and cramps. Clinical findings were summarized according to the neuropathy disability score (NDS) and neuropathy symptom score (NSS).\textsuperscript{28} Further DPN-related symptoms were assessed by PROMs using 11-point numeric rating scale (NRS) questionnaires for neuropathic pain, impacts on daily activities and on sleep quality, and complaint frequency with the terminal descriptors “no complaint” and “worst complaint possible”.\textsuperscript{29} Patients were asked to complete the PROMs questionnaires, outlining changes of medication, including pain medication and possible adverse events at every appointment before the treatment or assessment session. Adverse events were categorized as treatment or nontreatment related and graded for severity.\textsuperscript{30} Glycosylated hemoglobin (GHb) levels were monitored at baseline and week 15.

7 | STATISTICAL ANALYSIS

The null hypothesis was that the difference of sural SNAP from baseline to week 15 in the needle and laser acupuncture groups would be the same or smaller than in the placebo group. The alternative hypothesis was that the difference of SNAP would be larger in the needle and laser acupuncture groups than in the placebo group. An average difference of 1 \( \mu \text{V} \) was considered functionally relevant.\textsuperscript{31} Based on the previous case study,\textsuperscript{26} a sample size of 54 per group was estimated to detect the between-group difference of 1 \( \mu \text{V} \) with a SD of 1.83, an alpha of 0.05, and a power of 0.8. Assuming a conservative 10% dropout rate, the sample size was increased to 60 patients per arm, or 180 in total. The primary endpoint was analyzed according to the intent-to-treat principle. Statistical analysis was done by one-way analysis of variance, followed by Tukey post hoc tests comparing the three groups pairwise. Homogeneity of variances was confirmed by Levene’s test. \( P < .05 \) was regarded as statistically significant. Changes of SNAP were analyzed, evaluating the average values of each patient’s legs. For unilateral results, only the evaluable leg was analyzed. Missing data were imputed by the next-observation-carried-backwards option for initial values and last-observation-carried-forwards option for closing values. Descriptive statistical analysis was used to characterize mean, SD, SE of the mean (SEM), variance, and range. The same approach was used for secondary endpoints. Data are presented as mean (SD) with 95% confidence interval (CI); figures show mean changes (SEM). Statistical analysis was conducted after completion of data collection. Data assessment was performed with SPSS (IBM SPSS Statistics 22) and OriginPro 9.

8 | DATA AND RESOURCE AVAILABILITY

The datasets generated during the current study and the resources analyzed are available from the corresponding authors upon reasonable request.

9 | RESULTS

We screened 272 patients for eligibility; 180 participants (aged 70 [10] years, 42-89 years; 80 [44%] females, 100 [55%] males) were randomly assigned to three groups of 60 participants each, that is, to needle acupuncture,
laser acupuncture, or placebo laser acupuncture. Of these, 172 participants completed the study. Demographic baseline parameters, including gender, age, body mass index (BMI), duration of type 2 diabetes and DPN, GHb values, and severity of DPN-related signs and symptoms as measured by NDS and NSS, did not differ significantly between groups. Furthermore, demographic characteristics were not affected by recruitment methods. GHb values remained stable over the study period.

Table 1 summarizes participants' baseline characteristics.

### 10 PRIMARY OUTCOME

In the needle acupuncture group, the mean sural SNAP improved significantly from baseline to week 15 with a difference of 1.95 [2.36] μV, CI 95%, P < .001. In the laser acupuncture group, the mean sural SNAP improved significantly with a difference of 1.07 [2.21] μV, CI 95%, P < .001. In the placebo group, the mean sural SNAP improved significantly with a difference of 0.50 [1.62] μV, CI 95%, P = .016. The group comparison of mean sural SNAP at week 15 showed a significant difference of 1.45 μV, CI 95%, P < .001 between needle acupuncture and placebo, and a nonsignificant difference of 0.57 μV, CI 95%, P = .30 between laser acupuncture and placebo.

### 11 KEY SECONDARY OUTCOMES

In the needle acupuncture group, the mean sural SNCV improved significantly from baseline to week 15 with a difference of 13.49 [14.59] m/s, CI 95%, P < .001. In the laser acupuncture group, the mean sural SNCV improved significantly with a difference of 7.35 [13.32] m/s, CI 95%, P < .001. In the placebo group, the mean sural SNCV achieved a nonsignificant difference of 3.40 [11.5] m/s, CI 95%, P = .110. The group comparison of mean sural SNCV at week 15 showed a significant difference of 10.09 m/s, CI 95%, P < .001 between needle acupuncture and placebo, and a nonsignificant difference of 3.95 m/s, CI 95%, P = .23 between laser acupuncture and placebo.

In the needle acupuncture group, the mean tibial MNCV improved significantly from baseline to week 15 with a difference of 5.82 [13.52] m/s, CI 95%, P < .001. In the laser acupuncture group, the mean tibial MNCV achieved a nonsignificant difference of −0.10 [7.45] m/s, CI 95%, P = .63. In the placebo group, the mean tibial MNCV achieved a nonsignificant difference of −0.82 [9.44] m/s, CI 95%, P = .76. The group comparison of mean tibial MNCV at week 15 showed a significant difference of 6.64 m/s, CI 95%, P = .003 between needle acupuncture and placebo, and a nonsignificant difference of −0.27 m/s, CI 95%, P = .99 between laser acupuncture and placebo.

### TABLE 2 Results obtained by nerve conduction studies

|                  | Baseline          | Week 6           | Week 15          | Week 15–Baseline |
|------------------|-------------------|------------------|------------------|------------------|
| **Placebo**      |                   |                  |                  |                  |
| Sural SNAP (μV)  | 1.64 [1.93]       | 1.71 [1.82]      | 2.14 [2.43]      | 0.50 [1.62], P = .016 |
| Sural SNCV (m/s) | 30.65 [20.59]     | 31.79 [19.38]    | 34.05 [18.69]    | 3.40 [11.5], P = .110 |
| Tibial MNCV (m/s)| 37.55 [20.05]     | 36.86 [21.04]    | 36.77 [20.48]    | −0.82 [9.44], P = .76 |
| Tibial MNAP (mV) | 4.75 [5.41]       | 4.83 [5.20]      | 4.92 [5.60]      | 0.17 [3.11], P = .90 |
| **Laser**        |                   |                  |                  |                  |
| Sural SNAP (μV)  | 2.17 [3.45]       | 2.42 [3.44]      | 3.31 [3.78]      | 1.07 [2.21], P < .001 |
| Sural SNCV (m/s) | 29.84 [19.11]     | 30.74 [19.02]    | 37.16 [18.38]    | 7.35 [13.32], P < .001 |
| Tibial MNCV (m/s)| 31.31 [23.52]     | 30.89 [23.74]    | 30.42 [22.62]    | −0.10 [7.45], P = .63 |
| Tibial MNAP (mV) | 5.80 [5.40]       | 5.86 [6.11]      | 5.93 [5.77]      | 0.24 [2.51], P = .91 |
| **Acupuncture**  |                   |                  |                  |                  |
| Sural SNAP (μV)  | 1.69 [2.13]       | 2.29 [3.03]      | 3.59 [3.97]      | 1.95 [2.36], P < .001 |
| Sural SNCV (m/s) | 28.92 [18.22]     | 32.24 [17.50]    | 42.12 [13.40]    | 13.49 [14.59], P < .001 |
| Tibial MNCV (m/s)| 35.13 [22.98]     | 38.36 [23.05]    | 40.65 [23.48]    | 5.82 [13.52], P < .001 |
| Tibial MNAP (mV) | 5.83 [5.53]       | 5.67 [5.18]      | 5.80 [5.28]      | −0.18 [2.11], P = .99 |

Note: Data presented as mean values [SD], confidence interval 95%.
Abbreviations: MNAP, motor nerve action potential; MNCV, motor nerve conduction velocity; SNAP, sensory nerve action potential; SNCV, sensory nerve conduction velocity.
There were no significant changes of the mean tibial MNAP in any group at the \( P < .05 \) level.

Tables 2 and 3 summarize the results obtained by NCS. Figure 2 illustrates the results obtained by NCS.

### 12 | CLINICAL SCORES

The ACUDIN study population showed mean-moderate to severe stages of DPN of both NDS and NSS at baseline, which did not change significantly at the \( P < .05 \) level in any group.

Table 4 summarizes the results obtained from NDS and NSS.

### 13 | PROMS

Patient-related outcomes showed significant changes from baseline to week 15 in all queried items induced by needle acupuncture, in 11 of 12 items induced by laser acupuncture, and in nine of 12 induced by placebo laser. Needle acupuncture induced the largest improvement in neuropathic symptoms, impact on daily activities, and sleep quality. Laser acupuncture induced the largest improvement in heat sensation, burning pain, unsteadiness of gait, and symptom frequency. Placebo laser induced the fewest changes. However, significant group differences were reached only for hyperesthesia and cramps in the needle acupuncture group and for heat sensation in the laser acupuncture group. PROMs improved in all groups without statistical differences at the \( P < .05 \) level.

Table 5 summarizes significant group differences obtained by PROMs. Figure 3 illustrates the overall results obtained by PROMs.

### 14 | PATIENTS’ ASSUMPTION OF TREATMENT ALLOCATION

Patients were asked if they received a verum or placebo treatment at the final assessment. In the acupuncture group, 39 patients (65%) estimated their intervention as active treatment, 15 (25%) deemed their intervention placebo, and six (10%) were indecisive. In the laser acupuncture group, 41 patients (68%) estimated their intervention as active treatment, 16 (27%) deemed their intervention placebo, and three (5%) were indecisive. In the placebo group, 28 patients (47%) estimated their intervention as active treatment, 25 (42%) deemed their intervention placebo, and seven (11%) were indecisive. Results did not differ statistically between the three groups.

### 15 | DROPOUTS

Eight participants discontinued the treatment (two needle acupuncture, three laser acupuncture, three placebo patients). Two patients withdrew because of symptom progression, four declined to participate, and two were lost to follow-up.

### 16 | ADVERSE EVENTS

Minor hematomas following needle acupuncture were observed in 13 of 60 patients (22%) with a total of 67 incidences in 589 treatment sessions (11%) without requiring medical intervention. Seven of 180 patients (4%) reported a temporary increase of neuropathic pain and decreasing hypoesthesia during the treatment course. All events were classified as mild.30

### 17 | DISCUSSION

DPN is a common complication of type 1 and type 2 diabetes mellitus with severe clinical sequelae.1–10 Pharmaceutical management palliates neuropathic pain and paresthesia11 but does not address decreased nerve function. Furthermore, patients have to tolerate medication side effects.32 Longitudinal observations show a natural decline of sensory qualities and NCS values over time.33,34 At present, there is no disease modifying therapy established for DPN.35 Recently, regenerative therapy approaches have achieved more attention.35,36

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**Table 3** Group comparison of NCS values at week 15

|                  | Acupuncture–Placebo | Laser–Placebo | Acupuncture–Laser |
|------------------|----------------------|--------------|------------------|
| Sural SNAP (μV)  | 1.45, \( P < .001 \) | 0.57, \( P = .30 \) | 0.88, \( P = .058 \) |
| Sural SNCV (m/s) | 10.09, \( P < .001 \) | 3.95, \( P = .23 \) | 6.13, \( P = .032 \) |
| Tibial MNCV (m/s) | 6.64, \( P = .003 \) | –0.27, \( P = .99 \) | 6.92, \( P = .002 \) |
| Tibial MNAP (mV) | –0.35, \( P = .75 \) | 0.07, \( P = .99 \) | –0.42, \( P = .66 \) |

*Note: Data presented as mean values [SD], confidence interval 95%.*

*Abbreviations: MNAP, motor nerve action potential; MNCV, motor nerve conduction velocity; NCS, nerve conduction studies; SNAP, sensory nerve action potential; SNCV, sensory nerve conduction velocity.*
FIGURE 2  Legend on next page.
Table 4  Results obtained by clinical scores

|                     | Placebo  | Laser    | Acupuncture |
|---------------------|----------|----------|-------------|
| NDS at baseline     | 7.98 [2.42] | 8.26 [2.31] | 8.07 [2.44] |
| NDS at week 15      | 7.85 [2.32] | 8.0 [2.35]  | 8.05 [2.30] |
| NDS week 15–baseline | −0.13 [2.09] | −0.25 [1.82] | −0.05 [2.02] |
| NSS at baseline     | 6.88 [1.54] | 7.15 [1.48] | 7.16 [1.50] |
| NSS at week 15      | 6.57 [1.61] | 6.83 [1.60] | 7.10 [1.51] |
| NSS week 15–baseline | −0.32 [1.53] | −0.32 [1.72] | −0.05 [1.70] |

Note: Data presented as mean values (SD). Abbreviations: NDS, neuropathy disability score (mild = 3–5, moderate = 6–8, severe = 9–10 points); NSS, neuropathy symptom score (mild = 3–4, moderate = 5–6, severe = 7–10 points). Neither NDS nor NSS changed significantly during the treatment.

Table 5  Significant group differences obtained by PROM

|                     | Acupuncture–Placebo | Laser–Placebo |
|---------------------|---------------------|---------------|
| Hyperesthesia (NRS) | 0.97, P = .007      | 0.43, P = .35 |
| Cramps (NRS)        | 0.88, P = .047      | 0.78, P = .088|
| Heat sensation (NRS)| 0.78, P = .056      | 0.87, P = .030|

Note: Data presented as mean values [SD], confidence interval 95%. Note: Significant group differences were reached for hyperesthesia and cramps in the needle acupuncture group and for heat sensation in the laser acupuncture group as compared with placebo. Further PROMs improved in all groups without statistical differences at the P < 0.05 level. Abbreviations: NRS, 11-point numeric rating scales; PROM, patient-reported outcome measures.

Acupuncture is a promising complementary treatment, but its evidence is limited.12–14

The aim of the ACUDIN study was to quantify the effect of acupuncture on type 2 diabetes-induced DPN as compared with placebo. Laser acupuncture was implemented in the study to allow a double-blind treatment with an inert placebo procedure and thus avoid a noninert sham acupuncture for control.

Over a 15-week period, needle acupuncture induced significant improvement in the primary outcome variable sural SNAP and sural SNCV and tibial MNCV compared with placebo. Laser acupuncture induced improvement in both sural SNAP and SNCV compared with the baseline; however, it showed a later onset of effect compared with needle acupuncture and did not reach significance compared with placebo on completion of the study. Study design and power calculation were generated for needle acupuncture based on a prior case study.26 Laser acupuncture was implemented for the purpose of a double-blind comparison. Based on other publications,19,20,37 laser acupuncture was expected to yield equivalent effects to needle acupuncture. However, the results remained below those of needle acupuncture.

DPN affects primarily sensory rather than motor nerves.8 This was confirmed by fewer impaired baseline values and minimal, insignificant changes of tibial MNAP in all groups. Following needle acupuncture significant improvements could, compared with placebo, be demonstrated only for sural SNAP and SNCV and for tibial MNCV.

In a diabetic rat model, Pan et al38 demonstrated less impairment of sensory and motor nerve conduction.

Figure 2  Results Obtained by Nerve Conduction Studies. Data are presented as mean [SEM], CI 95%, *P < 0.05, **P < 0.001.

(A) Group comparison of delta sural SNAP at week 15; (B) mean changes of sural SNAP from baseline to weeks 6 and 15; (C) group comparison of delta sural SNCV at week 15; (D) mean changes of sural SNCV from baseline to weeks 6 and 15; (E) group comparison of delta tibial MNCV at week 15; (F) mean changes of tibial MNCV from baseline to weeks 6 and 15; (G) group comparison of delta tibial MNAP at week 15; (H) mean changes of tibial MNAP from baseline to weeks 6 and 15. Subfigure A shows a significant improvement in the primary outcome variable sural SNAP induced by needle acupuncture but not by laser acupuncture compared with placebo. Subfigure B shows a faster onset of action for needle acupuncture compared with laser acupuncture and more pronounced effects after 15 weeks compared with 6 weeks for needle and laser acupuncture. Subfigure C shows a significant improvement of sural SNCV induced by needle acupuncture but not by laser acupuncture as compared with placebo. Subfigure D shows a faster onset of action for needle acupuncture compared with laser acupuncture and more pronounced effects after 15 weeks compared with 6 weeks for both needle and laser acupuncture. Subfigures E and F show a significant improvement of tibial MNCV induced by needle acupuncture but not by laser acupuncture as compared with placebo. Subfigures G and H show that no significant change of MNAP was achieved in any treatment group. SNAP, sensory nerve action potential; SNCV, sensory nerve conduction velocity; MNCV, motor nerve conduction velocity; MNAP, motor nerve action potential; CNA, classical needle acupuncture, VLA, verum laser acupuncture, PLA, placebo laser acupuncture.
velocities of the sciatic nerve in the electroacupuncture treatment group. Improved NCS values were accompanied by reduced myelinated nerve fiber damage and decreased proportions of cell apoptosis due to the ERS pathway, in comparison with a nontreatment group indicating structural enhancement. Our ACUDIN study confirms these findings on a clinical level. Because changes in nerve conduction studies are associated with neural fiber density differences, the observed improvement in NCS values indicates structural regeneration of nerve fibers. Hence, acupuncture might induce regenerative processes that could represent disease modification in DPN.

Clinical variables showed improvement in a number of subitems such as pain perception and localization of symptoms. However, NDS and NSS in total did not reach statistically significant changes during the study. Our study participants presented a mean age of 70 with a range of 42 to 89 years. Given that most patients suffered from progressed DPN and comorbidities including restrictions of mobility, we presume that higher clinical effects could be achieved in patients in earlier stages of DPN.

Tissue and nerve regenerative capacity has been shown to be decreased in diabetic patients. Acupuncture increases the blood flow in the extremities. The selected acupoints at the distal end of the extremities were chosen to improve the perfusion of the vasa nervorum and dependent capillary beds supplying local neurons. Shin et al. demonstrated a positive effect of electroacupuncture on painful DPN, using distal acupuncture points (Bafeng) as facilitative points. All obligatory points were located proximal to the toes. There was a significant decrease in pain intensity as measured by NRS but no changes in NCS. However, in the ACUDIN protocol, points located at the toes were obligatory (Bafeng and Qiduan). This approach resulted in significant changes in NCS values, suggesting that local microcirculatory effects could be the predominant mechanism of acupuncture-induced peripheral nerve repair, combined with modulation of cortical network connectivity contributing to the analgesic effect. In this context, needle acupuncture may represent a stronger stimulus than laser acupuncture.

Mild adverse events confirm that professionally administered local acupuncture is a safe treatment procedure in DPN conditions.

PROMs showed superior effects of needle acupuncture to placebo in all 12 variables and of laser acupuncture in 10 of 12 variables, reaching significance for hyperesthesia and cramps following needle acupuncture and for heat sensation following laser acupuncture. Because these are pain-related symptoms, our results provide evidence for the value of acupuncture in pain therapy in DPN. Hyperesthesia and heat sensation can be signs of C-nociceptor hyperexcitability caused by fiber degeneration and alterations in channel expression, producing orthodromic and antidromic conduction and multiplication of spontaneously generated nerve impulses and receptor threshold reduction. Moreover, severity of muscle cramps in DPN correlates with small and large fiber measures. Hence, clinical improvement can be a sign of fiber repair, corresponding to positive NCS results in our study.

Nevertheless, PROMs showed fewer distinct group differences than NCS results together with a higher evidence for placebo effects. This indicates the necessity to measure acupuncture effects by variables less susceptible to placebo, such as NCS.

Effects measured by NCS were more pronounced after 15 weeks compared with 6 weeks in an over-proportional manner for both needle acupuncture and laser acupuncture. Hence, prolonged treatment protocols may induce further nerve regeneration and may be essential for better group distinctions of PROMs.
18  |  LIMITATIONS

The ACUDIN study had some limitations. First, data were obtained for patients with type 2 diabetes. The transferability of these results to patients with type 1 diabetes has to be further evaluated. Second, there is no reliable direct but inactive placebo control available for needle acupuncture, requiring an indirect pathway for double-blinding the procedure via laser acupuncture. Third, power calculation could be performed for needle acupuncture but not for laser acupuncture. This may have contributed to the disparity of needle and laser acupuncture results. Fourth, long-term treatment efficacy and mechanisms of action were not investigated.

19  |  CONCLUSIONS

The ACUDIN trial showed significant effects of acupuncture as compared with placebo on type 2 diabetes-induced DPN after 10 acupuncture sessions. Improvement in the primary outcome variable sural SNAP amplitude indicates structural neuroregeneration following acupuncture. This is of major importance because there have been, as yet, no disease modifying therapies for DPN. Furthermore, acupuncture applied at the lower extremities is a safe treatment in DPN. Electrophysiologically quantified data showed clearer group distinctions than PROMs. Effects detected by NCS increased with time in a linear manner, suggesting that prolonged acupuncture protocols may be necessary for better results of PROMs, which should be examined in future studies.

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CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

SVS had the original idea for the ACUDIN trial and is the guarantor of this work. As such, he had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. However, he remained blinded to patients’ group allocation until completion of the statistical analysis. SVS and CG are responsible for the study design, definition of primary and secondary outcomes, and preparation of the trial protocol. TF is responsible for sample size calculation and statistical analysis. SVS performed neurological assessments including nerve conduction studies. SVS and JG contributed to the determination of acupuncture point selection. GMH performed the participants’ enrollment and study treatments and wrote the manuscript. All authors have critically reviewed and approved the final version of the manuscript.

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