



RESEARCH ARTICLE

Fifteen-day Acupuncture Treatment Relieves Diabetic Peripheral Neuropathy

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Abstract

Our study aimed to investigate the effects of acupuncture on diabetic peripheral neuropathy. We compared 42 cases treated with acupuncture with 21 cases exposed to sham acupuncture and observed the effects on nerve conduction velocity and a variety of subjective symptoms associated with diabetic peripheral neuropathy. Three of the six measures of motor nerves, and two measures of sensory function, demonstrated significant improvement ($p < 0.05$) over the 15-day treatment period in the acupuncture group, while no motor or sensory function significantly improved in the sham acupuncture group. There were also significant differences in vibration perception threshold between the groups ($p < 0.05$) and when compared to the baseline levels ($p < 0.01$) in the acupuncture group. Acupuncture was significantly more effective than sham for treatment of numbness of the lower extremities, spontaneous pain in the lower extremities, rigidity in the upper extremities and alterations in temperature perception in the lower extremities after therapy. Our pilot study has, therefore, provided evidence that acupuncture may be clinically useful for the radical treatment of diabetic peripheral neuropathy.

1. Introduction

Diabetic peripheral neuropathy (DPN) is the most common late complication of diabetes, often associated with considerable morbidity and mortality [1]. It is estimated that 12–50% of people with diabetes have some degree of DPN [2]. Approximately 15% of people with diabetes develop at least one foot ulcer during their lifetime [3–4]. While vascular disease leading to ischemia is certainly a factor in the pathogenesis, 60–70% of diabetic foot ulcers are primarily neuropathic in origin [4].

DPN may be asymptomatic. When symptoms are present, they may be negative or positive. Negative

symptoms include loss of sensation and strength, while positive symptoms include prickling or pain [5]. Affected nerve functions include reduced nerve conduction velocity, decreased temperature sensation, decreased tendon reflex response, and a decreased ability to detect vibration and touch.

The pathophysiology of DPN remains unclear, although it is associated with increased age, duration of diabetes, lipotoxicity and glucotoxicity, genetic susceptibility, inflammation, and oxidative stress [6,7]. The total annual cost of DPN and its complications in the United States was estimated to be more than four billion. Up to 27% of the direct medical cost of diabetes may be attributed to DPN [8].

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Although several pivotal trials have shown that strict glycemic control reduces the occurrence and progression of diabetes-related complications [9,10], this approach alone does not completely eliminate complications. Thus the development of new therapy to manage diabetes complications remains a high priority.

Acupuncture, one of the oldest and most commonly used forms of alternative medicine, has existed for more than 2500 years. Acupuncture is a meridian-based therapy. In traditional acupuncture, needles are inserted into precisely defined, specific points on the body, each of which has distinct therapeutic actions [11]. According to traditional Chinese medicine (TCM), when an acupoint is stimulated, treatment effects tend to occur on the specific parts of the body along a particular meridian that contains this specific acupoint. Investigators have demonstrated that the nervous system and neurotransmitters respond to needling stimulation and electroacupuncture [12–14]. As a safe form of treatment [15,16], acupuncture offers clear clinical advantages in the reduction of symptoms related to nervous disorders. Paul et al [17] reported that two of the total three patients showed increased benefit when a series of six acupuncture sessions was added to the ongoing nefazodone therapy for the treatment of DPN. Unfortunately, to date, only a few trials on acupuncture have specifically targeted DPN. In a randomized controlled trial in China, Chen et al [18] concluded that the point through point method of acupuncture was superior to mecobalamin for the improvement of motor nerve conduction velocity (MNCV) of the common peroneal nerve. The results of another randomized trial showed that acupuncture lowered the pain caused by painful DPN [19]. Given these findings, we also performed a prospective randomized controlled trial to investigate whether acupuncture is useful for DPN.

2. Materials and Methods

2.1. Study site and participants

The study was conducted at the Jilin Chinese Medical Hospital between June 2005 and December 2005. DPN patients aged 35–52 years were invited to participate.

2.2. Study protocol

The study protocol was approved by the Jilin Chinese Medical Hospital. Protocol summaries were reviewed by the participants, and written, informed consent was obtained on the day of the

study after a detailed explanation of the study purpose and methods. These participants were diagnosed with mild DPN based on subjective symptoms, no foot ulceration, and neurological dysfunctions (at least two parameters: MNCV [indispensable] and vibration perception threshold [VPT] or Achilles tendon reflex). MNCV in the tibial nerve of patients ranged between 30m/s and 45m/s. Participants' sensory nerve conduction velocity (SNCV) in the median nerve (the distal area) ranged between 35m/s and 55m/s with stable glycemic control ($HbA_{1c} \leq 9\%$, with $\pm 0.5\%$ variation in the previous 3 months). Subjects were excluded if their primary cause of neurologic disorder was not diabetes (e.g., alcoholic neuropathy, carpal tunnel syndrome, sequelae of cerebrovascular disease), if their F-wave response had disappeared, if they had arteriosclerosis obliterans (ankle brachial pressure index of ≤ 0.8) or severe hepatic or renal disorder, if they were participating in other interventional studies, or if they were receiving other experimental medications for DPN, prostaglandin E1 preparations, or any other medication that affects symptoms of DPN. After the baseline period, 63 participants meeting the inclusion criteria were randomized (by random number table) into one of the two groups in a 2:1 ratio (acupuncture group and sham acupuncture group) which differed only in the type of needle manipulation used. This randomization meant 42 cases were allocated to the acupuncture group and 21 cases to the sham acupuncture group. There were no statistically significant differences ($p > 0.05$) between the two groups in any of the baseline characteristics. Table 1 shows the baseline characteristics for all 63 patients.

Both groups continued conventional therapy (diet treatment, hypoglycemic agents, insulin and hypotensive agents) with medication to aid neuropathy control prohibited. No major changes in diabetic management had taken place during the 3 months before the study, and no therapeutic alteration was made throughout the study. All patients participated in one session per day lasting 30 minutes for 15 days, during which a total of five acupuncture point locations on the body received acupuncture needling. Sterile disposable one-time-use needles were used. For each location, a pair of corresponding acupoints on the right and left sides of the body were identified and marked with a skin marker (10 acupoints total). These acupoints were Hegu (LI4), Fenglong (ST40), Quchi (LI11), Zusanli (ST36), and San Yin Jiao (SP6) identified by an experienced acupuncturist (Jianmin Lang) according to traditional methods. Approximate position was determined in relation to anatomic landmarks (e.g., bones, tendons) and proportional measurements (e.g., fraction of the distance between wrist and

Table 1 Baseline characteristics of all patients*

Characteristic	Acupuncture (n=42)	Sham acupuncture (n=21)
Age (yr)	43.5 (5.0)	45.8 (6.2)
Female n (%)	33 (78.6)	16 (76.2)
BMI (kg/m ²)	23.5 (0.4)	22.9 (0.3)
Duration of diabetes (mo)	152.0 (13.5)	148.8 (15.3)
Duration of DPN (mo)	25.6 (7.5)	23.5 (8.0)
Type of diabetes n (%)		
Type 1	23 (46.0)	10 (45.5)
Type 2	27 (54.0)	12 (54.5)
HbA _{1c} (%)	6.8 (1.3)	6.6 (1.2)
MNCV in the tibial nerve (m/s)	39.5 (0.5)	38.8 (0.6)
SNCV in median nerve (distal) (m/s)	48.0 (0.7)	46.1 (0.8)
VPT (s)	8.05 (3.22)	8.04 (3.30)
Medication n (%)		
None	4 (9.5)	2 (9.5)
Oral hypoglycemic agent	23 (54.8)	11 (52.4)
Insulin	13 (31.0)	7 (33.4)
Oral hypoglycemic agent/insulin	2 (4.7)	1 (4.7)
Diabetic proteinuria n (%)		
No	23 (54.8)	10 (47.6)
Intermittent	12 (28.6)	7 (33.3)
Persistent	7 (16.6)	4 (19.1)
Previous acupuncture (for any condition) n (%)	23 (54.8)	10 (47.6)

*Values expressed as mean (SD) unless otherwise indicated. BMI=body mass index; DPN=diabetic peripheral neuropathy; MNCV= motor nerve conduction velocity; SNCV=sensory nerve conduction velocity; VPT=vibration perception threshold.

elbow creases) [20]. Within this delineated area, the precise position of each acupoint was determined by palpation, feeling for a slight depression or yielding of tissues.

For each acupoint, a needle 0.3 mm in diameter and 50 mm in length was used with 1.2–2.3 cm penetration, in a direction perpendicular to the surface of skin. The depth of insertion was between 1.20–1.53 cm for LI4, 1.82–2.25 cm for ST40, 1.38–1.50 cm for LI11, 2.11–2.30 cm for ST36 and 1.73–2.00 cm for SP6 with achievement of “De qi” (a sensory component perceived by the patient as an ache or heaviness in the area surrounding the needle and another simultaneous component, needle grasp, perceived by the acupuncturist [20]). The needle was then rotated alternately either clockwise or counterclockwise every 5 minutes. For sham acupuncture treatment, the same acupoints were punctured with the same acupuncture needles; however, the needle was inserted to a depth of only 0.3 cm, and no manipulation of the needle was performed, to avoid De qi [21]. Number, duration and frequency of the sessions in the sham acupuncture group were the same as for the acupuncture group.

At the end of treatment, the success of blinding was tested by asking all patients the following question: “When you volunteered for the trial, you were informed that you had an equal chance of receiving acupuncture or sham (pretend) acupuncture. Which acupuncture do you think you received?”

The primary end points for clinical efficacy were the differences between baseline and post-treatment electrophysiological measurements of the median motor nerve (F-wave minimum latency, MNCV, and F-wave conduction velocity [FCV]), the tibial motor nerve (F-wave minimum latency, MNCV, and FCV), and the median sensory nerve (forearm SNCV and distal SNCV). The method to measure nerve function was that according to Kohara et al [22] using electromyography (DISA1500; DISA, Herlev, Denmark). F-wave was measured 16 times, and the minimum was adopted. VPT was measured on the medial malleolus in the lower extremities using a hand-held biothesiometer (Biomedical Instruments, Newbury, OH, USA) [23,24]. The voltage of vibration was increased until the patient could perceive a vibration. This was conducted three times. The mean of these three trials was used to determine the VPT.

Symptoms were assessed using a standardized and comprehensive questionnaire at baseline and following 15 days of treatment. The symptoms assessed included measures of numbness, pain, rigidity (rigidity is a state of continuous, firm and tense muscles with marked resistance to passive movement), alterations in temperature perception, paresthesia, hypesthesia and weakness. For these symptoms, both the severity and extent were scored on an ascending 0–4 scale. For each symptom category, data were analyzed for all subjects in the efficacy pool who reported the symptom during the course of the study. Because not all symptoms were present in each subject, different subsets of subjects were included for each symptom.

The specific scoring for severity of symptoms was as follows: 0=none (disappeared); 1=very slight (sometimes, but causes no problem at all in daily life); 2=slight (always, but causes no problem in daily life); 3=moderate (always, sometimes makes daily activity troublesome); and 4=severe (it makes daily activity troublesome). For the extent of symptoms, the scoring was as follows: 0=none; 1=only fingertips or ends of toes; 2=from wrist to fingertip or from ankle to toe; 3=from elbow to fingertip or from knee to toe; and 4=from above the elbow or above the knee.

2.3. Statistical analysis

Statistical methods used included two-sample *t* tests for comparison of mean values between groups, paired *t* tests for comparison of mean values within groups, and two-way repeated analysis of variance for changes in glycemic control. All analyses were carried out using SAS version 8.02 (SAS Institute, Cary, NC, USA). A *p* value <0.05 was considered statistically significant.

3. Results

3.1. Blinding data

At the end of treatment, all patients were asked the following question: “When you volunteered for the trial, you were informed that you had an equal chance of receiving acupuncture or sham acupuncture. Which acupuncture do you think you received?” Of the 63 patients who gave an answer, two (9.5%) in the sham group believed that they had received sham acupuncture, all in the real acupuncture group believed that they had received real acupuncture. The blinding index was 0.32 (95% confidence interval [CI], 0.27 to 0.37) in the acupuncture group and –0.65 (95% CI, –0.61 to –0.69) in the sham group. The two proportions of unblinding were not significantly different (*p*=0.25).

3.2. Changes in glycemic control

In the acupuncture group (*n*=42), HbA_{1c} (mean±SD) at baseline and day 15 was 6.8±1.3 and 6.7±1.2% respectively. Corresponding values in the sham acupuncture group were 6.6±1.2% and 6.7±1.3%, respectively. There were no significant differences between the two groups at any time point.

3.3. Change in nerve function

Table 2 outlines each electrophysiological measure (mean±SD) at baseline and end-of-treatment time points. Six measures assessed function in motor nerves, including F-wave minimum latency, MNCV and FCV in the median and tibial nerves. In the acupuncture group, three of the six measures in motor nerves demonstrated significant improvement (*p*<0.05) over the 15-day treatment period. As expected, no electrophysiological measures of motor or sensory function significantly improved in the sham acupuncture group.

The two measures of sensory function, forearm and distal SNCV, also improved in the acupuncture group. The change of forearm SNCV from baseline was significant (*p*<0.05).

There were also significant differences in VPT between groups (*p*<0.05) and when compared to the baseline levels (*p*<0.01) in the acupuncture group.

3.4. Changes in subjective symptoms over time

Figures 1–8 show some of the changes in the score for subjective symptoms, in which a significant difference between the two groups was observed. As shown in the figures, the difference between the two groups gradually increased with continuous treatment. Acupuncture was significantly better than sham acupuncture for the treatment effects on numbness of lower extremities (severity *p*<0.05, extent *p*<0.05; Figures 1 and 2, respectively), spontaneous pain in lower extremities (severity *p*<0.05, extent *p*<0.01; Figures 3 and 4), rigidity in upper extremities (severity *p*<0.05, extent *p*<0.05; Figures 5 and 6), and alterations in temperature perception in lower extremities (severity *p*<0.01, extent *p*<0.05; Figures 7 and 8, respectively).

Although the data are not shown in the figures, numbness in the upper extremities (severity), and sensation of rigidity (extent) were significantly improved in the acupuncture group compared with the sham acupuncture group (*p*<0.05, and 0.01, respectively) after 15 days treatment. There was no significant difference between the two groups in the sensation of paresthesia, hypesthesia, and weakness of extremities.

Table 2 Changes in nerve function at baseline and end-of-treatment timepoints

Parameter	Acupuncture (n=42)	Sham acupuncture (n=21)	Difference
F-wave minimum latency in median			
Baseline (m/s)	32.5±0.5	32.5±0.3	
End of treatment (m/s)	32.7±0.4	32.5±0.4	
Difference (m/s)	0.2±0.2	0.0±0.2	0.2
95% CI	-0.19 to 0.59	-0.39 to 0.39	
F-wave minimum latency in tibial			
Baseline (m/s)	52.6±0.5	52.5±0.6	
End of treatment (m/s)	53.0±0.3	52.5±0.7	
Difference (m/s)	0.4±0.3*	0.0±0.1	0.4
95% CI	-0.19 to 0.99	-0.20 to 0.20	
MNCV in median			
Baseline (m/s)	40.3±0.3	40.5±0.4	
End of treatment (m/s)	40.6±0.3	40.4±0.5	
Difference (m/s)	0.3±0.2	-0.1±0.2	0.4
95% CI	-0.09 to 0.69	-0.49 to 0.29	
MNCV in tibial			
Baseline (m/s)	39.5±0.5	38.8±0.6	
End of treatment (m/s)	40.2±3.9	38.8±0.5	
Difference (m/s)	0.7±0.3†	0.0±0.2	0.7
95% CI	0.11 to 1.29	-0.39 to 0.39	
FCV in median			
Baseline (m/s)	55.6±0.4	55.7±0.5	
End of treatment (m/s)	56.5±0.5	55.8±0.6	
Difference (m/s)	0.9±0.5†	0.1±0.4	0.8
95% CI	-0.08 to 1.88	-0.68 to 0.88	
FCV in tibial			
Baseline (m/s)	48.3±0.5	48.3±0.4	
End of treatment (m/s)	48.8±0.6	48.3±0.5	
Difference (m/s)	0.5±0.4	0.0±0.3	0.5
95% CI	-0.28 to 1.28	-0.59 to 0.59	
SNCV in median (forearm)			
Baseline (m/s)	47.8±0.5	47.8±0.6	
End of treatment (m/s)	48.3±0.7	47.8±0.6	
Difference (m/s)	0.5±0.3*	0.0±0.5	0.5
95% CI	-0.09 to 1.09	-0.98 to 0.98	
SNCV in median (distal)			
Baseline (m/s)	48.0±0.7	46.1±0.8	
End of treatment (m/s)	48.2±0.6	46.2±0.7	
Difference (m/s)	0.2±0.5	0.1±0.3	0.1
95% CI	-0.78 to 1.18	-0.49 to 0.69	
VPT			
Baseline (s)	8.05±3.22	8.04±3.30	
End of treatment (s)	8.56±3.43	8.08±3.28	
Difference (s)	0.51±0.70†	0.04±0.13	0.47
95% CI	-0.86 to 1.88	-0.21 to 0.29	

* $p < 0.05$ when compared to baseline, and when compared to sham acupuncture (SA) group; † $p < 0.01$ when compared to baseline and when compared to SA group; ‡ $p < 0.01$ when compared to baseline, $p < 0.05$ when compared to SA group. CI=confidence interval; MNCV=motor nerve conduction velocity; FCN=F-wave conduction velocity; SNCV=sensory nerve conduction velocity; VPT=vibration perception threshold.

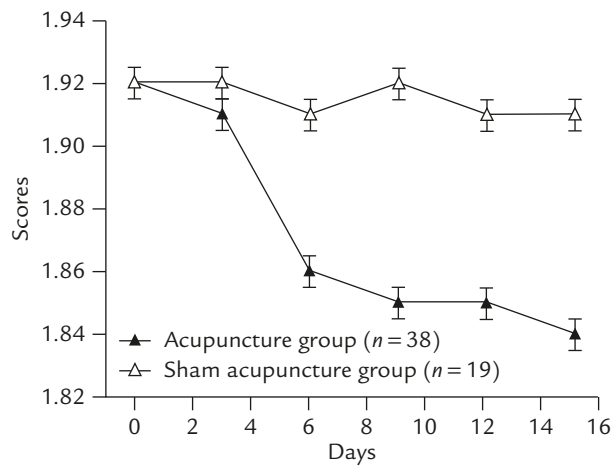


Figure 1 Changes in scores for severity of numbness.

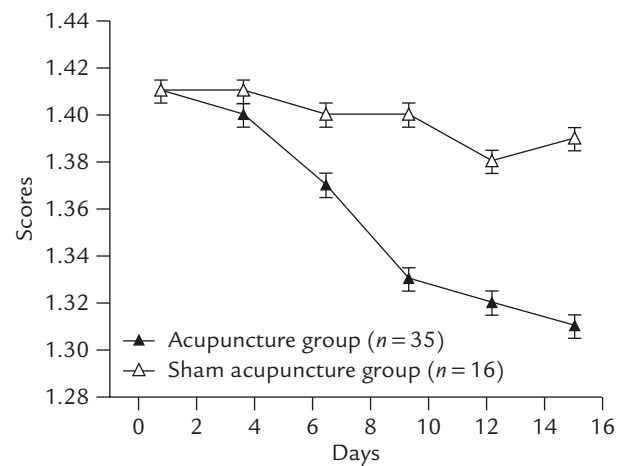


Figure 4 Changes in scores for extent of pain.

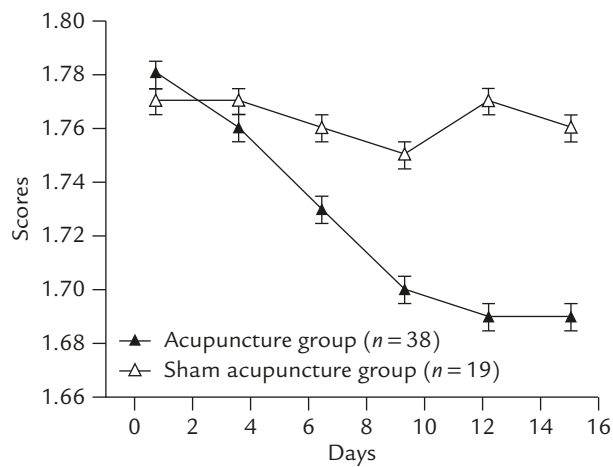


Figure 2 Changes in scores for extent of numbness.

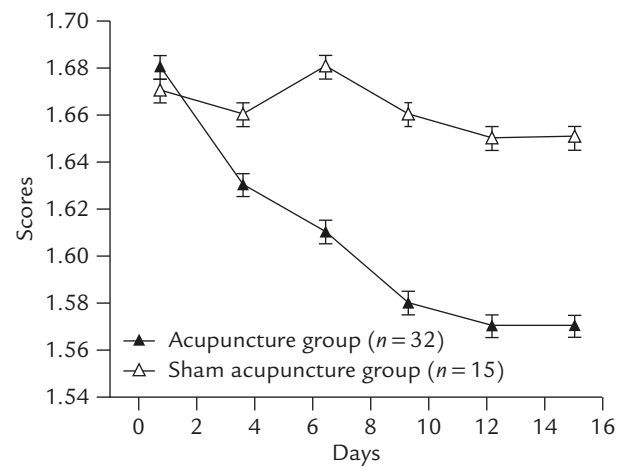


Figure 5 Changes in scores for severity of rigidity.

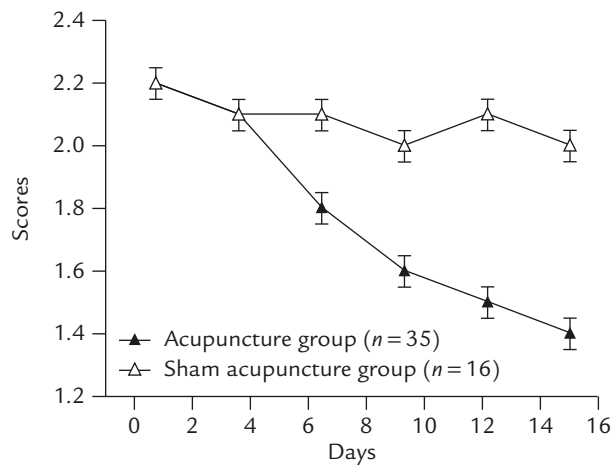


Figure 3 Changes in scores for severity of pain.

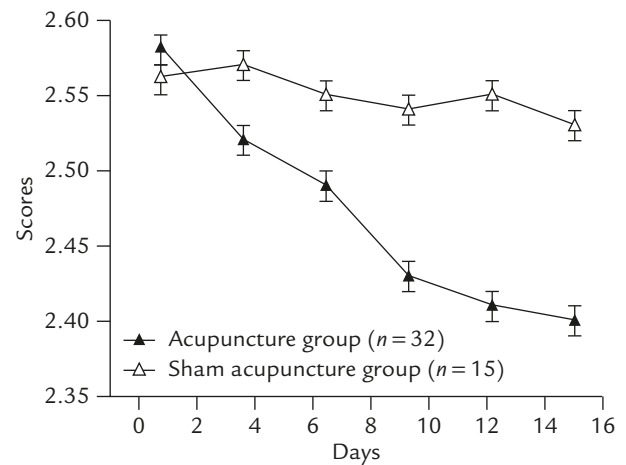


Figure 6 Changes in scores for extent of rigidity.

4. Discussion

The peripheral nervous system is commonly affected in diabetic patients and the sequelae of nerve dysfunction often influence the final outcome of the

disease. The pathophysiology of DPN remains controversial. Little is known about the etiology of loss of peripheral sensory neurons that accompanies DPN. Programmed cell death, or apoptosis, has been implicated in diabetic retinopathy and neuropathy

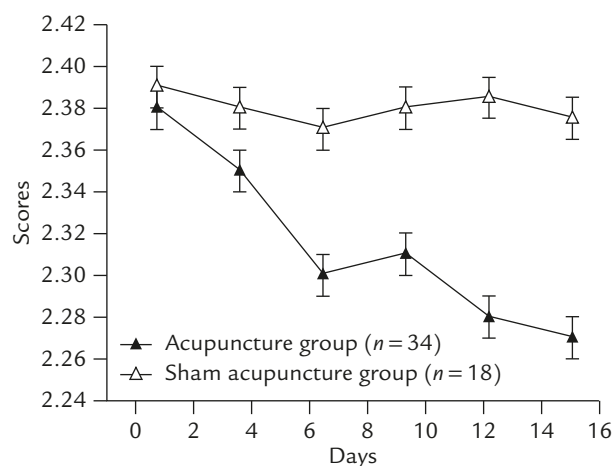


Figure 7 Changes in scores for severity of alterations in temperature perception.

[25], with impaired mitochondrial function being implicated in the promotion of apoptosis [26]. Increased polyol pathway activity has also been implicated in the pathogenesis of DPN [27].

Acupuncture is a safe form of treatment [15,16,28] and offers clear clinical advantages in the reduction of DPN related symptoms. This technique from Chinese medicine dates back at least 2500 years. According to the theory of Chinese medicine, health is a state of balance between yang and yin, between Qi and Xue, and between the five elements of wood, fire, earth, metal, and water [29]. Qi, or life energy, flows through the body in hypothesized channels called “meridians” and may be accessed at several hundred points. The traditional theory of acupuncture is based on the concept that an imbalance of yang and yin, through the meridians, can be corrected by manipulation of identifiable points close to the skin. The skilled acupuncturist is able to restore balance by using selected acupoints to adjust the energy flow. Each acupoint has distinct therapeutic actions. The stimulation of acupoints can be achieved by either a mechanical action of needling or electrical point stimulation [30].

Acupuncture was performed according to the rules of Chinese medicine, including diagnostic palpation to identify sensitive spots [20]. Acupoints refer to certain specifically located sites on the body, and according to TCM, these different specific points can be grouped into different categories in terms of their functional properties. Different groups of acupoints of the same type of functional property, which are located regularly on specific parts of the body, are the equivalent of 12 main meridians that respond to 12 major functions or “organs” of the body according to TCM. For DPN related symptoms, the most commonly used acupoints are

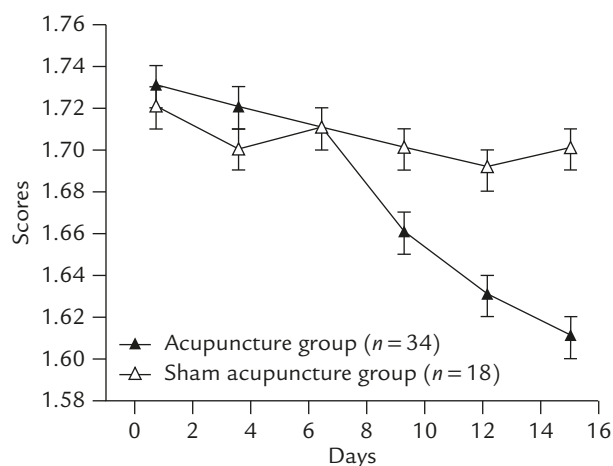


Figure 8 Changes in scores for extent of alterations in temperature perception.

Hegu (LI4), Fenglong (ST 40), Quchi (LI11), Zusanli (ST36) and San Yin Jiao (SP6).

LI4, as Yuan-Source point, is of great significance in treating internal organ disease. LI4 strongly moves the Qi and blood in the body to remove stagnation, so indicated in every type of sensory or motor nerve disorders. The Yuan-source point from the affected meridian is often combined with the Luo-Connecting point of the internally-externally related meridians in use. ST40 is known as the Luo-Connecting point which can communicate with two meridians. ST40 is used to treat collateral disease and can be used to treat chronic diseases, especially chronic diseases of the Zang-Fu organs. It calms the Shen and clears phlegm from the heart by activating the meridian. So LI4 and ST40 are often used in combination for nervous disorders.

LI11 and ST36 are the He-Sea points, where the Qi of the meridian collects and goes deep into the body. LI11 can clear heat, cool blood, resolve dampness, regulate Qi and blood, and activate the meridian. ST36 tonifies Qi and blood, harmonizes and strengthens the spleen and stomach, strengthens the body and Wei Qi, raises Yang, and calms the Shen. These two acupoints are also proven to be effective in nervous disorders.

SP6 is one of the most commonly used points, and also one of the most versatile. Because SP6 crosses the spleen, kidney and liver meridians, it can treat many conditions associated with all three organs. This point nourishes blood and yin, cools and invigorates the blood, and calms the Shen.

In this randomized trial, randomization was successfully concealed, achieving good credibility and blinding of participants receiving the nonpenetrating acupuncture intervention. The results show that acupuncture was more effective than sham acupuncture in improving nerve conduction velocity

and a variety of subjective symptoms associated with DPN.

F-wave measurements are particularly useful because they can detect abnormalities in any region of a peripheral nerve [31]. In the present study, differences in the reproducibility of F-wave minimum latency and FCV versus NCV measurements may account for the greater sensitivity of the former for detecting evidence of disease progression and acupuncture treatment effects. Also, acupuncture showed a significant improvement compared with sham acupuncture in F-wave minimum latency in tibial nerve measurements, FCV in measurements of the median motor nerve and MNCV in tibial nerve measurements. Improvement of nerve conduction function was considered to result in the effect of nerve degeneration, such as axonal atrophy in diabetic neuropathy [32]. These results suggest that acupuncture can delay the progressive deterioration of nerve function secondary to DPN.

Although small and not present in every nerve, the observed significant changes in electrophysiological measures, combined with the improvement in symptoms, is especially encouraging in the diabetic population included in the present study. During the study, the difference in the subjective symptom scores between the acupuncture and sham acupuncture groups increased with time. Acupuncture treatment appeared to significantly improve subjective symptom scores, particular numbness, pain, rigidity and alterations in temperature perception. In DPN, although nerve fiber regeneration after nerve fiber loss is frequently observed in peripheral nerves, the process of regeneration appears to be delayed, and thus some regenerated nerve fibers remain immature. Abnormal excitement of these immature regenerated nerve fibers is thought to lead to numbness and spontaneous pain [33,34]. Acupuncture treatment improved these symptoms, suggesting that it may accelerate the nerve regenerative process in DPN patients.

Blinding indices, 0.32 (95% CI, 0.27 to 0.37) and -0.65 (95% CI, -0.61 to -0.69) in the acupuncture group and sham acupuncture group, respectively, imply that 32% of patients correctly guessed the treatment identity beyond chance, while 65% of patients in the sham acupuncture group incorrectly guessed that they had received acupuncture. Following the logic of Bang et al [35], these results indicate high "response bias", which implies that a majority of study participants tend to believe that they were assigned a more effective intervention [36].

As mentioned above, acupuncture treatment not only improved nerve conduction velocity decreased by DPN, but also improved a variety of subjective symptoms associated with this progressive disabling disorder. Our pilot study has shown

that the effects of acupuncture treatment on subjective symptoms as well as other measures of nerve function provide evidence that acupuncture, a form of alternative medicine, may be clinically useful for the radical treatment of DPN. Further studies with larger patient numbers are required to confirm our findings, to determine whether the effects are sustained, and to ascertain whether there are any effects on other sensory symptoms associated with DPN.

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