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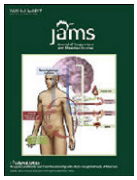

RESEARCH ARTICLE

Acupuncture Treatment of Diabetic Peripheral Neuropathy in an American Indian Community

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Abstract
Diabetic peripheral neuropathy (DPN) develops in 30% of type 2 diabetes patients, increases the risk for foot ulcers and amputation, and is a significant source of disability and medical costs. Treatment remains challenging, propelling research to focus on therapeutic methods that aim to improve blood circulation or ameliorate oxidative stress that drives development of DPN. The aim of this study was to assess the effectiveness of acupuncture treatment for DPN symptoms and lower extremity arterial circulation in people with type 2 diabetes. Twenty-five patients seen at a Southern California Tribal Health Center who reported a threshold level of diabetic neuropathy symptoms in the lower extremities during the previous 4 weeks received acupuncture treatment once per week over a 10-week period between 2011 and 2013. The Neuropathy Total Symptom Scale (NTSS-6), Neuropathy Disability Score (NDS), and laser Doppler fluxmetry (LDF) were used for assessment at baseline and 10 weeks. A total of 19 of 25 study participants completed the study and reported a significant reduction in the NTSS symptoms of aching pain, burning pain, prickling sensation, numbness, and allodynia. Lancinating pain did not decrease significantly. LDF measures improved but not significantly. Acupuncture may effectively ameliorate selected DPN symptoms in these American Indian patients.

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1. Introduction

With increasing obesity among young people, the prevalence of type 2 diabetes mellitus (DM) is growing worldwide with diagnosis occurring at an earlier age [1]. In the United States, American Indians and Alaska Natives (AIAN) are at greater risk for DM diagnosis [2] and suffer disproportionately higher rates of diabetic amputation than the general United States (US) population [3].

Overall, one third of adults with DM are estimated to suffer with diabetic peripheral neuropathy (DPN) symptoms. Pain management is challenging, with multiple medications typically prescribed for those with greater severity of symptoms [4]. Symptomatic treatment generally includes prescription and/or over-the-counter pain medications; specifically, nonsteroidal anti-inflammatory drugs (NSAIDS), opioids, anticonvulsants, selective serotonin reuptake inhibitors/selective norepinephrine reuptake inhibitors, and tricyclic antidepressants [5].

There is increasing interest in researching therapeutic treatments that address the pathophysiology of DPN [6]. Diabetic hyperglycemia initiates a cascade of detrimental effects to both the arterial endothelium and to the nerve cells and drives the progression of DPN via impaired nitric oxide-induced vasodilation, tissue ischemia, and direct damage to nerves [7]. Two prominent aspects of therapeutic treatment include counterbalancing the effects of oxidative stress [8] and improving blood circulation [9]. Previous research suggests acupuncture may facilitate the latter [10].

Clinical studies and animal models investigating the physiological mechanisms of acupuncture have demonstrated an association between acupuncture treatment and an increase in blood circulation. One of the first such studies applied photoplethysmography (PPG) to demonstrate that acupuncture needle insertion into the muscle layer accompanied by *deQi* sensation was significantly associated with increased skin and muscle blood flow in healthy patients [11]. By using laser Doppler fluxmetry (LDF) among health volunteers, Hsiu et al [12] showed that the tissues at acupuncture point locations had higher mean LDF signals, and hence greater blood supply, than surrounding tissue. Tsuchiya et al [13] specifically addressed the role of endothelial nitric oxide (NO) in increased blood flow and vasodilation by showing significantly increased plasma concentrations of nitrate and nitrite in the arms of healthy people after acupuncture treatment. The observed increase in plasma nitrate and nitrite correlated significantly with palmar blood flow [13]. Also using a measure of plasma NO, Su et al [14] observed that warm needling at St-36 in middle aged and older adults with hypertension could significantly increase NO release

The primary aim of this study was to evaluate the effectiveness of acupuncture treatment on patient-reported DPN symptoms and pain. The secondary aim was to determine if acupuncture significantly improved endothelial function as measured by LDF in the lower extremities of patients with DPN. An American Indian population was chosen because of their risk for diabetes and its related comorbidity.

2. Materials and methods

2.1. Study population

This study segued from a DPN prevalence and risk factors study conducted at a Southern California Tribal Health Center (SCTHC) and was approved by both the University of California, San Diego (UCSD) and Southern California Tribal Health Center (SCTHC) institutional review boards. Participants were recruited and treated between August 2011 and October 2013. The original design was a pragmatic effectiveness study [15] with random allocation to either acupuncture treatment or usual care, with 20—25 patients per group, according to sample size analysis. The first 10 participants were randomly assigned, six to the treatment group and four to the usual care group. The study eventually encountered barriers to recruitment of the eligible pool of participants with the most common obstacles including lost contact with prevalence study participants, the rural location of the health center, and expense of travel, and the increasingly frail health of some of the elderly patients. Randomization was also viewed unfavorably in this community with particular resistance to allocation to the usual care group. Consequently, recruitment was eventually prioritized for the acupuncture treatment group only.

2.2. Intervention

The study was explained to each participant who, in turn, gave written consent. Patients were treated once per week for 10 consecutive weeks with acupuncture point combinations individualized and relevant to each patient's symptoms in order to reflect real-world practice. Commonly chosen points included ST-32, ST-37, ST-42, SP-7, SP-9, KI-1, KI-3, KI-9, LR-4, LR-7, GB-34, GB-37, and the Bafeng points. *DeQi* sensation was confirmed by patient feedback and needles were left *in situ* for 30 minutes. All treatments were carried out by one researcher (AB).

2.3. Materials

The Neuropathy Total Symptom Scale (NTSS-6), the Neuropathy Disability Score (NDS), and laser Doppler fluxmetry (LDF) were assessed at baseline and 10 weeks. Duration of diabetes, HbA1c, and diagnosis of cardiovascular disease, peripheral vascular disease, retinopathy, and nephropathy were obtained from medical records.

2.4. NTSS

We utilized the NTSS-6 to detect response to treatment [16]. Patients were asked to rate the frequency and intensity of six sensory neuropathy symptoms in the lower extremities during the past 4 weeks. Frequency is rated as never, occasionally, often, and almost continuously; intensity is rated as not present, mild, moderate, and severe. Numerically, both the frequency and intensity responses are rated from 0 for "never" and "not present" up to 3 for "almost continuously" and "severe". The neuropathy symptoms include aching pain, burning pain, tingling/

prickling sensation, numbness, electrical/lancinating pain, and allodynia/sensitivity to touch. A threshold rating of often or almost always in frequency and moderate or severe in intensity is considered a positive assessment of peripheral neuropathy.

2.5. NDS

The NDS assesses vibration threshold, temperature sensation, pinprick sensation, and Achilles' reflex. Each test is rated "0" for a normal response and "1" for an abnormal response, separately for right and left feet. It has a range of 0–8.

2.6. LDF

LDF measures the skin microvascular response to iontophoretically administered acetylcholine (Ach) and sodium nitroprusside (SNP), which are indicative of endothelial-dependent and endothelial-independent vasodilation, respectively. That is, response to Ach is nitric oxide specific [17] while SNP stimulates vasodilation in the endothelial smooth muscle cells of the artery media directly. Although LDF is most often measured on the forearm as a measure of cardiovascular disease risk, it has also been shown to reliably measure microcirculation in the legs [18]. Among diabetes patients, the presence of neuropathy is associated with poorer endothelial function of both the upper and lower extremities [19,20].

Participants were asked to refrain from eating, smoking, and consuming caffeinated beverages for 2 hours prior to testing. After resting in the supine position for 30 minutes, baseline LDF measures were obtained on the lower leg at 6 cm and 11 cm proximal to the medial malleolus. After 1 minute, the LDF probes were removed and cotton soaked in 1% acetylcholine chloride (Ach) solution was placed 6 cm proximal to the medial malleolus and connected to the positive electrode and cotton soaked in 1% sodium nitroprusside (SNP) solution was placed 11 cm proximal to the medial malleolus and connected to the negative electrode. The Ach and SPN solutions were administered by iontophoresis for 10 minutes. The skin was dried and the LDF probes were returned to their baseline positions for another 15 minutes to record the response to Ach and SPN.

2.7. Statistical analysis

Paired-group *t* tests were used to analyze NTSS-6, NDS, and LDF measures at baseline and 10 weeks (SPSS version 22; SPSS Inc., Chicago, IL, USA). Continuous scores for each NTSS-6 item were calculated using an algorithm that combines frequency and intensity responses; it has a range from 0 to 3.66. LDF values are expressed as percent change from pre-iontophoresis baseline. All NTSS-6, NDS, and LDF outcomes were assessed by one researcher (PS).

3. Results

Among the 322 DM patients screened with the NTSS-6 questionnaire for the DPN prevalence and risk factors study, 84 reported one more neuropathy symptom at the threshold of often or always in frequency and moderate or severe in intensity. Three patients were ineligible for recruitment to the acupuncture treatment study as they were already being treated, 11 had moved away, and 19 had died or were in very frail health. Among the remaining 51 eligible patients, 22 refused participation and 29 consented. There were no significant age or gender differences between the refused and consented groups (data not shown). Outcomes for the four usual care participants were not included in the statistical analysis.

Six participants among the 25 in the treatment group did not complete the course of acupuncture. There were no significant differences in age, gender, or baseline symptoms between those who completed the study and those who did not (Table 1). The most prominent reason for dropping out of the study involved concerns with other diabetes comorbidity. Those who did not complete the treatment were more likely to have cardiovascular disease, nephropathy, peripheral vascular disease, and/or retinopathy. There were no adverse events from the acupuncture treatment.

The 19 participants who completed the 10 weeks of acupuncture treatment reported significantly reduced severity and frequency of neuropathy symptoms for the following NTSS-6 questionnaire items: aching pain, burning pain, tingling/prickling sensation, numbness, and allodynia/sensitivity to touch (Table 2). Aching pain, either in the toes or as muscle cramps in the lower legs, was the most commonly reported symptom. Both aching and burning pain were responsive to acupuncture treatment in this patient group, unlike lancinating pain, which is shooting or electric in nature, and did not diminish significantly over the 10

Table 1 Comparison of completed and incomplete participants, Southern California Tribal Health Center, 2011–2013.

Demographic factors	Completed $N = 19$	Incomplete $N = 6$	p
Gender (male)	47	33	Ns
Current age (y)	61 ± 13	57 ± 12	Ns
Age at diagnosis (y)	48 ± 12	41 ± 10	Ns
Duration of diabetes (y)	12 ± 7	16 ± 14	Ns
Diabetes comorbidity			
Cardiovascular disease	26	50	Ns
Stroke or risk factors	11	17	Ns
Peripheral vascular disease	26	67	Ns
Microalbuminuria	35	50	Ns
Nephropathy	11	17	Ns
Retinopathy	6	33	Ns
Baseline NTSS-6 scores			
Aching pain	2.4 ± 1.3	2.2 ± 0.3	Ns
Burning pain	1.7 ± 1.5	1.2 ± 1.0	Ns
Prickling sensation	2.2 ± 1.2	1.7 ± 1.3	Ns
Numbness	1.7 ± 1.2	1.9 ± 1.2	Ns
Lancinating pain	2.0 ± 1.3	1.7 ± 1.1	Ns
Allodynia	1.9 ± 1.4	0.9 ± 1.4	Ns
Baseline NDS total score	5.2 ± 3.3	6.0 ± 3.6	Ns

Data are presented as % or mean ± standard deviation.
NDS = Neuropathy Disability Score; Ns = Not significant; NTSS = Neuropathy Total Symptom Scale.

Table 2 Comparisons of NTSS-6, NDS, and LDF measures at baseline and after 10 weeks of acupuncture treatment among 19 patients with diabetic peripheral neuropathy, Southern California Tribal Health Center, 2011–2013.

Measures	Baseline	10 wk	Pairwise *t* test
	Mean (95% CI)	Mean (95% CI)	*p*
NTSS-6 scores			
Aching pain	2.4 (1.8, 3.0)	1.6 (1.1, 2.0)	0.035
Burning pain	1.7 (1.0, 2.4)	1.0 (0.4, 1.6)	0.008
Tingling/prickling	2.2 (1.7, 2.8)	1.2 (0.6, 1.7)	0.003
Numbness	1.7 (1.1, 2.3)	1.0 (0.4, 1.6)	0.004
Lancinating pain	2.0 (1.3, 2.6)	1.6 (1.0, 2.2)	Ns
Allodynia	1.9 (1.3, 2.6)	1.2 (0.5, 1.8)	0.029
NDS score	5.2 (3.6, 6.8)	4.9 (3.4, 6.5)	Ns
LDF measures			
Ach	84.2 (52.8, 115.6)	99.6 (61.4, 137.8)	Ns
SNP	77.3 (51.6, 102.9)	97.7 (72.6, 122.7)	Ns

Ach = acetylcholine chloride (endothelial-dependent response); CI = confidence interval; LDF = laser Doppler fluxmetry; NDS = neuropathy disability score; Ns = Not significant; NTSS = neuropathy total symptom scale; SNP = sodium nitroprusside (endothelial-independent response).

week period. Nonpainful DPN symptoms such as tingling/prickling sensation, allodynia/sensitivity to light touch, and numbness were also responsive to acupuncture treatment in this group. The NDS reflects established nerve damage and was not expected to change significantly during the study period.

Changes in LDF values with acupuncture were nonsignificantly different although there was a mean increase in endothelial response to both Ach and SNP from baseline to 10 weeks.

4. Discussion

Individuals living with DPN often experience inadequate symptom control with pain medication and are motivated to seek complementary and alternative medicine treatments such as acupuncture [21]. In this regard, previous studies have assessed acupuncture's effect on neuropathy symptoms as well as nerve conduction velocity. Garrow et al [22] have published the only randomized, placebo-controlled acupuncture study of DPN, reporting moderate symptom improvement in the acupuncture group with little change over the 10-week treatment period in the sham group. Abuaisha et al [23], also using a 10-week course of treatment, reported significant symptom improvement before and after acupuncture treatment as measured by visual analogue scores. Participants in this study were followed for up to 1 year with the majority able to cease or reduce intake of pain medications post-treatment. In a pilot study comparing active and sham acupuncture over a 15-day course of treatment, Tong et al [24] found significant improvements in both motor and sensory nerve function as well as numbness, pain, and temperature perception in the acupuncture treatment group, but not in the sham group. All three efficacy studies controlled for treatment variation with standardized acupuncture point selection of conventionally used points.

Our project was designed as a pragmatic effectiveness study with acupuncture point selection tailored to each patient's symptoms as would be carried out in a real world practice [15]. ST-32 was chosen to enhance circulation in the lower extremities. SP-7, SP-9, LR-7, KI-9, GB-34, and GB-37 address cramping in the gastrocnemius muscle which is a common source of discomfort for people with neurovascular disease. ST-37 was included as a master point of the lower leg. ST-42, KI-3, and LR-4 were added as local points for the foot. The Bafeng points are specific for aching and numbness in the toes. KI-1 was applied in cases of burning pain or numbness on the bottoms of the feet. Participants reported significantly diminished aching and burning pain, tingling/prickling sensation, numbness, and allodynia/sensitivity to touch, while lancinating pain did not decrease significantly over the 10-week treatment period.

The concept of random allocation to treatment group was not well-received in this community, with the majority of eligible and willing candidates agreeing to participation contingent on inclusion into the acupuncture treatment group. The resulting one-group design limits statistical analysis to within-group before and after comparisons, rather than the between-group longitudinal analysis that was in the original design. This constitutes a substantial loss of statistical power and generalizability as treatment group results could not be compared with the natural fluctuation in DPN symptoms that may occur with usual care.

Our study also sought to assess whether acupuncture treatment could improve blood circulation in adults with the neurovascular disease characteristic of DPN, as has been demonstrated in healthy volunteers. The LDF measures of endothelial functioning did increase over the 10 week study period, with a mean 18% increase in endothelial-dependent and a 26% increase in endothelial-independent vasodilation, but this was not statistically significant. LDF measures tend to have high statistical variance which require larger samples sizes to detect greater than chance differences. Further studies could ascertain whether this observed increase: (1) has biological validity; and (2) is related to the release of endothelial NO by measuring plasma levels of nitrate and nitrite pre and

post acupuncture treatment as Tsuichiya et al [13] and Su et al [14] have done.

Nerve cells and endothelial cells are vulnerable targets of diabetes comorbidity as they lack the ability to regulate glucose uptake in a hyperglycemic environment. The mitochondria in these cells attempt to accommodate excess glucose in the electron transport chain, hindering the normal production of ATP, and leading to the overproduction of reactive oxygen species (ROS) [25]. Nerve cells are particularly susceptible to oxidative stress as they have a high metabolic rate to accommodate the amount of energy required to maintain ionic gradients and carry out neurotransmission [26]. Mitochondrial ROS production leads to impaired axonal transport and nerve fiber damage, manifesting as abnormal action potential [27]. Skin biopsy confirms early damage to small myelinated and unmyelinated nerve fibers and nerve conduction studies assess large fiber abnormalities that tend to develop later; collectively there are diagnosed as diabetic sensorimotor polyneuropathy [28].

Hyperglycemia-induced oxidative stress also damages the endothelial lining of the blood vessels and compromises NO function. Under normal conditions, endothelial NO: (1) relaxes arterial smooth muscle allowing vasodilation and increased blood flow; (2) acts as an antioxidant to offset the ROS produced in the mitochondria during regular oxidative phosphorylation; and (3) protects blood vessels from atherosclerotic plaque formation by inhibiting platelet aggregation [7]. Under hyperglycemic conditions and excessive production of ROS, NO is consumed, decreasing its availability for vasodilation. Depletion of endothelial NO in the small arterioles results in tissue ischemia which further damages nerve cells [29].

Improving endothelial function and restoring NO levels is a worthwhile treatment goal to ameliorate the pathophysiology of DPN. Statins have been shown to improve endothelial function and research into new pharmacological compounds that would similarly benefit DPN patients is currently underway [30]. Acupuncture studies have demonstrated a link between acupuncture treatment and an increase in plasma endothelial NO levels in healthy adults, and our objective was to assess this effect in individuals with neurovascular disease. Although the LDF Ach measure used in this study is NO specific, our lack of a comparison group and nonsignificant increase in this measure hinders our ability to draw a conclusion whether acupuncture benefits the endothelium in people with DPN.

Disclosure statement

The authors have no conflicts of interest with the content of this study.

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