

2012

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Recommended Citation

Kowalczuk, Sherri A., "Is Acupuncture An Effective Treatment For Diabetic Peripheral Neuropathy?" (2012). *PCOM Physician Assistant Studies Student Scholarship*. Paper 74.

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Is Acupuncture An Effective Treatment For Diabetic Peripheral Neuropathy?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

December 16, 2011

ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not acupuncture is an effective treatment for diabetic peripheral neuropathy

STUDY DESIGN: Review of three English language primary studies, one published in 2007 and two of which were published in 2010.

DATA SOURCES: Randomized controlled trials investigating the use of acupuncture for the treatment of diabetic peripheral neuropathy (DPN). Sources were found using PubMed and Cochrane databases.

OUTCOMES MEASURED: The outcomes measured include the severity of pain from DPN, blood glucose control, and effects on quality of life such as sleep, mood states, and gain or loss of sensations. The tools used to measure were the participant's opinions on whether the symptoms were relieved, improved, or failed to improve, the 11-point Likert Scale daily pain severity score, glucose levels or use of insulin, nerve conduction velocity, and standardized and comprehensive questionnaires provided to participants.

RESULTS: Two of the three studies results supported acupuncture for the treatment of DPN. Ahn et al demonstrated that acupuncture improved blood circulation, controlled blood glucose, and helped promote functional recovery of damaged nerves. Tong et al determined that acupuncture improved nerve conduction velocity and decreased the painful symptoms of DPN. According to Zhang et al' results were inconclusive due to the small sample size however, did suggest improvement in patients symptoms.

CONCLUSIONS: The results of the RCT's reviewed are inconclusive however, do suggest that acupuncture may be an effective treatment for DPN. Due to small sample sizes and limitations within studies, this topic does warrant additional research. Further studies conducted should include patients that are acupuncture naïve and blinded to the type of acupuncture administered.

KEY WORDS: Acupuncture; diabetes; neuropathy

INTRODUCTION

Diabetic peripheral neuropathy (DPN) is a painful and debilitating complication of diabetes. The pain is a result of nerve damage due to inadequate blood flow and high blood sugar levels.⁴ The symptoms of DPN are considered to be some of the most difficult and distressing complications of diabetes.² DPN is found to be prevalent in 12–50% of people with the diagnosis diabetes.⁴ DPN is often associated with significant morbidity and mortality.⁴ “The total annual cost of DPN and its complications in the United States was estimated to be more than four billion.”⁴ DPN may be attributed to almost 27% of the direct medical cost of diabetes.⁴ “It is estimated that there are 1.4 million physician office visits by adults aged 20 years and older with a diagnosis of DPN.”¹

“Strict glycemic control alone does not completely eliminate the complications of DPN; therefore the development of new therapies remains a high priority.”⁴ This paper evaluates three randomized control trials (RCTs) investigating the efficacy of acupuncture for the treatment of DPN. The direct cause of DPN remains unclear, although it is associated with increased age, duration of diabetes, lipotoxicity and glucotoxicity, genetic susceptibility, inflammation, and oxidative stress.⁴ DPN can present as pain or loss of sensation or both.² Some of the common methods used to treat DPN include counseling, proper footwear, strict glycemic control with insulin therapy, and management of pain with one or more of the following: analgesics, anti-inflammatories, tricyclic agents, selective serotonin reuptake inhibitors, anticonvulsants, local anesthetic arrhythmic agents, NMDA antagonists, opioid analgesics, topical capsaicin, or topical nitrate.³ “Symptoms of DPN include prickling, pain, loss of sensation and strength, reduced nerve conduction velocity, decreased temperature sensation, decreased tendon reflex response, and a decreased ability to detect vibration and touch.”⁴ Acupuncture has shown clear clinical

advantages in the reduction of symptoms related to nervous disorders, therefore may improve the symptoms associated with DPN.⁴

OBJECTIVE

The objective of this selective EBM review is to determine whether or not acupuncture is an effective treatment for diabetic peripheral neuropathy.

METHODS

The selected articles included men and women over the age of 18 with type 1 or type 2 diabetes and symptoms of DPN. The intervention chosen was acupuncture and compared Chinese Traditional Medicine (TCM) acupuncture to Japanese style acupuncture, sham (pretend) acupuncture to true acupuncture, and oral Inositol to acupuncture. The outcomes addressed were POEMs (patient oriented evidence that matters) and included the severity of pain from DPN, blood glucose control, and effects on quality of life such as sleep, mood states, and loss or gain of sensations. The types of studies included were all RCTs.

Articles were investigated using the search engines PubMed and Cochrane Database. English articles were searched using the key words acupuncture, diabetes, and neuropathy. The RCTs selected were peer reviewed articles all published from 2007-2010 and had not been previously used in a systematic review or meta-analysis. Inclusion criteria for these studies were RCTs published in 1996 or later that investigated the effectiveness of acupuncture for the treatment for DPN. The exclusion criteria consisted of studies investigating patients with neuropathy due to other causes, patients using any other experimental treatments for the symptoms of DPN, and patients under the age of 18. Statistics were reported using confidence intervals, p-values, patient questionnaires, and number needed to treat.

Table 1 - Demographics & Characteristics of Included Studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Ahn ² 2007	RCT	7	42-79	Patients >18yo with type 1 or type 2 diabetes with symptoms of PDN for >6 months; Scored >40/100 on the SF-MPQ; Had a score >2 on the MNSI; were acupuncture naïve	Pregnant; vascular insufficiency or claudication; neuropathy from other causes; amputations; drug use in the past 6 months; change in pain medications 2 months before enrollment	1	Acupuncture; Japanese style (Kiiko-Matsumoto's) acupuncture; Chinese Traditional Medicine style acupuncture.
Tong ⁴ 2010	RCT	63	35-52	Patients with mild DPN were diagnosed based on subjective symptoms; neurological dysfunctions included at least two parameters: MNCV and VPT or Achilles tendon reflex; participants with stable glycemic control.	Patients who primary cause of neurologic disorder was not diabetes; disappeared F-wave response; patients with arteriosclerosis obliterans, or hepatic or renal disorder; patients participating in other studies; patients receiving other medications for DPN that affects symptoms of DPN.	N/A	Acupuncture; sham (pretend) acupuncture
Zhang ⁵ 2010	RCT	65	36-68	Diabetic patients with diagnostic criteria for WHO in 1999; patients with signs and symptoms of DPN; Treatment group: Men and women aged 36-68 with an illness course of 1-5 years; Control group: Men and women aged 40-66 with an illness course of 1-5 years	Patients with peripheral neuropathy caused by other factors such as heredity, alcoholism, uremia, infection, malnutrition, drug intoxication, and mental intoxication.	N/A	Acupuncture after basic treatment; Inositol PO 2g per day x 3 days, after basic treatment

OUTCOMES MEASURED

The addressed outcomes were measured via several different methods. Ahn et al used the 11-point Likert Scale daily pain severity score, sleep interference score, glucose control or use of insulin, use of pain medication, profile of mood states scores, SF-MPQ (pain rating index portion), SF63 quality of life questionnaires, blood tests, quantitative sensory tests, and psychological effects. Clinical efficacy was determined for Tong et al according to Hemoglobin A1c levels (HbA1c) as well as the differences between baseline and post-treatment electrophysiological measurements of the median motor nerve, tibial motor nerve, median sensory nerve, and vibration perception threshold. Zhang et al determined outcomes according to participant's opinions on whether the symptoms were relieved, improved, or failed to improve.

RESULTS

Two of the three RCTs presented in this review had continuous data, which could not be converted to dichotomous data. In the study performed by Ahn et al, the reported statistics compared Japanese style (Kiiko-Matsumoto's) acupuncture and TCM style acupuncture. The TCM acupuncture group had less glucose control as documented by the HbA1c levels. The HbA1c levels in the TCM acupuncture group were consistently elevated at 8.8 (week 0) and 9.2 (week 10), whereas the Japanese acupuncture group had levels of 6.6 (week 0) and 6.5 (week 10)² (Table 2). The TCM acupuncture group noted greater improvement in sensation by both cooling and warming compared to the Japanese group for quantitative sensory testing. Both groups noted a decrease in pain according to the Pain Rating Index of the SF-MPQ. The SF-MPQ is an index that measures sensory and affective descriptors of pain that is scaled from 0 to 45 (45 being worst). The TCM acupuncture group had a decrease from 19 at week 0 to 14.3 at week 10, while the Japanese Acupuncture group had a decrease from 17.8 at week 0 to 13.5 at

week 10² (Table 2). The TCM style improved nerve sensation according to quantitative sensory testing while the Japanese style had a more indecisive effect. Japanese style acupuncture lowered symptoms of pain associated with neuropathy according to the daily pain severity score. There were no remarkable differences in changes of profile of mood states or blood test results. The weekly blood glucose levels and insulin usage did not particularly change with acupuncture. The sleep interference score and SF36 Quality of Life Questionnaire could not be significantly analyzed. Psychological tests proved to be inadequate for interpretation.²

Table 2- Hemoglobin A1c levels and Pain Rating Index of the SF-MPQ performed by Ahn et al

	HbA1c Week 0	HbA1c Week 10	SF-MPQ Week 0	SF-MPQ Week 10
Chinese Traditional Medicine style acupuncture	8.8	9.2	19	14.3
Japanese style acupuncture	6.6	6.5	17.8	13.5

In the study performed by Tong et al, statistics were reported comparing an acupuncture group to a sham (pretend) acupuncture group. One way symptoms were assessed was a standardized and comprehensive questionnaire at baseline and following 15 days of treatment. At the end of treatment all patients were asked, “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?”⁴ Of the answers reported from the 63 patients who completed the study, 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 (-0.65 CI, -0.61 to -0.69) in the sham group⁴ (Table 3). The two proportions of unblinding reported a p-value that showed no significant difference (p=0.25). In regards to changes in glycemic control the acupuncture group (n=42), HbA1c (mean±SD) at baseline and

day 15 was 6.8 ± 1.3 and $6.7 \pm 1.2\%$ respectively. Corresponding values in the sham acupuncture group were $6.6 \pm 1.2\%$ and $6.7 \pm 1.3\%$, respectively⁴ (Table 3).

According to Tong et al, “the primary end points for clinical efficacy were the differences between baseline and post-treatment electrophysiological measurements of the median motor nerve, the tibial motor nerve, and the median sensory nerve”⁴ (Table 4). At baseline and end-of-treatment electrophysiological measures (mean \pm SD) were recorded for changes in nerve function. “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.”⁴ There were no significant improvements in electrophysiological measures of motor or sensory function in the sham acupuncture group. Other improvements in the acupuncture group included the two measures of sensory function, forearm and distal SNCV. The change of forearm SNCV from baseline reported a p-value that was significant ($p < 0.05$). Significant differences were also reported in VPT between groups ($p < 0.05$) and when compared to the baseline levels ($p < 0.01$) in the acupuncture group. Continuous treatment caused a gradual increase in the difference between the two groups. Acupuncture was notably better than sham acupuncture for the treatment effects on numbness of lower extremities (severity $p < 0.05$, extent $p < 0.05$), spontaneous pain in lower extremities (severity $p < 0.05$, extent $p < 0.01$), rigidity in upper extremities (severity $p < 0.05$, extent $p < 0.05$), and alterations in temperature perception in lower extremities (severity $p < 0.01$, extent $p < 0.05$).⁴ Significant improvement in the acupuncture group was noted for numbness in the upper extremities (severity), and the sensation of rigidity (extent) when compared with the sham acupuncture group ($p < 0.05$, and

0.01, respectively) after 15 days treatment. A significant difference between the two groups in the sensation of paresthesia, hypesthesia, and weakness of extremities was not reported.⁴

Table 3- Blinding Data & Changes in Glycemic Control performed by Tong et al

	Blinding Index	Confidence Interval	HbA1c Baseline	HbA1c Day 15
Acupuncture	0.32	95%, 0.27 to 0.37	6.8±1.3	6.7±1.2%
Sham Acupuncture	-0.65	95%, -0.61 to -0.69	6.6±1.2%	6.7±1.3%

Table 4- Change in Nerve Conduction Velocity performed by Tong et al

Parameter	Acupuncture	Sham acupuncture	Difference	P-value
F wave minimum latency in median				
Change from baseline (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				
Change from baseline (m/s)	0.4 ± 0.3	0.0 ± 0.1	0.4	< 0.05
95% CI	-0.19 to 0.99	-0.20 to 0.20		
MNCV in median				
Change from baseline (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				
Change from baseline (m/s)	0.7 ± 0.3	0.0 ± 0.2	0.7	< 0.01
95% CI	0.11 to 1.29	-0.39 to 0.39		
FCV in median				
Change from baseline (m/s)	0.9 ± 0.5	0.1 ± 0.4	0.8	< 0.01
95% CI	-0.08 to 1.88	-0.68 to 0.88		
FCV in tibial				
Change from baseline (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)				
Change from baseline (m/s)	0.5 ± 0.3	0.0 ± 0.5	0.5	< 0.05
95% CI	-0.09 to 1.09	-0.98 to 0.98		
SNCV in median (distal)				
Change from baseline (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				
Change from baseline (m/s)	0.51 ± 0.70	0.04 ± 0.13	0.47	< 0.01
95% CI	-0.86 to 1.88	-0.21 to 0.29		

CI = confidence interval; MNCV = motor nerve conduction velocity; FCV = F-wave conduction velocity; SNCV = sensory nerve conduction velocity; VPT = vibration perception threshold.

The final study performed by Zhang et al, the outcomes were presented as dichotomous data.

This study compared acupuncture to Inositol PO 2g per day x 3 days. Both treatments were given

after basic treatment which included the following: FBG below 7.0 mmol/L and 2 h BG below 11.1 mmol/L; those diabetics complicated with hypertension and hyperlipidemia, their blood pressure and blood lipid were controlled to the normal range; diet was rationally controlled.⁵ “In the treatment group of 32 cases, 16 cases were markedly relieved, 12 cases improved, and 4 cases failed, with a total effective rate of 87.5%.⁵ In the control group of 33 cases, 7 cases were markedly relieved, 14 cases improved, and 12 cases failed, with a total effective rate of 63.6%⁵ (Table 5).

Table 5- Post Treatment DPN Symptoms according to Zhang et al

Treatment Group	Markedly relieved	Improved	Failed to Improve	Effective Rate
Acupuncture (32)	16	12	4	87.5%
Inositol (33)	7	14	12	63.6%

Table 6- Efficacy of Acupuncture for DPN Compared to Inositol performed by Zhang et al

Inositol Group (CER)	Acupuncture Group (EER)	RRR	ARR	NNT	P-Value
63.6%	87.5%	37.6%	23.9%	5 patients	<0.05

Of the studies investigated, there were significant differences in the control groups. Control groups included pretend acupuncture, the oral medication Inositol, TCM acupuncture and Japanese acupuncture.

Each individual study had specific inclusion/exclusion criteria. All studies included patients from hospitals or primary care clinics with type 1 or type 2 diabetes and symptoms of DPN. Ahn and Tong et al excluded patients using pain medication that may affect symptoms of DPN. The study by Ahn et al was the only study to use patients that were acupuncture naïve. All three studies excluded patients with neuropathy due to causes other than diabetes.

The study conducted by Ahn et al, only six out of the seven study subjects fully completed the 10 weekly treatments. One subject from the Japanese acupuncture treatment

group left the trial midway (about six weeks into treatment), stating worsening of symptoms.² No other safety issues or side effects were reported in any of the studies.

The study performed by Ahn et al determined “Japanese versus TCM acupuncture differed in their clinical and mechanistic effects on diabetic neuropathy, but overall showed a decrease in pain and associated symptoms.”² In the study conducted by Tong et al, acupuncture compared to sham acupuncture showed no significant difference in Hgb A1C values (Table 3) however, did show improvement of nerve function in the acupuncture group (Table 4). In the study conducted by Zhang et al, “the chi-squared test showed a significant difference in clinical effects between the two groups.”⁵

DISCUSSION

The studies performed contained some factors that may have affected the outcome results. In the study conducted by Ahn et al, the opinions of the participants were very positive in regards to acupuncture however, patients felt the outcome results did not express this adequately. Several screening tools in this study were deemed “unable to analyze” or “too poor for interpretation.” Psychological markers were unable to disclose why there were clinical differences observed. The two styles of acupuncture in this study did not fully utilize the large amount acupuncture styles available in the clinical setting. Acupuncturists were restricted to specific techniques within the protocol. Several of the acupuncturists stated that they would have added additional treatment but were unable to do so because of the need to stay within the treatment guidelines.²

Ahn et al and Tong et al explain that the outcome may have been affected due to the small sample size. Tong et al goes on to explain that “further studies with larger patient numbers are required to confirm the findings, to determine whether the effects are sustained, and to ascertain

whether there are any effects on other sensory symptoms associated with DPN.”⁴ Zhang et al does not mention factors that may have affected outcomes of the study.

Tong et al was the only study that was able to successfully blind the patients in regards to receiving acupuncture versus sham acupuncture. Due to the style of the treatment the other two studies were unable to successfully blind their patients. This may have swayed the results of the participants due to the placebo effect.

Acupuncture is considered an alternative medicine and therefore is not typically covered under medical insurance plans.⁴ As a result; there is limited access for patients to this type of treatment. However, due to studies such as those mentioned, the effectiveness of acupuncture is starting to become more recognized. This will hopefully encourage more health insurance plans to cover acupuncture and other alternative medicine treatments.

There are very few contraindications to the use of acupuncture for the treatment of DPN. “Needling should not be used on areas of an open wound and special attention should be paid to sterilize the skin and needles so as to prevent secondary pathological changes.”⁵ It is important to take these precautions into consideration because skin infection can further complicate the symptoms of DPN.⁵

CONCLUSION

The results of the RCT’s reviewed are inconclusive however, do suggest that acupuncture may be an effective treatment for DPN. Ahn et al states acupuncture can promote blood circulation and control blood glucose. According to Zhang et al, “acupuncture has effects on improving microcirculation, enhancing the concentration of blood oxygen around the affected area, can promote functional recovery of affected nerves, and may correct endocrine dysfunction and restore normal function.”⁵ Tong et al results show that acupuncture was more effective than

sham acupuncture in improving nerve conduction velocity as well as many of the painful symptoms associated with DPN. “Acupuncture is a safe form of treatment and offers clear clinical advantages in the reduction of DPN related symptoms.”⁴ Due to the small sample size, the results of the data from Ahn et al determined that the evidence is inconclusive about the efficacy of TCM acupuncture or Japanese acupuncture for the treatment of DPN however; the majority of patients did experience an improvement in symptoms after treatment.

Although the studies conducted were thorough and concise, some inaccuracies do exist. This includes the difficulty of blinding patients to acupuncture, due to the way the treatment is performed. Patients with previous exposure to acupuncture treatments may also affect the study results because they may be able to differentiate between the two types of acupuncture. Future studies should be conducted with patients that are strictly acupuncture naïve and blinded to the use of sham versus true acupuncture (a placebo control). With these criteria, a more definitive answer for the treatment of acupuncture for DPN may be identified.

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