Diabetic Peripheral Neuropathy: Amelioration of Pain With Transcutaneous Electrostimulation

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OBJECTIVE — To evaluate the efficacy of transcutaneous electrotherapy for chronic painful peripheral neuropathy in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS — Thirty-one patients with symptoms and signs of peripheral neuropathy were randomized to the electrotherapy or sham treatment (control) group. The electrostimulation was given by a portable unit (H-Wave machine) that generated a biphasic, exponentially decaying waveform (pulse width 4 ms, 25–35 V, ≥2 Hz). Patients treated each of their lower extremities for 30 min daily for 4 weeks at home. Nine patients from the sham-treatment group participated for a second period, during which all of them received the active electrotherapy. Patient's degree of pain and discomfort was graded on a scale of 0 to 5.

RESULTS — In the sham-treated group (n = 13), the neuropathic symptoms improved in five (38%) patients, and the pain score declined from 2.92 ± 0.13 to 2.38 ± 0.26 ($P < 0.04$), suggesting a procedure-related placebo effect. In the electrotherapy group (n = 18), symptomatic improvement was seen in 15 (83%) cases, 3 of which were completely asymptomatic; the pain score declined from 3.17 ± 0.12 to 1.44 ± 0.25 ($P < 0.01$) and the posttreatment pain scores were considerably lower ($P < 0.03$), indicating a substantial treatment effect over and above any placebo influence. Patients in the electrotherapy group reported greater reduction in symptoms (52 ± 7% vs. 27 ± 10% in control subjects, $P < 0.05$) on an analog scale. Moreover, the electrotherapy decreased pain scores (from 3.0 ± 0.62 to 1.56 ± 0.32, $P < 0.02$) in nine patients who had received sham treatment earlier.

CONCLUSIONS — A form of transcutaneous electrotherapy ameliorated the pain and discomfort associated with peripheral neuropathy. This novel modality offers a potential nonpharmacological treatment option.

Peripheral neuropathy is a common complication of diabetes, afflicting >36% of NIDDM individuals (1). Because the etiology of diabetic neuropathy is not well understood, symptomatic treatment remains the mainstay of management. Analgesics, tricyclic antidepressants, and anticonvulsant drugs are often prescribed, with variable responses (2,3). The aldolase reductase inhibitors are investigational at present (4,5). Electrotherapy, a nonpharmacological approach, has been used to alleviate chronic pain associated with arthritis and rheumatological conditions (6). It is conceivable that electrotherapy may also help in chronic painful peripheral neuropathy associated with diabetes. We have evaluated the efficacy and safety of such a therapeutic modality.

RESEARCH DESIGN AND METHODS

Study patients

Patients referred for evaluation and treatment of peripheral neuropathy were invited to participate in a study protocol approved by our institutional review board. Patients with the following characteristics were included in the study: men or women, age 31 to 70 years, with documented type 2 diabetes and symptoms of painful peripheral neuropathy involving both lower extremities for >2 months. We excluded patients having clinical evidence of vascular insufficiency of legs or feet (history of claudication, discoloration of skin, ulceration), uncontrolled angina pectoris, cardiac arrhythmia, congestive heart failure, myocardial infarction within the past 6 months, untreated hypertension, cerebrovascular ischemia, psychiatric disease or substance abuse including alcohol, biochemical evidence of significant renal (serum creatinine >177 μmol/l) or liver disease. Patients on corticosteroid, dilantin, or chemotherapeutic agents were also excluded.

Study design

A detailed history and a physical examination were performed to establish eligibility on the initial visit. The patient's pain was graded (Table 1), and patients with scores of ≥2 were selected for the study. All patients were advised to discontinue analgesics, including tricyclic antidepressants. Participants were randomly assigned, in a single-blind fashion, to either (1) transcutaneous electrotherapy or (2) sham-treatment (control) group. The former group received working electrotherapy machines, and the control group received machines with inactive electrodes. Each patient was individually instructed how to place the electrodes and how to use the machine. One of the investigators explained to each patient individually that one might not feel electrical sensations at the electrodes because of possible variation in patients' sensory perception thresholds. The treatment process was demonstrated with an assigned machine, thereby providing experience and feel of the electrodes. The assigned electrotherapy machine was then lent for home use. Patients returned after 1 week, and one of the investigators reviewed treatment technique and proper use of the machine. The symptoms and signs of

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Abbreviations: TENS, transcutaneous electrical nerve stimulation.

Table 1—*Criteria used for grading pain*

Grade	Symptoms and affective description
0	No symptoms
1	Minimal burning pain with or without paresthesias. Some discomfort but bearable. Insignificant problem in daily activities.
2	Mild burning pain with or without paresthesias. Uncomfortable most of the day. Occasional pain during night. Some disturbance of daily activities. Patient wants treatment.
3	Burning pain of moderate intensity with paresthesias disturbing the night sleep. Distressing and distracting, causing difficulty in daily activities.
4	Intense burning pain, intermittent. Presence of paresthesias. Significantly disturbed night sleep due to pain. Unbearable. Patient unable to function.
5	Extremely intense burning pain, constant, excruciating. Presence of paresthesias. Very disturbed night sleep. Patient asking for strong analgesics.

peripheral neuropathy were re-evaluated after 1 month. At that visit, the electrotherapy machine was returned.

We offered participation for a second treatment period to those patients who were in the control group but had continued pain scores of ≥2. During that phase of study, all patients were treated with working machines.

Patients were examined 1 month after discontinuation of electrotherapy to assess neuropathic symptoms. If the pain had returned or worsened, they were offered the electrotherapy in office.

Grading of pain

Patients' descriptions of symptoms, paresthesias, intensity and frequency of pain, sleep disturbance (due to neuropathic pain), and functional impediment were used to grade the pain and discomfort level on a scale of 0 to 5 (Table 1). The verbal pain descriptors were adapted from a previously validated instrument (7,8). In addition, an analog scale was used to record the overall improvement in symptoms at follow-up visits.

Transcutaneous electrotherapy

Electrotherapy was given by a portable, rechargeable unit, the H-Wave machine (Electronic Waveform Lab, Huntington Beach, CA), which has output parameters that are distinct from the other available transcutaneous electrical nerve stimulation (TENS) modalities. It generates a biphasic, exponentially decaying waveform with pulse widths of 4 ms and ≤35 V. The electric current strength varies with voltage setup to a maximum of 35 mA, and the pulse frequency is user adjustable (2–70 Hz). Because of a specific waveform, the muscular contractions are nonfatiguing. The portable unit has two channels and delivers bipolar electrical stimuli via four skin-applied electrodes.

For the transcutaneous electrostimulation, four self-adhesive electrodes were positioned in the following fashion: *1*) 3 inches above the patella and 3 inches medially, over the vastus medialis oblique; 2) 3 inches above patella and 3 inches laterally, over the lower portion of vastus lateralis; 3) on the neck of fibula; and 4) on the gastrocnemius muscle about 3 inches below the center of popliteal fossa. The electrode positions were marked by a skin marker. Patients were instructed to treat each lower extremity for 30 min every day at home. They adjusted the intensity dial between 7 and 9 (25–35 V) and the frequency above minimum (≥2 Hz) depending on individual comfort levels.

Statistical analysis

Wilcoxon's rank-sum test was used for analyzing changes in the pain scores among groups. The percent improvement in symptoms was analyzed by Student's *t* test. Statistical calculations were performed using Dyna-stat Professional Statistics Software (Dynamic Microsystems, Washington, DC) on an IBM PC.

RESULTS — The clinical features of the 31 patients studied are summarized in Table 2. At the initial visit, each patient complained of pain and burning in the feet. Physical examination revealed total loss of touch sensation at toes and plantar aspects in nine cases. The vibration sense at big toes was lost in 10 patients, and the ankle jerk was absent in 21. On pain grading, 23 patients scored 3, 5 patients scored 4, and 3 patients scored 2. The pain scores and duration of neuropathic symptoms did not differ between the patients randomized to the electrotherapy or sham-treatment (control) group.

Sham treatment

There were 13 patients in this group. Neuropathic symptoms did not change in eight (62%) of these patients, and their pain scores remained unaltered (Figure 1*A*). The pain scores improved by one grade in three cases and by two grades in two other patients. Mean pain score declined from 2.92 ± 0.13 to 2.38 ± 0.26; this grade reduction of 0.54 ± 0.21 was significant (Wilcoxon matched-pair test, $Z = -2.023$, $P = 0.04$), suggesting a procedure-related placebo effect.

Transcutaneous electrotherapy

Symptomatic improvement was seen in 15 (83%) of the 18 patients in this group; 3 of them improved by 3 grades, 8 by 2, and the other 4 by 1 (Fig. 1*B*). Three patients, who had initial pain scores of 3, became completely asymptomatic. The group mean score declined from 3.17 ± 0.12 to 1.44 ± 0.25, and these changes were highly significant (Wilcoxon matched-pair test, $Z = -3.45$, $P < 0.01$). The posttreatment pain

Table 2—*Clinical data*

	Treatment group	
	Sham (control)	Electrotherapy
n	13	18
Age (years)	59 ± 3	53 ± 4
Sex (M/F)	5/8	7/11
BMI (kg/m²)	30.5 ± 1.8	29.2 ± 2.9
Duration of diabetes (years)	12 ± 2	9 ± 2
Duration of neuropathic symptoms (months)	22 ± 4	16 ± 3
Average pain grade	2.92 ± 0.13	3.17 ± 0.12

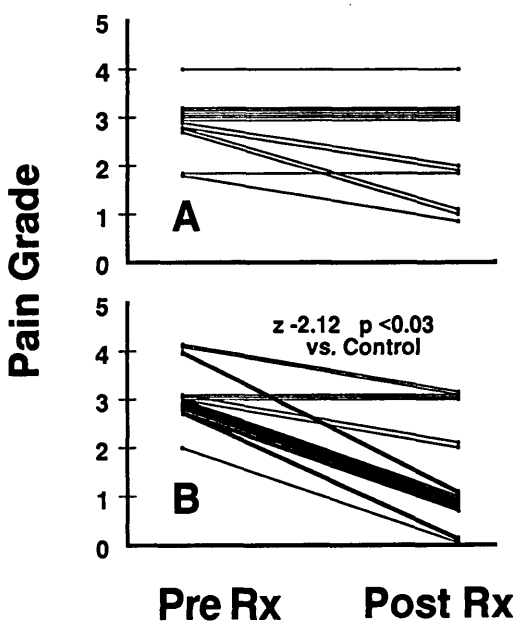

Figure 1—*Change of pain grades in individual patients in the sham-treatment (control) group (A) and active electrotherapy group (B).*

scores were lower for these patients compared with those for the sham-treated patients (1.44 ± 0.25 vs. 2.38 ± 0.26, Wilcoxon's rank-sum test, $Z = -2.12$, $P < 0.03$), indicating a substantial treatment effect over and above any placebo influence.

Three (17%) patients failed to have any symptomatic relief with electrotherapy. Each of them had scored 3 on pain grading. There was no discernable difference in clinical features between them and the responders.

Nine patients who were in the sham-treatment (control) group initially participated in the second phase of study, where each of them received active electrotherapy. Their pain scores decreased significantly, from 3.0 ± 0.62 to 1.56 ± 0.32 (Wilcoxon matched-pair test, $Z = -2.25$, $P = 0.02$); one of them was completely pain-free (Figure 2).

Patients were questioned for subjective improvements in their overall neuropathic symptoms using an analog scale. Amelioration was significantly greater in the electrotherapy group (52 ± 7% reduction in symptoms) as compared with the control group (27 ± 10% reduction, $P < 0.05$).

Patients felt treatment effect during the 2nd week of electrotherapy, and most symptomatic relief was achieved by the 3rd week. On the follow-up visit, a month after the discontinuation of electrotherapy, there was a tendency for recurrence of symptoms, and therapeutic gains were being lost progressively.

Side effects

There was no discernable improvement or deterioration of the neurological signs during the study period. One patient in the control group reported burning sensation at the site of electrode placement. No other local or systemic side effects were noticed.

Metabolic control

Patients were free from symptoms of uncontrolled diabetes and had stable body weights, but their glycosylated hemoglobin levels were in the "poor" range (>8%) (9). No attempt was made to modify medical treatment during the study period.

CONCLUSIONS — In this randomized, two-arm clinical study, we observed that the transcutaneous electrotherapy reduced the pain and discomfort of peripheral neuropathy in 15 of the 18 (83%) patients. This noninvasive treatment was safe, with no side effects. It appears that such a nonpharmacological modality could be useful for symptomatic relief and offers a potential treatment option.

The natural course of neuropathic symptoms is highly variable, and caution must be exercised in interpreting the outcome of a short-term treatment modality. To control this difficulty to some extent, we had a parallel group of sham-treated patients. It was of interest that those patients had significant reduction in pain scores. While this may represent the course of disease, we also considered an alternate explanation that it was a procedure-related placebo effect. Assuming that the patients in active transcutaneous electrotherapy group had similar course, a greater magnitude of response (as judged by the pain scores and reduction in symptoms) provides evidence for the therapy-induced beneficial effects. Moreover, when the sham-treated patients were switched to active electrotherapy, their pain scores decreased significantly, giving further support to our conclusion.

Transcutaneous electrotherapy produced transient relief of symptoms. We observed recurrence of patients' pain and discomfort a few weeks after discontinuation of therapy. This implies that the treatment must be continued. A limited experience with patients followed in our office suggests that the treatment can be given weekly until the patient becomes pain-free, and then once every month.

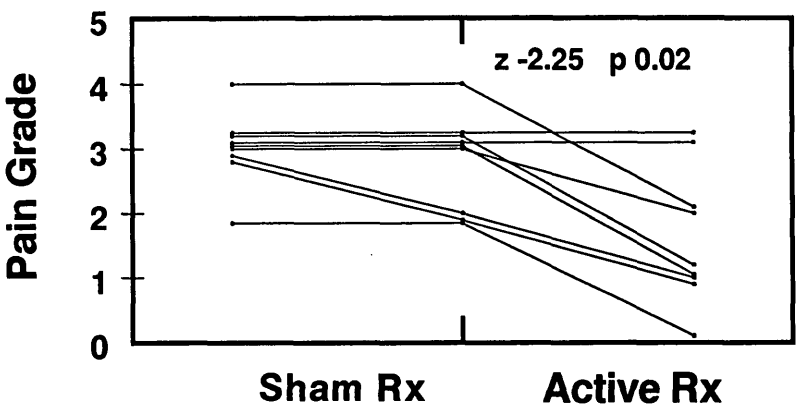

Figure 2—*Change of pain grades in nine patients who had initial sham treatment followed with the active electrotherapy.*

Individual responses to electrotherapy varied significantly. While 1 of 6 patients became asymptomatic, an equal number of cases failed to respond. This should not be surprising because none of the currently prescribed treatments has any better outcome. In a group of 53 drug-treated patients studied by Pfeifer et al. (10), 66% showed some symptomatic improvement, 21% became pain-free, and the remaining 13% were treatment failures. This corresponds closely with our study outcome, where 66% improved, 17% were pain-free, and other 17% were treatment failures. Since it may be feasible to combine the electrotherapy with pharmacotherapy, we are investigating the clinical effectiveness of such a strategy (11).

TENS has neurophysiological and chemical effects. Walsh et al. (12) observed an increase in peripheral nerve conduction latency and mechanical pain threshold when TENS (0.2 ms pulse, 110 Hz for 5 min) was applied directly over the course of nerve. It influences neuronal afferent transmission and conduction velocity, increases the nociceptive flexion reflex threshold, and changes the somatosensory evoked potentials (13–15). A number of publications show beneficial effect of TENS in neuromuscular disorders, but its efficacy is not universally accepted (6,16–19). Since the wave form, duration, and frequency of electrostimulation determine the therapeutic response (12,20,21), a careful selection of those parameters is critical. It was fortuitous that the equipment (H-Wave machine), wave form (bipolar, exponentially decaying), and conditions (4 ms pulse, ≥2 Hz for 30 min) used in this study produced a clinically meaningful outcome. Would another set of electrostimulatory parameters enhance symptomatic relief in such patients? That remains to be investigated.

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References

1. Harris MH, Eastman R, Cowie C: Symptoms of neuropathy in adults with NIDDM in the U.S. population. *Diabetes Care* 16:1446–1452, 1993
2. Max MB, Lynch SA, Muir J, Shoaf SE, Smoller B, Dubner R: Effects of desipramine, amitriptyline and fluoxetine on pain in diabetic neuropathy. *N Engl J Med* 326:1250–1256, 1992
3. Schoemaker JH: Pharmacological treatment of diabetic peripheral neuropathy, challenges and possibilities. *Br J Clin Pract* 48:91–96, 1994
4. Martyn CN, Reid W, Young RJ, Ewing DJ, Clarke BF: Six month treatment with sorbinil in asymptomatic diabetic neuropathy, failure to improve abnormal nerve function. *Diabetes* 36:987–990, 1987
5. Nicolucci A, Carinci F, Cavaliere D, Scorpiglione N, Belfiglio M, Labbrozzi D, Mari E, Benedetti MM, Tognoni G, Liberati A: A metaanalysis of trials on aldose reductase inhibitors in diabetic peripheral neuropathy. *Diabet Med* 13:1017–1026, 1996
6. Neumann V: Electrotherapy (Editorial). *Br J Rheumatol* 32:1–2, 1993
7. Gracely RH, McGrath P, Dubner R: Ratio scales of sensory and affective verbal pain descriptors. *Pain* 5:5–18, 1978
8. Gracely RH, McGrath P, Dubner R: Validity and sensitivity of ratio scales of sensory and affective verbal pain descriptors: manipulation of affect of diazepam. *Pain* 5:19–29, 1978
9. American Diabetes Association: Standards of medical care for patients with diabetes mellitus (Position Statement). *Diabetes Care* 20 (Suppl. 1):S5–S13, 1997
10. Pfeifer MA, Schumer MP, Ross DR, Crain GM, Schrage JP, Markwell SJ, Gelber DA, Jung S: A highly successful and novel model for treatment of chronic painful diabetic peripheral neuropathy. *Diabetes Care* 16:1103–1115, 1993
11. Kumar D, Marshall HJ, Nadra WE, Mahfoud A, Valdez Y: Painful peripheral neuropathic treated with bi-polar exponentially decaying electro-waves (Abstract). *Diabetes* 45 (Suppl. 2):290A, 1996
12. Walsh DM, Foster NE, Baxter GD, Allen JM: Transcutaneous electrical stimulation: relevance of stimulation parameters to neurophysiological and hypoalgesic effects. *Am J Phys Med Rehabil* 74:199–206, 1995
13. Ashton H, Golding JF, Marsh VR, Thompson JW: Effects of transcutaneous electrical nerve stimulation and aspirin on late somatosensory evoked potentials in normal subjects. *Pain* 18:377–386, 1984
14. Janko M, Trontelj JV: Transcutaneous electric nerve stimulation: a microneurographic and perceptual study. *Pain* 9:219–230, 1980
15. Facchinetti F, Sandrini G, Petraglia F, Alfonsi E, Nappi G, Genazzani AR: Concomitant increase in nociceptive flexion reflex threshold and plasma opioids following transcutaneous nerve stimulation. *Pain* 19:295–303, 1984
16. Nicholas JJ: Physical modalities in rheumatological rehabilitation. *Arch Phy Med Rehabil* 75:994–1001, 1994
17. Simmonds MJ, Kumar S: Pain and the placebo in rehabilitation using TENS and laser. *Disabil Rehabil* 16:13–20, 1994
18. Marchand S, Charest J, Li J, Chenard J-R, Lavignolle B, Laurencelle L: Is TENS purely a placebo effect? A controlled study on chronic low back pain. *Pain* 54:99–106, 1993
19. Meyler WJ, deJongste MJL, Rolf CAM: Clinical evaluation of pain treatment with electrostimulation: a study of TENS in patients with different pain syndromes. *Clin J Pain* 10:22–27, 1994
20. Katims JJ, Long DM, Ng LK: Transcutaneous electrical nerve stimulation: frequency and waveform specificity in humans. *Appl Neurophysiol* 49:86–91, 1986
21. Taylor DN, Katims JJ, Ng LK: Sine-wave auricular TENS produces frequency-dependent hypesthesia in the trigeminal nerve. *Clin J Pain* 9:216–219, 1993