Percutaneous Electrical Nerve Stimulation

A novel analgesic therapy for diabetic neuropathic pain

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OBJECTIVE — To evaluate the use of percutaneous electrical nerve stimulation (PENS) in the management of patients with painful diabetic peripheral neuropathy.

RESEARCH DESIGN AND METHODS — A total of 50 adult patients with type 2 diabetes and peripheral neuropathic pain of >6 months duration involving the lower extremities were randomly assigned to receive active PENS (needles with electrical stimulation at an alternating frequency of 15 and 30 Hz) and sham (needles only) treatments for 3 weeks. Each series of treatments was administered for 30 min three times a week according to a standardized protocol. After a 1-week washout period, all patients were subsequently switched to the other modality. A 10-cm visual analog scale (VAS) was used to assess pain, physical activity, and quality of sleep before each session. The changes in VAS scores and daily requirements for oral analgesic medication were determined during each 3-week treatment period. Patients completed the MOS 36-Item Short-Form Health Survey (SF-36), the Beck Depression Inventory (BDI), and the Profile of Mood States (POMS) before and after completion of each treatment modality. At the end of the crossover study, a patient preference questionnaire was used to compare the effectiveness of the two modalities.

RESULTS — Compared with the pain VAS scores before active (6.2 ± 1.0) and sham (6.4 ± 0.9) treatments, pain scores after treatment were reduced to 2.5 ± 0.8 and 6.3 ± 1.1, respectively. With active PENS treatment, the VAS activity and sleep scores were significantly improved from 5.2 ± 1.0 and 5.8 ± 1.3 to 7.9 ± 1.0 and 8.3 ± 0.7, respectively. The VAS scores for pain, activity, and sleep were unchanged from baseline values after the sham treatments. Patients' daily oral nonopioid analgesic requirements decreased by 49 and 14% after active and sham PENS treatments, respectively. The post-treatment physical and mental components of the SF-36, the BDI, and the POMS all showed a significantly greater improvement with active versus sham treatments. Active PENS treatment improved the neuropathic pain symptoms in all patients.

CONCLUSIONS — PENS is a useful nonpharmacological therapeutic modality for treating diabetic neuropathic pain. In addition to decreasing extremity pain, PENS therapy improved physical activity, sense of well-being, and quality of sleep while reducing the need for oral nonopioid analgesic medication.

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Abbreviations: BDI, Beck Depression Inventory; MCS, Mental Component Summary; PCS, Physical Component Summary; PENS, percutaneous electrical nerve stimulation; POMS, Profile of Mood States; SF-36, MOS 36-Item Short-Form Health Survey; TENS, transcutaneous electrical nerve stimulation; VAS, visual analog scale.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Peripheral neuropathy is the most common complication of type 2 diabetes, occurs in the distal extremities, and typically affects the sensory, motor, and autonomic systems (1,2). In diabetic patients, chronic hyperglycemia can produce neuropathic changes that affect peripheral nerve function and produce extremity pain (3,4). The persistence of these painful symptoms can interfere with the patient's physical activity and sleep pattern.

Conventional pharmacotherapy for painful diabetic neuropathy remains largely symptomatic. Analgesics, tricyclic antidepressants, and anticonvulsants are the mainstays of therapy (5). Nonpharmacological therapies such as transcutaneous electrical nerve stimulation (TENS) (6), acupuncture (7), and spinal cord stimulation (8) have also been used successfully to alleviate the pain and discomfort associated with peripheral neuropathy. Percutaneous electrical nerve stimulation (PENS) is a novel electroanalgesic therapy that combines the advantages of both TENS and electroacupuncture by using percutaneously placed disposable acupuncture-like needle probes to stimulate peripheral sensory nerves innervating the region of neuropathic pain. This therapy has recently been reported to be highly effective in the short-term management of a wide variety of acute and chronic pain syndromes (9–13).

The present randomized sham-controlled crossover study was designed to evaluate the effectiveness of PENS therapy in diabetic patients with peripheral neuropathic pain. In addition to examining the acute analgesic effects of PENS, changes in physical activity, quality of sleep, and requirements for analgesic medication were examined during a 3-week treatment period.

RESEARCH DESIGN AND METHODS

Study patients

After local institutional review board approval and after patients gave their written informed consent, 50 adult diabetic patients (28 women and 22 men), ranging in age from 34 to 71 years (means ± SD 55 ± 9

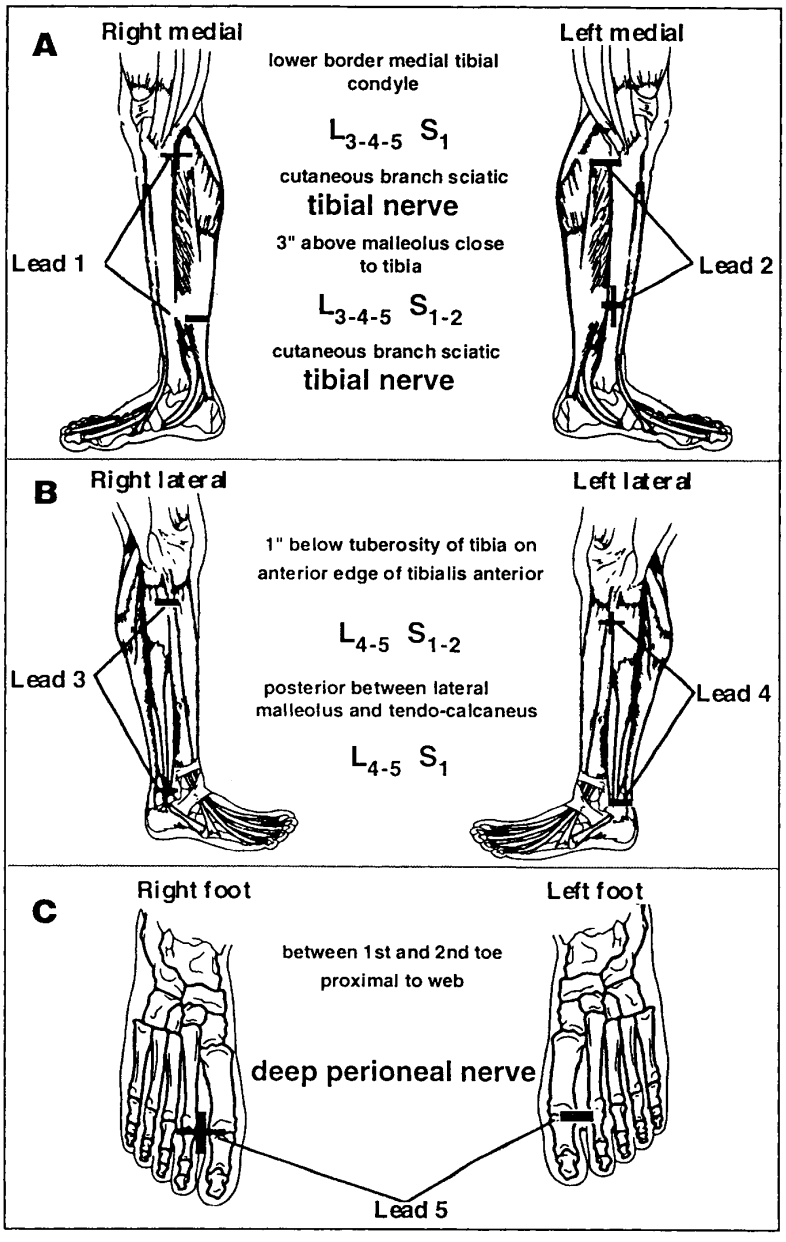

Figure 1—*The needle locations for each pair of positive (+) and negative (−) lead. A total of 10 needles were connected to five sets of leads.*

years) and in body weight from 46 to 113 kg (70 ± 17 kg) were enrolled in this sham-controlled investigator-blinded crossover study. The patients had longstanding type 2 diabetes associated with painful peripheral neuropathic symptoms of >6 months (18 ± 7) duration involving both lower extremities. The study patients were referred from the diabetes clinic with a diagnosis of peripheral neuropathy confirmed by an abnormal nerve conduction study. These patients complained of burning pain with paresthesia in both legs. Neurological examination of the patients revealed sensory abnormalities in both lower extremities. Exclusion criteria included pregnancy, cardiac arrhythmias or cardiac pacemakers, infection or gangrene, history of vascular insufficiency in the legs, drug or alcohol abuse, psychiatric disease, major organ disease, radicular pain (sciatica), psychiatric disease, and inability to complete the psychological assessment forms reliably. Patients receiving steroids, dilantin, or chemotherapeutic agents were also excluded. All patients were stable regarding control of their diabetes, and their medical management was unchanged during the study period. The patients were instructed to use their current nonopioid analgesic medications on an as-needed basis.

Study design

The patients were randomly assigned to receive active PENS (needles with electrical stimulation) or sham PENS treatment (needles only). The crossover study design mandated a 1-week recovery (washout) period after completing the initial series of treatments. The protocol also stipulated 30 min of active or sham electrical stimulation treatment three times a week for 3 consecutive weeks. Each treatment session required placement of 10 32-gauge (0.2-mm) stainless steel acupuncture-like needle probes (ITO, Tokyo, Japan) to a depth of 1–3 cm into the soft tissue and/or muscle in the leg and foot bilaterally as illustrated in Fig. 1*A–C*. The 10 needle probes were connected to five bipolar leads from an investigational (i.e., not approved by the U.S. Food and Drug Administration) low-output electrical generator. These probes were stimulated at alternating frequencies of 15 and 30 Hz every 3 s or at 0 Hz for the active and sham treatments, respectively. The generator produced a maximum of 25 m ampheres electrical stimulation with a biphasic square-wave pattern and a pulse width of 0.5 ms in a continuous duty cycle. The intensity of the electrical stimulation was adjusted to the highest tolerable level without producing muscle contractions.

Before initiating either treatment modality, patients completed a baseline psychological assessment. Both the Physical Component Summary (PCS) and the Mental Component Summary (MCS) scores of the MOS 36-Item Short-Form Health Survey (SF-36) (14) were determined 24 h before the first treatment and were repeated 48 h after completing the 3-week treatment session with each modality. The Beck Depression Inventory (BDI) (15) and the Profile of Mood Status (POMS) (16) were also administered at these same three time points. As a result of questionnaire completion problems, only 46 BDI and 44 POMS tests were analyzed. For all other measures, data from all 50 subjects were analyzed. Before the first treatment session, all patients were asked to record their baseline levels of pain, physical activity, and quality of sleep by using three separate 10-cm visual analog scales (VASs), where 0 = minimal (lowest) and 10 = maximal (highest). In addition, each patient was asked to record the number of doses of oral analgesic medication taken each day. Repeat

VAS assessments of pain, activity, and sleep were performed before each treatment session, after each week of treatment, and again at the end of the 3-week treatment period with each modality. Daily oral analgesic requirements were recorded in the patient's diary. At 24 h after the final treatment session, each patient completed a questionnaire assessing the relative effectiveness of the two treatment modalities.

Statistical analysis

The NCSS software package (Version 6.0.1 for Windows, Kaysville, UT) was used for all statistical analyses. An a priori power analysis with $\alpha = 0.05$ and $\beta = 0.10$ (power = 90%) determined that a group size of 40 should be adequate to demonstrate a 25% change in the VAS pain scores between the two treatment modalities. The changes in the VAS scores and oral analgesic medications over time were analyzed by using repeated measures of analyses of variance and Student's *t* test. Analysis of discrete data was performed by using the χ^2 test. Changes and differences in the psychological assessment were analyzed by using *t* tests. Data are means ± SD and percentages, and *P* values <0.05 were considered statistically significant.

RESULTS

The demographic characteristics and treatment effects after the initial 3-week study period are summarized in Table 1. The post-treatment VAS scores for extremity pain, physical activity, and quality of sleep were significantly improved after each week of PENS treatment compared with baseline values ($P < 0.05$), but no significant changes were evident after the sham treatments (Table 1). The overall percentage reduction in pain after the 3-week treatment with active PENS (56 ± 17%) was significantly greater than with sham (14 ± 11%) treatments (Table 2). Similarly, the overall average percentage increases in physical activity and quality of sleep were also significantly higher after active PENS (48 ± 19 and 41 ± 22%, respectively) compared with sham treatments (13 ± 16 and 11 ± 13%, respectively) ($P < 0.05$). Moreover, a cumulative effect of PENS therapy was noted during the course of the 3-week treatment block.

Evaluation of pretreatment SF-36 values suggested that the study population had significantly lower health-related scores compared with the general population. The prestudy scores were 31.2 ± 7.3 and 41 ± 5.8 for the PCS and MCS, respectively, compared with the general population norm of 50. With PENS therapy, the SF-36 scores were significantly improved compared with the prestudy scores for both the PCS (36.8 ± 6.7) and MCS (43.9 ± 5.6) components ($P < 0.01$). Although the sham treatments also produced an improvement in the SF-36 regarding both PCS (32.4 ± 7.5) and MCS (42 ± 5.5) scores ($P < 0.05$), the effect was significantly less than with active PENS therapy ($P < 0.05$).

Analysis of the pretreatment BDI scores indicated that the study population had a mean depression level of 30.2 ± 11.6, which reflects a severe level of depression. The post-PENS treatment BDI scores revealed a significant improvement in the level of depression (8.1 ± 4.6) relative to the pretreatment score ($P < 0.01$). Although the post-sham treatment BDI score was also significantly decreased compared with the prestudy baseline value (20.7 ± 8.2), this level is still in the moderately depressed range. Finally, a comparative analysis revealed that the decrease in the BDI scores was significantly greater after PENS versus sham treatments ($P < 001$).

The overall results of the POMS evaluation are summarized in Table 3. A multivariate analysis of variance revealed a significant multivariate effect (Hotelling's T^2 revealed $P < 0.01$) that justified univariate analyses of the individual POMS measures. These *t* tests revealed that, relative to pretreatment values, the postactive and post-sham PENS treatments displayed significant improvement on all POMS measures except for the vigor activity measure. More importantly, the postactive PENS treatment was associated with greater decreases on all POMS measures relative to the post-sham treatment ($P < 0.05$).

In addition to its salutary analgesic effects, active PENS treatments significantly

Table 1—*Demographic characteristics and effects of sham and active PENS treatments on VASs for pain, activity, and sleep and on oral nonopioid analgesic intake after each week of the initial 3-week treatment block (before crossover to the second modality)*

	PENS	
	Sham	Active
n	25	25
Age (years)	54 ± 9	56 ± 8
Weight (kg)	70 ± 16	68 ± 19
Duration of diabetes (years)	9 ± 2	10 ± 3
Duration of symptomatic neuropathy (months)	17 ± 6	19 ± 8
Pain score (cm)*		
Baseline	6.4 ± 0.9	6.2 ± 1.0
Week 1	5.9 ± 1.1	3.6 ± 1.2†‡
Week 2	6.1 ± 1.2	3.3 ± 1.1†‡
Week 3	6.3 ± 1.1	2.5 ± 0.9†‡§‖
Activity score (cm)*		
Baseline	5.3 ± 0.9	5.2 ± 1.0
Week 1	5.7 ± 1.0	6.4 ± 0.8†‡
Week 2	5.9 ± 1.1	6.8 ± 0.9†‡
Week 3	6.0 ± 1.1	7.9 ± 1.0†‡§‖
Sleep score (cm)*		
Baseline	6.0 ± 1.5	5.8 ± 1.3
Week 1	6.9 ± 1.2	7.5 ± 0.9†‡
Week 2	6.7 ± 1.3	7.8 ± 0.8†‡
Week 3	6.6 ± 1.3	8.3 ± 0.7†‡§‖
Oral analgesics (pills/day)		
Baseline	3.1 ± 1.1	3.3 ± 1.3
Week 1	2.8 ± 0.9	2.2 ± 0.9†‡
Week 2	2.7 ± 1.0	2.0 ± 0.8†‡
Week 3	2.9 ± 0.8	1.3 ± 0.6†‡§‖

Data are *n* or means ± SD. *VASs (0 = minimal [lowest] to 10 = maximal [highest]); †significantly different from the baseline ($P < 0.05$); ‡significantly different from sham ($P < 0.05$); §significantly different from week 1 ($P < 0.05$); ‖significantly different from week 2 ($P < 0.05$).

Table 2—*Comparative effects of sham versus active PENS treatments after completion of the crossover study*

	PENS	
	Sham	Active
Pain score (cm)		
Baseline	5.2 ± 1.6	6.2 ± 1.3†
Week 1	4.6 ± 1.5	3.8 ± 1.2*
Week 2	4.6 ± 1.4	3.5 ± 1.0*
Week 3	4.8 ± 1.2	2.6 ± 0.9*‡§
Activity score (cm)		
Baseline	5.9 ± 1.3	4.8 ± 1.2†
Week 1	6.4 ± 1.1	6.5± 0.8*
Week 2	6.2 ± 1.3	7.0 ± 1.0*
Week 3	6.3 ± 1.2	7.8 ± 1.1*‡§
Sleep score (cm)		
Baseline	6.8 ± 1.5	5.7 ± 1.3†
Week 1	7.3 ± 1.3	7.5 ± 1.2*
Week 2	7.0 ± 1.1	7.9 ± 1.0*
Week 3	7.1 ± 1.2	8.6 ± 1.0*‡§

Scores are for pain, physical activity, and quality of sleep 24 h before receiving the first treatment (baseline) and at the end of the first, second, and third weeks of each treatment after completion of the crossover study. Data are means ± SD. VASs (0 = minimal [lowest] to 10 = maximal [highest]. *Significantly different from the baseline ($P < 0.05$); †significantly different from sham baseline ($P < 0.05$); ‡significantly different from Week 1 ($P < 0.05$); §significantly different from Week 2 ($P < 0.05$).

decreased the need for daily oral (nonopioid) analgesic medication during each of the 1st, 2nd, and 3rd weeks of treatment ($P < 0.05$), whereas sham treatments produced no significant change in the patients' use of oral analgesic medications (Fig. 2). The overall reduction in the analgesic medication requirement was significantly greater with active (49 ± 19%) than with sham (14 ± 10%) PENS treatments.

Finally, the poststudy evaluation of the two treatment modalities revealed that active PENS was clearly the preferred therapy (92%) for alleviating the pain and numbness in the lower extremities. In addition, 88% of the patients reported an improved sense of well-being after PENS treatment, and 92% of the patients expressed a willingness to "pay extra money" for PENS therapy in the future. No side effects were reported with either therapeutic modality.

CONCLUSIONS —

In this prospective crossover sham-controlled study, PENS provided highly effective short-term pain relief for patients with diabetic peripheral neuropathy. The beneficial effects of the active versus sham PENS treatments were remarkably similar before and after the crossover treatments were performed. However, a carry-over effect was evident from the prior PENS therapy, despite the 1-week recovery (washout) period, as evidenced by the lower overall baseline pain scores in the sham group (Table 2). These findings support earlier publications that described the beneficial effects of electroanalgesic therapy in diabetes-induced neuropathic symptoms (6–8). In addition, the apparent cumulative benefits of PENS therapy over time suggest that this therapy may have long-term benefits consistent with the experimental findings of Mo et al. (17) involving electroacupuncture and TENS in animals with experimental (drug-induced) diabetes and associated neuropathic changes.

Although the precise mechanism of PENS-induced analgesia is not known at this time, it appears to be related to both neural modulation (18) and an increase in endogenous opioid-like substances (e.g., dynorphins, endorphins, enkephalins) within the central nervous system (19). Interestingly, both Cameron et al. (20) and Mo et al. (17), have reported that peripheral electrical stimulation can normalize the changes in nerve conduction velocity when using an experimental diabetic rat model. Walsh et al. (21) also observed a decrease in nerve conduction latency and mechanical pain threshold when TENS was applied directly over the nerve. In addition, clinical studies have suggested that the use of electrotherapy in diabetic patients produces decreases in mechanical pain threshold, a local vasodilatory effect, and enhanced wound healing (21–24).

Active PENS treatments produced significant pain relief, increased levels of mood and physical activity, and improved quality of sleep compared with the sham treatments during the course of the 3-week treatment period. Improvements in activity level and sleep quality may be secondary to improved pain control with PENS therapy. Interestingly, pain relief appeared to be maximal at the end of the 3rd week of treatment. However, within 1 week of the last PENS treatment session, the pain scores began to return to pretreatment (baseline) levels. These data suggest that the use of PENS will require a maintenance treatment program to achieve a more sustained beneficial effect, which is consistent with the findings of Kumar and Marshall (6), that involved using TENS to treat neuropathic pain. In the future, a randomized crossover study involving PENS and TENS therapies in the management of diabetic neuropathic pain should be performed.

Previous studies involving the use of PENS in patients with chronic pain syndromes showed that alternating low- and high-frequency stimulation for 30–45 min produced the optimal analgesic effect (25,26). Therefore, we chose to use stimulus frequencies of 15 and 30 Hz at 30-min intervals during each of the active PENS treatment sessions. Because the natural course of neuropathic symptoms is highly variable, these data supporting the short-term benefits of PENS therapy must be interpreted with caution. To minimize investigator and patient bias, all assessments were performed by a blinded observer, and the patients, none of whom had ever undergone acupuncture, were told that the needle-only (sham) treatments represented an acupuncture-like therapy. Nevertheless, these preliminary data clearly require validation by a follow-up study that replicates these findings.

Although neuropathic pain is most commonly treated with a combination of antidepressants, opioids, and nonopioid

Table 3—*Pretreatment (baseline) and post-treatment POMS scores for the active and sham PENS treatments after completion of the crossover study*

	Baseline	After sham	After active PENS
Tension-anxiety	54.6 ± 7.4	50.4 ± 7.1	44.1 ± 5.6
Depression-dejection	58.6 ± 9.4	56.1 ± 10.8	47.5 ± 7.2
Anger-hostility	62.9 ± 12.2	59.3 ± 12.1	51.1 ± 9.1
Vigor-activity	53.1 ± 6.1	50.6 ± 7.7	50.9 ± 12.4
Fatigue-inertia	56.1 ± 6.6	51.4 ± 6.8	43.3 ± 7.1*
Confusion-bewilderment	53.5 ± 7.4	50.2 ± 8.3	44.4 ± 6.3*
Total mood disturbance	71.3 ± 32.1	57.8 ± 34.4	29.5 ± 27.6*

Data are means ± SD. *Significantly greater decrease from baseline values after active PENS (vs. sham) treatment ($P < 0.01$).

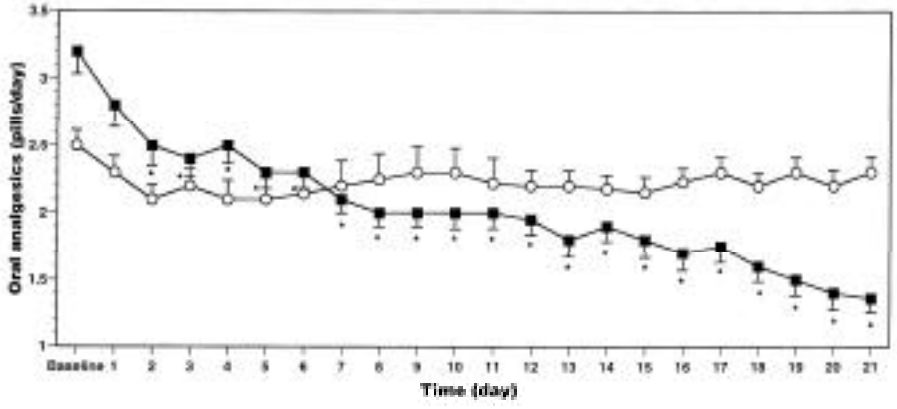

Figure 2—*Effect of active (■) and sham (○) PENS therapies on daily oral analgesic requirements (changes in the daily intake of nonopioid analgesic medication during the 3-week treatment period). Data are means ± SEM. *Data are significantly different from prestudy data (*$P < 0.05$*).*

analgesics, gastrointestinal side effects and excessive sedation can be problematic in patients with diabetes (27). Analogous to our earlier findings with PENS in chronic pain conditions (10,13), these data suggest that this form of electroanalgesia can significantly decrease a diabetic patient's daily oral analgesic requirements. The analgesic-sparing effects of PENS may also minimize the side effects of commonly used pharmacological agents.

The improvements in post-treatment SF-36 and mood levels (as assessed by the BDI and POMS questionnaires) suggest that the beneficial effects of PENS may also be related to an antidepressant action. These psychological data further support the clinical utility of PENS as a nonpharmacological treatment modality in this patient population. After completing the crossover study, these patients also reported that PENS produced an improved sense of well-being, and most patients expressed a willingness to pay additional money (out of pocket) to receive PENS therapy in the future. Many of the patients have elected to continue with PENS treatments on a less frequent basis as part of a maintenance therapy program. The need for further treatments to maintain the beneficial effects of PENS therapy is consistent with the findings for other forms of electrotherapy in this patient population (6,7).

The deficiencies of the study design include: *1*) the possibility of patient bias as a result of our inability to perform the study in a double-blind fashion because we could not "blind" the patients regarding the electrical sensation; *2*) the failure to monitor serial blood glucose and glycated hemoglobin levels and nerve conduction velocities; and *3*) the decrease in the beneficial effects of PENS over time will necessitate a maintenance treatment program to achieve a sustained effect. Long-term outcome studies are needed to ascertain the cumulative effects of PENS in this patient population. Comparative studies involving PENS and other forms of electroanalgesic therapy (e.g., TENS, electroacupuncture) and interaction studies involving pharmacological modalities (28) should be performed in the future. Although clearly less invasive than spinal cord stimulation, PENS is more complex than TENS.

In conclusion, PENS therapy produces short-term pain relief; improves mood, functionality, and quality of sleep; and decreases the oral nonopioid analgesic requirements in patients with painful peripheral diabetic neuropathy. However, PENS should be viewed as a supplementary (or complementary) therapy rather than as an alternative to conventional pharmacological therapy.

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