

# Diabetic Peripheral Neuropathy

## Effectiveness of electrotherapy and amitriptyline for symptomatic relief

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

**RESEARCH DESIGN AND METHODS** — Patients ( $n = 26$ ) with peripheral neuropathy were treated with amitriptyline. After 4 weeks, those patients ( $n = 23$ ) who failed to respond to amitriptyline or who only had partial relief were randomized between a sham treatment group (control) or an electrotherapy group. Transcutaneous electrotherapy was given for 12 weeks by a portable unit (H-wave machine) that generated a biphasic exponentially decaying waveform (pulse width 4 ms, 25–35 V,  $\geq 2$  Hz). The degree of pain and discomfort was graded on a scale of 0–5. An analog scale was used to record the overall change in symptoms.

**RESULTS** — Amitriptyline produced some degree of symptomatic relief in 15 (60%) of the 26 patients by the 4th week; pain scores decreased from  $3.8 \pm 0.1$  to  $2.9 \pm 0.2$  ( $P < 0.1$ ) and the overall reduction in pain was  $26 \pm 5\%$  on an analog scale. In the amitriptyline plus sham treatment group ( $n = 9$ ), pain scores declined from  $2.8 \pm 0.3$  to  $1.9 \pm 0.5$  ( $P < 0.03$ ) and the overall reduction in pain was  $55 \pm 12\%$ , suggesting a procedure-related placebo effect. In the group receiving combined electrotherapy and amitriptyline ( $n = 14$ ), symptomatic improvement occurred in 12 (85%) patients. Five (36%) of the patients in this group became asymptomatic. Pain scores declined from  $3.2 \pm 0.2$  to  $1.4 \pm 0.4$  ( $P < 0.01$ ) and the overall reduction in pain was  $66 \pm 10\%$ . The degree of reduction in pain scores and the incremental relief (above the amitriptyline effect) were significantly greater ( $P < 0.03$ ) with electrotherapy as compared with sham treatment. The outcomes indicate a substantial beneficial effect of electrotherapy over and above any placebo influence.

**CONCLUSIONS** — Our clinical observations suggest that transcutaneous electrotherapy is effective in reducing the pain associated with peripheral neuropathy. This form of therapy may be a useful adjunctive modality when it is combined with a pharmacological agent, such as amitriptyline, to augment symptomatic relief.

Peripheral neuropathy is a common complication of diabetes, affecting nearly 1 of every 3 patients with type 2 diabetes and increasing in incidence with the duration of diabetes (1). Advanced neuropathic deficits underlie most foot ulcers and amputations (2). Peripheral neuropathy adversely affects the patient's well-being and functional status and contributes to a great extent to disability and diabetes-related health care costs (3). Unfortunately, diabetic neuropathy remains untreatable

except by palliative measures. For symptomatic relief, various analgesics and tricyclic antidepressants have been tried with variable success (4–6). New drugs (7,8) and nonpharmacological approaches such as electrotherapy (9,10) and acupuncture (11) are being explored.

Prompted by the beneficial effects of electrotherapy in alleviating pain associated with arthritis and rheumatological conditions (12), we evaluated the efficacy of such a therapy in painful peripheral neuropathy

(9). In a placebo-controlled, randomized study, we observed significant amelioration of pain in the patients treated with transcutaneous electrotherapy (9). Because the mechanism by which electrostimulation relieves pain is most likely distinct from that of the pharmacological analgesia, it is conceivable that the combination of these two treatment modalities could be clinically useful. We evaluated the use of electrotherapy combined with amitriptyline.

### RESEARCH DESIGN AND METHODS

#### Study patients

Patients referred for treatment of peripheral neuropathy participated in a study protocol approved by the institutional review board. The study included 26 men and women age 31–70 years with type 2 diabetes, symptoms of painful peripheral neuropathy for  $>2$  months, and clinical signs of neurological deficit involving lower extremities. Excluded from the study were patients who had evidence of vascular insufficiency (claudication, skin discoloration, ulceration), 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), and biochemical evidence of significant renal disease (serum creatinine  $>177$   $\mu\text{mol/l}$ ) or significant liver disease. Patients on corticosteroids, dilantin, or chemotherapeutic agents were also excluded. Participants in previous peripheral neuropathy studies were also excluded.

#### Study design

The study design was a single-blind placebo-controlled randomized two-arm study. All participants were prescribed amitriptyline throughout a 20-week study period and were randomly assigned in a single-blind fashion to either electrotherapy or sham treatment (control group). On the initial visit, a detailed history and physical examination was performed to establish eligibility. The patient's pain was graded (Table 1) and a current perception test (CPT) was performed. Each patient was prescribed amitriptyline, 50 mg at bed-

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**Abbreviations:** CPT, current perception test; TENS, transcutaneous electrical nerve stimulation.

time. After 4 weeks, the neuropathic symptoms were again evaluated and patients who continued to have considerable pain (pain grade >2) entered the electrotherapy phase of the protocol.

Patients assigned to the electrotherapy group received working electrotherapy machines, and patients assigned to the sham treatment group received machines that had inactive output terminals. Each patient was individually instructed by one of the investigators (H.J.M. or M.S.A.) on how to place the electrodes and how to use the machine. The investigator explained to each patient individually that electrical sensations at the electrodes might not be felt because of possible variation in sensory perception thresholds. The treatment process was demonstrated with an assigned machine, thereby providing experience and feeling of the electrodes. The assigned electrotherapy machine was then loaned to the patient for home use. Patients returned after 1 week, and one of the investigators (H.J.M. or M.S.A.) reviewed the treatment technique and proper use of the machine. Electrotherapy was given for 12 weeks. Patients were followed at 4-week intervals, and the last visit was scheduled 4 weeks post-electrotherapy. At each visit, symptoms of peripheral neuropathy were evaluated by an investigator who was blinded for the patient's treatment group assignment.

### Grading of pain

The pain and discomfort level was graded on a scale of 0–5 (Table 1) on the basis of the patient's description of symptoms, paresthesias, intensity and frequency of pain, sleep disturbance due to neuropathic pain, and the functional impediment as described in our previous study (9). Pain was graded on three visits: at the initiation of amitriptyline therapy, at the beginning of electrotherapy, and at the end of electrotherapy. In addition, an analog scale was used to record the overall change in symptoms.

### Current Perception Test

The CPT was performed with a neurometer (13) (Int-Med, New Port Richey, FL) placed at the medial side of the right and left big toes and at the lateral side of both small toes. The manufacturer's suggested protocol was used. Each site was tested at 5, 250, and 2,000 Hz.

### Transcutaneous electrotherapy

Transcutaneous electrotherapy was given by a portable, rechargeable unit, H-wave

**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.                         |

Reproduced from Kumar and Marshall (9).

machine (Electronic Waveform Laboratory, Huntington Beach, CA) that generates a biphasic exponentially decaying waveform with pulse widths of 4 ms,  $\leq 35$  mA,  $\leq 35$  V, and 2–70 Hz. These output parameters are distinct from the other available transcutaneous electrical nerve stimulation (TENS) modalities. The placement of electrodes and other details were as described in our previous report (9).

### Statistical methods

Wilcoxon's rank sum test was used for analyzing changes in pain scores. The percentage of 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 personal computer.

**RESULTS** — A total of 26 patients completed the study protocol. At the initial visit, each patient reported pain and burning sensations in the feet. Physical examination revealed total loss of touch sensation at the toes and plantar aspects in 12 patients. Vibration sense at big toes was lost in 9 patients, and the ankle jerk was absent in 14 patients. On pain grading, 1 patient scored 5, 15 scored 4, and 10 scored 3. The CPT revealed sensory loss to 1 or more electrical frequencies at 1 or more toes tested in all but 2 patients.

### Amitriptyline therapy

Amitriptyline produced symptomatic relief in 15 (60%) of the 26 patients by the 4th week of therapy. Eight patients had no improvement. Three patients could not tolerate amitriptyline, even at a reduced dose

of 25 mg/day, because of drug-induced sedation. With amitriptyline, the pain scores decreased significantly from  $3.8 \pm 0.1$  to  $2.9 \pm 0.2$  ( $P < 0.01$ ), and there was  $26 \pm 5\%$  symptomatic relief on the analog scale. Three amitriptyline responders had pain scores of 0 or 1 at the 4th week of therapy. They were discharged from the study.

### Electrotherapy

Twenty-three patients (including 3 who could not take amitriptyline) were randomized to receive sham treatment or electrotherapy. Pain scores, duration of neuropathic symptoms, and other clinical characteristics were similar in the two groups (Table 2).

**Sham treatment group.** There were nine patients in this group; one of them had discontinued amitriptyline because of side effects. Pain scores improved by 1 grade in 2 patients, by 2 grades in 3 patients (one of them became completely asymptomatic, with the pain score changing from 2 to 0), and no change in 4 patients (44%). The average pain score declined from  $2.8 \pm 0.3$  to  $1.9 \pm 0.5$  (Fig. 1); this  $0.9 \pm 0.3$  grade reduction was statistically significant (Wilcoxon's matched-pair test,  $Z = -2.15$ ,  $P < 0.03$ ), suggesting a procedure-related placebo effect.

**Electrotherapy group.** There were 14 patients in this group. Two of them did not tolerate amitriptyline. Symptomatic improvement occurred in 12 (85%) patients; 11 received the combination of amitriptyline and electrotherapy and 1 received electrotherapy only. Three patients improved by 3 pain grades, 8 by 2 grades, and 1 by 1 grade. Five (36%) of them experienced complete symptomatic relief. The mean pain score (Fig. 1) declined significantly,

Table 2—Clinical data

|   | Treatment groups |                |
|---|------------------|----------------|
|   | Sham therapy     | Electrotherapy |
| <i>n</i>                                  | 9                | 14             |
| Age (years)                               | 58 ± 4           | 59 ± 2         |
| Sex (M/F)                                 | 6/3              | 4/10           |
| BMI (kg/m <sup>2</sup> )                  | 32.4 ± 2.9       | 32.4 ± 1.8     |
| Duration of diabetes (years)              | 7 ± 2            | 8 ± 1          |
| Diabetes treatment: insulin/sulfonylurea  | 4/5              | 9/5            |
| Duration of neuropathic symptoms (months) | 21 ± 5           | 22 ± 6         |
| Average pain grade*                       | 2.8 ± 0.3        | 3.2 ± 0.2      |
| Number of toes with sensory loss (CPT)†   | 2.9 ± 0.4        | 2.4 ± 0.4      |

Data are means ± SEM. \*Measured while receiving amitriptyline therapy; †CPT was performed on four toes.

from 3.2 ± 0.2 to 1.4 ± 0.4 (Wilcoxon's matched-pair test,  $Z = -3.11$ ,  $P < 0.01$ ). The pain score reduction of 1.8 ± 0.3 grade in this group was significantly more than that in the sham treatment group (0.9 ± 0.3,  $P < 0.03$ ), indicating a substantial treatment effect over and above any placebo influence.

Two (15%) patients failed to have any relief with electrotherapy. Both patients had scored 4 on pain grading; 1 of them could not tolerate amitriptyline and the other had no relief with drug therapy. There were no other clinical features to distinguish nonresponders from responders.

Patients were questioned for any change in their overall neuropathic symptoms using an analog scale. At the end of electrotherapy period, the sham treatment patients had 55 ± 12% relief of pain and discomfort, and the electrotherapy patients had 66 ± 10% amelioration of pain and discomfort (Fig. 2). The incremental relief (above the amitriptyline effect) was significantly greater with electrotherapy (47 ± 8% reduction in symptoms) as compared with sham treatment (24 ± 8% reduction,  $P < 0.02$ ).

Patients felt the treatment effect by the 4th week of electrotherapy, and symptomatic relief was sustained during the next 8 weeks. After discontinuation of electrotherapy, there was a tendency for recurrence of symptoms even though amitriptyline therapy was continued.

**Side effects**

No local or systemic side effects were noticed with electrotherapy. There was no discernible improvement or deterioration of neurological signs during the study period.

**Metabolic control**

Patients were free of symptoms of uncontrolled diabetes and had stable body weight

but their glycosylated hemoglobin levels were in the "poor" range (>8%) (14). No attempt was made to modify medical treatment during the study period.

**CONCLUSIONS** — This study extends our previous observations (9) of the beneficial effects of transcutaneous electrotherapy for painful diabetic peripheral neuropathy. Electrotherapy was given by proprietary equipment, H-wave machine, approved for physiotherapy purposes. In our earlier study (9), no pain-relieving medication was used. In contrast, all participants in this study were prescribed amitriptyline, a commonly recommended tricyclic drug that modulates the pain threshold at the hypothalamic level (4); amitriptyline was continued throughout the 20-week observation period. Furthermore, electrotherapy was prolonged from 4 weeks to 12 weeks. Electrotherapy was effective in reducing pain in patients who failed to respond to amitriptyline or who had partial relief only. Combining electrotherapy with amitriptyline augmented symptomatic relief, suggesting that electrotherapy may be a useful adjunctive modality.

The symptomatic response rate was fairly satisfactory. Almost 85% of the patients experienced beneficial effects. A more impressive observation was that about 36% of the patients had become asymptomatic. The effects of combined amitriptyline and electrotherapy appear to be superior to those of a drug (6) or electrotherapy alone (9), where ~17% of the cases became symptom free. On the other hand, the treatment failure rate of ~15% was not different from that reported in various studies (6,9). Because symptoms recurred after discontinuation of electrotherapy, we recommend continuance of

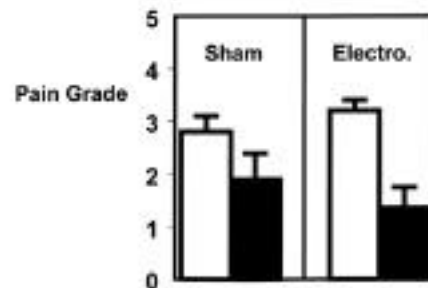


Figure 1—Neuropathic pain grades of the sham treatment (control) and electrotherapy groups. Mean grades at the beginning (□) and at 12 weeks (■) are shown.

treatment in a responder; however, the frequency and duration may be modified (9).

The effectiveness of electrotherapy in pain management has been viewed with some skepticism (12,15,16). There are at least two possible reasons. First, studies often lack a control group (10,12) and any claim of effectiveness becomes suspect. Second, a paucity of convincing scientific explanations for the observed improvement makes it difficult to rationalize this form of treatment. We designed our study to include sham treatment control subjects. It was of interest that the control group reported appreciable symptomatic improvement, indicating a procedure-related placebo effect. The data would appear to support critics who contend that electrotherapy is merely a placebo. However, when we analyzed the outcome of patients receiving active electrotherapy, it was obvious that this group reported profound improvement, which was substantially more than that reported by the sham treatment group. Similar observations were

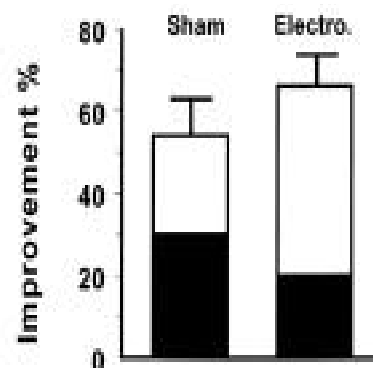


Figure 2—Subjective improvement in pain and discomfort with the combination of amitriptyline and electrotherapy. Shaded areas represent the relief observed with amitriptyline treatment after 4 weeks when the electrotherapy was initiated.

made in our previous study (9). It may be argued that these are subjective data derived from an individual patient's perception. While the estimates of pain and suffering could be considered crude, the fact that each patient's sequential perceptions were analyzed provides reasonable credence to our data.

What is the mechanism of symptomatic relief with electrotherapy? Our clinical study does not provide any direct clue. However, considering that microangiopathic changes, reduced blood flow, nerve oxygen tension (17), and other vascular factors (18) all contribute to the pathogenesis of diabetic neuropathy, it is conceivable that our treatment affected the circulatory status and improved the oxygen tension in peripheral nerves. This possibility stems from the fact that the electrical impulses from electrodes positioned around the knee region produced visible muscular contractions in the thigh and leg muscles. While the treatment was delivered in the knee region, symptomatic improvement occurred at a far distal site—the foot. Studies of the effects of transcutaneous electrotherapy on wound healing also suggest that such treatment could improve tissue circulation (19,20), although the equipment and treatment parameters used were different from those used in our study. In addition, some of the electrotherapy-induced neurophysiological changes (21–24), such as nerve conduction latency, mechanical pain threshold, nociceptive flexion reflex threshold, and somatosensory evoked potentials, could have contributed to the observed benefits.

In summary, our clinical observations suggest that electrotherapy may be a useful noninvasive, nonpharmacological treatment modality for the management of painful peripheral neuropathy in patients with type 2 diabetes. This form of therapy may be combined with a pharmacological agent to augment symptomatic relief.

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