Original Article

IMPROVEMENT OF SENSORY IMPAIRMENT IN PATIENTS WITH PERIPHERAL NEUROPATHY

J. Joseph Prendergast, MD, Galdina Miranda, MA, and Manuel Sanchez, MA

ABSTRACT

Objective: To report the findings in 27 patients with peripheral neuropathy (21 with lower extremity sensory impairment associated with diabetic peripheral neuropathy and 6 with other causes), who received treatment with monochromatic near-infrared photoenergy (890 nm) delivered by the Anodyne Therapy System (ATS).

Methods: All enrolled patients exhibited abnormal sensory perception (either hyperesthesia or hypoesthesia) based on a qualifying examination with the Neurometer CPT (current perception threshold) (baseline CPT). The patients received 10 ATS treatments (each lasting 40 minutes) during a 2-week period and then underwent CPT retesting to determine the extent of improvement of sensory impairment in myelinated and unmyelinated sensory fibers of the peroneal nerve.

Results: All patients obtained improvement in sensory impairment in comparison with baseline CPT measures, and 16 of the 27 patients achieved normal sensory responses in all nerve fiber subpopulations. Ten patients had been tested previously (initial CPT) and did not exhibit spontaneous improvement in sensory impairment during a mean period of 27 months before baseline CPT. After receiving the ATS treatments, however, this group of patients showed improvement in comparison with both initial CPT results and baseline CPT.

Conclusion: On the basis of the data from this study, the ATS seems to be a safe and effective treatment to improve sensory impairment associated with peripheral neuropathy due to diabetes and other causes. **(Endocr Pract. 2004;10:24-30)**

Abbreviations:
ATS = Anodyne Therapy System; **CPT** = current perception threshold; **DPN** = diabetic peripheral neuropathy; **HbA1c** = hemoglobin A1c; **SD** = standard deviation; **SWM** = Semmes-Weinstein monofilament

Submitted for publication May 7, 2003
Accepted for publication October 1, 2003
From the Endocrine Metabolic Medical Center, Redwood City, California.
Address correspondence and reprint requests to Dr. J. J. Prendergast, Endocrine Metabolic Medical Center, 805 Veterans Boulevard, Suite 100, Redwood City, CA 94063.

INTRODUCTION

Sensory impairment is a common consequence of the nerve damage associated with diabetes and other causes. In patients with diabetes, it is referred to as diabetic peripheral neuropathy (DPN). Sensory impairments associated with DPN often begin as tingling, or a "stocking and glove sensation," and often progress toward pain. At some stage of progression of DPN, patients exhibit diminished sensation to light touch, vibration, and temperature, placing them at high risk for lower extremity ulcers, amputations, and falls. In some patients, symptoms are not appreciated or are ignored, attributing their lifestyle accommodations to aging. Frequently, patients with DPN first present to a clinician with hypersensitive symptoms similar to those in nerve fiber inflammation or neuritis. As the disease state progresses, the symptoms manifest as loss of nerve fiber function or hyposensitivity and sometimes as anesthesia, wherein the nerve fibers are unresponsive to various stimuli (1). Sensory impairments associated with diabetes have been thought to be progressive and irreversible (2) and possibly caused by microvascular dysfunction (3).

A recent study reported temporary reversal of neuropathic symptoms associated with DPN with the use of a near-infrared modality, the Anodyne Therapy System (ATS) (4). That study evaluated sensory deficits with use of graded sizes of Semmes-Weinstein monofilament (SWM) as its primary endpoint. The SWM test is widely used, and the failure to sense the SWM 5.07 is clinically recognized as highly predictive of foot ulceration and lower extremity amputation (5). Sole use of the SWM 5.07 is a gross measure of sensory impairment, and the SWM test is able to measure only diminished sensation (hypoesthesia). The purpose of the current study was to determine whether quantifiable changes in sensory impairment, both hyperesthetic and hypoesthetic, are demonstrable in patients with neuropathy after treatment with the ATS by using the Neurometer CPT (current perception threshold), an established neurodiagnostic tool (1,6,7).

MATERIALS, METHODS, AND PATIENTS

Measurement Apparatus and Protocol

We used the Neurometer CPT sensory nerve conduction threshold (Neurotron, Inc., Baltimore, MD) electrodi-

agnostic examination to obtain objective and quantitative measures of the functional integrity of the peroneal sensory nerve fibers. The Neurometer CPT emits transcutaneous electrical stimuli through a pair of gold-plated electrodes that, when placed over the great toe, quantifies neuroselective CPT of the peroneal nerve fibers. The test site is stimulated with three different sinusoidal frequencies of electrical stimuli. These frequencies—2,000 Hz, 250 Hz, and 5 Hz—evoke a response from different subpopulations of sensory nerve fibers—large myelinated, small myelinated, and small unmyelinated fibers, respectively—which constitute 90% of the sensory nerve fibers.

Neurometer testing is a fully automatic, forced-response test of patient response to randomly generated outputs of electrical stimuli in milliamperes. Because neither the testing professional nor the patient can influence the test outcome, it is a doubled-blind evaluation of sensory nerve function. CPT values are calculated and printed at each of the three sinusoidal frequencies (2,000 Hz, 250 Hz, and 5 Hz) in numerical units. Each numerical unit represents 0.01 mA of output intensity that was necessary to evoke a patient response. For example, a CPT measure of 100 units denotes that a stimulus output intensity of 1.0 mA was needed to evoke a patient response.

The Neuval CPT Evaluation and Database program (CPT software) allows analysis of CPT test data in several ways. First, CPT test results are compared with normative values (Table 1) to determine whether the patients have either abnormally low (hyperesthetic) or abnormally high (hypoesthetic) CPT values in comparison with healthy subjects for each nerve subpopulation. Second, the CPT software calculates a range analysis within each nerve subpopulation, ranging from −2 (moderate hyperesthesia) to +4 (profound hypoesthesia) and with a score of 0 being normal. Severity scoring is as follows: 4 = profound hypoesthesia, indicating no response to the stimulus at a maximal output of 999 mA; 3 = severe hypoesthesia, which indicates a CPT above the healthy normal range and 4 or more standard deviations (SD) above the mean; 2 = moderate hypoesthesia, which indicates a CPT above the healthy normal range and 3 to 4 SD above the mean; 1 = mild hypoesthesia, which indicates a CPT above the healthy normal range and 2 to 3 SD above the mean; and 0 = no detection of abnormality. Third, the CPT software provides a grade severity, ranging from 0 to 12, and an associated commentary classification. A grade severity of 0 indicates that the patient's response shows no abnormal measures in any nerve fiber subpopulation. The maximal level of abnormality is a grade severity of 12, which indicates that all nerve subpopulations are completely hypoesthetic.

We determined CPT values before and after performance of the treatment protocol with the ATS to obtain quantitative measures of sensory nerve responses, which were then clinically analyzed with use of the CPT software. Posttreatment CPT testing was done within 1 hour after the last ATS treatment in 19 patients, but 8 patients were retested between 3 and 96 days after the last ATS treatment.

Treatment Protocol

We used the ATS model 480 (Anodyne Therapy LLC, Tampa, FL) to deliver ATS treatments. The ATS consists of the following: (*1*) a 12-V DC power source, (*2*) a control unit, and (*3*) eight flexible therapy pads, on which are mounted 60 superluminous gallium-aluminum arsenide diodes that are connected to the power source by means of insulated leads. The diodes mounted on the flexible therapy pads emit photoenergy in the near-infrared spectrum (890 nm) that is pulsed 292 times per second, having a duty cycle (time on) of 50%. The power density is 8 mW/cm^2, and the average power per flexible therapy pad is 480 mW.

The flexible therapy pads of the ATS were placed in contact with each patient's skin during the treatment period. Specifically, one therapy pad was placed on the dorsal and one on the plantar aspect of the foot as well as one on the lateral and one on the medial aspect of both lower extremities, immediately above the ankle in each patient. All but one patient (who received only 5 treatments) received a total of 10 treatments delivered during the course of 2 weeks. Each treatment lasted 40 minutes. No adverse symptoms or events were noted in any patient.

Table 1
Normal Values for Current Perception Threshold

Stimulus	Range		Mean	Standard deviation
	Minimum	Maximum		
5 Hz	18	170	78	31.9
250 Hz	44	208	123	38.8
2,000 Hz	179	523	330	79.5

Study Subjects

Patients, recruited from the clinical endocrinology practice of one of us (J.J.P.), who presented with clinical symptoms of peripheral neuropathy, including either hyperesthetic or hypoesthetic symptoms based on CPT testing, were offered treatment. No patient willing to undergo treatment and posttreatment CPT testing during the period from March 2002 through September 2002 was excluded for any reason, regardless of the extent of the sensory impairment, the duration of the condition, or comorbidities. Thus, these data are reported on an intention-to-treat basis. Twenty-seven patients (18 men and 9 women; mean age, 73 years [range, 61 to 89]) agreed to receive treatment and undergo diagnostic testing. Of this group, 21 patients had a diagnosis of DPN, and 6 patients had neuropathy attributable to nondiabetic causes. Three patients were diagnosed with type 1 diabetes, and 18 were diagnosed with type 2 diabetes. The duration of diabetes before treatment was a mean of 16 ± 11 years (range, 1 to 30). Pretreatment routine laboratory testing revealed that none of the six nondiabetic patients had hyperglycemia. Of this group, three patients (ages 74, 75, and 83 years) had hypothyroidism, one patient (age 79 years) had hypoglycemia, one (age 74 years) had peripheral vascular disease, and one (age 74 years) had hypercholesterolemia. All had normal blood pressure, and homocysteine levels were less than 9.0 μmol/L in all six patients.

Recent hemoglobin A1c (HbA1c) data, available for 17 of the 21 patients with diabetes, indicated that these patients exhibited reasonably good glycemic control (mean ± SD, 6.9 ± 1.4%); no patient was excluded on the basis of available HbA1c. During the treatment protocol, there was no change in medications taken by any of the patients.

Of interest, 10 patients (9 with diabetes and 1 without diabetes) had undergone prior CPT examination and CPT software analysis (initial CPT), a mean of 27 months before the baseline CPT conducted at the beginning of this study. Comparison of the sensory impairment findings in these 10 patients (the "conventional management group") between the initial CPT and baseline CPT, during which they received standard care for their condition, was separately analyzed to determine any changes in their sensory impairment both before and after ATS treatment.

Statistical Analysis

Data were analyzed by paired and unpaired *t* test where appropriate and by repeated measures with a null hypothesis that treatments would have no effect on either (*1*) numerical CPT measure of nerve fiber response to stimulation at 2,000 Hz, 250 Hz, or 5 Hz or (*2*) clinical analysis with use of the CPT software. *P* values of less than 0.05 were considered significant. The statistical package used was StatView (Abacus Concepts, Inc., Berkeley, CA). Values are reported as means ± 1 SD.

RESULTS

Conventional Management Group

The 10 patients in the conventional management group (7 men and 3 woman) had a mean age of 74 ± 6 years at baseline testing. Between initial CPT and baseline CPT, the patients in this group remained reasonably constant in the severity of their neuropathic symptoms in all nerve fiber groups tested, as reflected in the CPT numerical scores (2,000 Hz = 615 ± 279 to 683 ± 286; 250 Hz = 290 ± 291 to 286 ± 278; and 5 Hz = 224 ± 290 to 152 ± 217; no statistically significant changes). Grade severity, already elevated at initial CPT, had also increased modestly but not significantly (6.3 ± 4.6 to 8.3 ± 2.1; $P = 0.16$) when measured again at baseline CPT. No patient whose grade severity was "abnormal" at initial CPT had improvement to "normal" at baseline CPT, an indication that these patients had not experienced a spontaneous or medical treatment-related improvement in sensory impairment with standard care. Consistent with reported pathologic features of this condition, individual sensory impairment remained the same or worsened.

After ATS treatment, this conventional management group demonstrated significant improvement ($P<0.05$) in sensory impairment based on CPT numerical scores at 2,000 Hz (476 ± 120) compared with baseline CPT (683 ± 286). Changes in mean CPT values at 250 Hz and 5 Hz after ATS treatment, however, were not statistically significant ($P = 0.14$ and $P = 0.4224$, respectively).

Each of the 10 patients presented at baseline CPT with an abnormal grade severity (maximum, 12.0). After ATS treatment, grade severity determined with the CPT software decreased significantly to 2.7 ± 3.9 in comparison with initial CPT (6.3 ± 4.6) and with baseline CPT (8.3 ± 2.1) ($P<0.03$ and $P<0.002$, respectively). The mean reduction in grade severity from initial CPT to posttreatment CPT was 3.5 grade severity points ($P<0.03$), a 56% reduction. After treatment, 6 of the 10 patients (60%) in the conventional management group attained a grade severity score of 0, indicating no abnormalities in any sensory nerve fiber subpopulation. Associated commentary classification ranged from very mild hyperesthetic to profound sensory loss; nonetheless, 8 of the 10 patients (80%) showed improvement with ATS treatment.

In a comparison of posttreatment CPT with baseline CPT, 9 of the 10 patients (90%) demonstrated an improvement in grade severity and thus an improvement in sensory impairment after treatment. The mean reduction in grade severity from baseline CPT to posttreatment CPT in these 10 patients was 5.6 ($P<0.002$), a 67% improvement.

Range analysis (maximum, 4.0) after treatment (2,000 Hz = 0.7 ± 0.9; 250 Hz = 0.7 ± 1.2; and 5 Hz = 0.0 ± 0.0) was decreased when compared with initial CPT (2,000 Hz = 1.8 ± 1.5; 250 Hz = 1.3 ± 1.5; and 5 Hz = 1.1 ± 1.5) and baseline CPT (2,000 Hz = 2.0 ± 1.7; 250 Hz = 1.7 ± 1.3;

and 5 Hz = 0.3 ± 1.0). A statistically significant decrease, however, was apparent only between baseline CPT and after treatment at 2,000 Hz ($P<0.03$).

Full Patient Cohort

In the overall study group of 27 patients, the CPT numerical scores for 2,000 Hz, 250 Hz, and 5 Hz were abnormal at baseline CPT (Fig. 1). Specifically, mean scores were 657 ± 297, 324 ± 289, and 193 ± 251, respectively, which were higher than the maximal normal scores (shown in Table 1). After treatment, CPT scores decreased significantly at 2,000 Hz to 481 ± 195 ($P<0.001$) and at 250 Hz to 221 ± 213 ($P<0.02$) but not at 5 Hz (153 ± 246; $P<0.423$). The 5-Hz scores varied substantially both before (range, 9 to 999) and after (range, 13 to 999) treatment.

The CPT numerical scores assessed at 2,000 Hz were within normal ranges (see Table 1) in only 5 of the 27 patients at baseline (Fig. 2). After treatment, 20 of the 27 patients exhibited a normal sensory response to stimuli at 2,000 Hz. The CPT numerical scores were within normal ranges in only 10 of the 27 patients when tested with 250 Hz at baseline, but the number increased to 19 of the 27 patients after ATS treatment. Finally, 16 of the 27 patients exhibited responses within normal ranges to 5 Hz at baseline, and this number increased to 24 of the 27 patients after treatment. Of the 27 patients, 26 (96%) experienced a reduction in overall grade severity of sensory impairment, the mean (Fig. 3) decreasing from 8.3 ± 2.1 at baseline to 3.2 ± 4.2 after ATS treatment ($P<0.0001$)—a 61% improvement. After ATS treatment, 16 of the 27 patients (59%) had a grade severity of 0, indicating normal sensory responses in all nerve fiber subpopulations.

Posttreatment range analysis (2,000 Hz = 0.59 ± 1.18; 250 Hz = 0.55 ± 1.08; and 5 Hz = 0.42 ± 1.20) was substantially less than at baseline CPT (2,000 Hz = 2.08 ± 1.57; 250 Hz = 1.29 ± 1.29; and 5 Hz = 0.92 ± 1.20). These decreases were statistically significant at 2,000 Hz ($P<0.001$) and at 250 Hz ($P<0.002$) but not at 5 Hz.

DISCUSSION

The effect of ATS treatments to improve sensory perception, supported by the data from this study, is extraordinary in light of the marginal success of current medical or pharmacologic interventions in reducing sensory impairment, particularly that associated with DPN. By a comparison of baseline CPT with posttreatment CPT, these data offer quantifiable objective evidence that all sensory nerve fiber subpopulations had improved function, regardless of whether the nerve fiber originally was hyperesthetic or hypoesthetic.

Although ATS treatments resulted in improvements in sensory perception of stimuli at 2,000 Hz, 250 Hz, and 5 Hz, the changes were statistically significant only at 2,000 Hz and 250 Hz. Range analysis on these patients suggests that large and small myelinated nerves may have been affected to a greater extent than small unmyelinated nerves, inasmuch as the nerve fiber response to 5 Hz was less impaired than were responses to 2,000 Hz and 250 Hz at baseline CPT. Small nerve fiber dysfunction has been reported more often than large fiber dysfunction in DPN (8,9). One possible explanation for this result is that CPT values for the 5-Hz frequency have greater variability than the other frequencies, which is supported by these data. As a result, a larger number of patients would have to be examined at this frequency to obtain a statistically significant result. These data also seem to support recently published findings in more than 2,000 patients that indicate that response to a stimulus at 5 Hz may not be predictive of hypersensitivity and early neuropathy among those with diabetes (10).

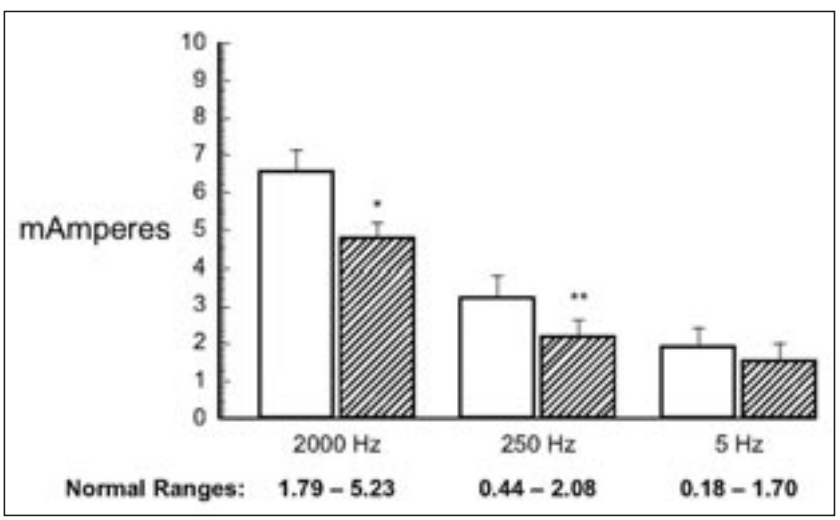

Fig. 1. Effect of treatment with Anodyne Therapy System on current perception threshold scores in milliamperes (means ± standard errors). Baseline (*open bars*) and after treatment (*hatched bars*). Normal ranges for each current are shown at bottom. * = $P<0.001$ versus baseline; ** = $P<0.02$ versus baseline.

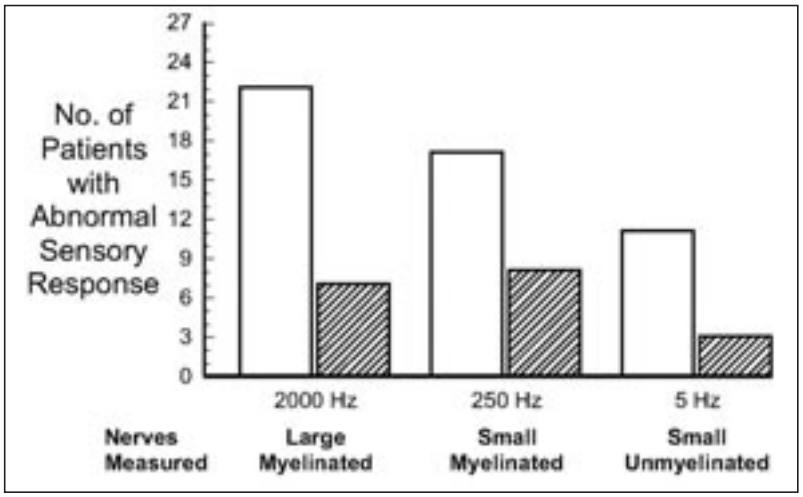

Fig. 2. Number of patients with abnormal sensory response to current perception threshold testing before treatment (baseline; *open bars*) and after treatment (*hatched bars*) with Anodyne Therapy System.

Among the patients with diabetes, these results seemed unrelated to changes in blood glucose control because HbA1c levels before treatment were, for the most part, well controlled. Additionally, because HbA1c tests the average glucose levels for the prior 3 months, no change would be expected within the 2- to 3-week treatment protocol that would account for the sensory improvement that was observed.

No correlation was found between outcome of ATS treatment and either the duration of the diabetes or the type of diabetes; this result suggests that the duration of sensory impairment and the type of diabetes are not predictive of responses to treatment. Review of the data does suggest that those patients with the highest level of impairment (in the sense of having one or more nerve fibers that were completely hypoesthetic) might expect less profound improvement than those who exhibited no nerve fibers that had reached the completely hypoesthetic state. Moreover, the improvement in sensory perception was also observed in patients without diabetes; therefore, the cause of the neuropathic impairment may be irrelevant to the effectiveness of this treatment protocol.

Because medications that might have been considered an additional variable in the current study were not changed during the treatment protocol, the likelihood that a unique medication affected these results is minimal. Inclusion criteria were extremely broad and were based solely on the existence of sensory impairment and willingness of patients to undergo treatment and diagnostic evaluation. Indeed, the level of sensory impairment of the patients at baseline CPT was extremely broad, ranging from anesthetic hypoesthetic to very mild hyperesthetic. Thus, bias in terms of patient selection was minimized. CPT testing is a double-blind procedure in its evaluation of nerve fiber impairment; hence, investigator or patient bias can be ruled out as contributing to these results. Because all patients received actual treatment with the ATS, the potential for a placebo effect cannot be completely discounted. In the medical literature, however, no evidence suggests that DPN spontaneously reverses. This hypothesis is fully supported by these data, in that none of the patients in the conventional management group exhibited spontaneous reversal of the sensory impairment during a mean period of 27 months of medical management of their condition.

A growing body of evidence suggests that DPN may be related, in part, to endothelial dysfunction and an impaired microcirculation to the peripheral nerves (11-14). Clearly, one important consequence of the progressive vascular disease that characterizes patients with diabetes is a reduction in capillary blood flow to the tissues of the feet (15). Part of this reduction is due to the formation of arteriovenous shunts that carry arterial blood to the low-pressure venous circulation rather than into the capillaries. Recently, several studies demonstrated that a circulation-induced increase in oxygenation and nutrition both promotes new nerve growth and, in existing nerves, reestablishes nerve membrane potential that has been altered by hypoxic conditions associated with poor blood flow in patients with diabetes (16,17). Similar acute and sustained increases in local blood flow have been achieved by using a single diode emitting photoenergy in the near-infrared spectrum in a rat model (18). Because enhanced circulation is produced by some near-infrared devices as well as the ATS system, a microcirculatory increase seems to be the most plausible mechanism of action with respect to improvement in sensory perception noted in this study, although we have not directly evaluated this hypothesis.

It is important to consider the validity of CPT analysis, the endpoint used in this study. CPT was chosen to measure changes in sensory impairment in this study for several reasons, including the following factors: (*1*) painless, noninvasive, ease of use; (*2*) double-blinding of test results to evoked stimuli; (*3*) high sensitivity (0.001 mA);

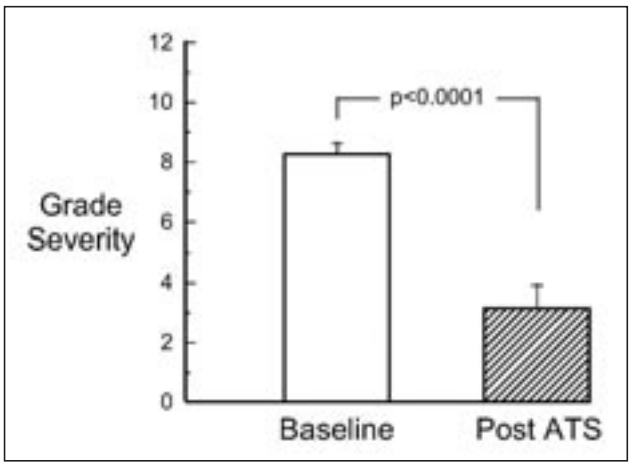

Fig. 3. Grade severity of sensory impairment after treatment with Anodyne Therapy System (*ATS*) (*hatched bar*) in comparison with baseline (*open bar*) in 27 patients with peripheral neuropathy.

(*4*) ability to measure response of 90% of the nerve fibers (including large myelinated, small myelinated, and small unmyelinated fibers, which might be selectively affected by neuropathic symptoms); (*5*) existence of normative values; (*6*) availability of CPT software analysis of severity grades of impairment; (*7*) reports of both hyperesthetic and hypoesthetic nerve fiber function; (*8*) irrelevance of skin thickness, edema, or ambient or skin temperatures to the test results; (*9*) ability of nerves to serve as their own controls; and (*10*) acceptance of CPT analysis by a wide variety of clinicians, including the American Association of Clinical Endocrinologists. Additionally, CPT analysis had been used as a primary endpoint in at least 15 previously published clinical studies that have examined nerve function. As is the case with other methods of testing, CPT is subject to some limitations. To our knowledge, the ability of CPT to measure functional abnormalities of selective nerve fibers has not been validated by pathologic examination. Additionally, no correlating data between sensory impairment as measured by CPT and clinical endpoints of neuropathic foot ulceration and amputation are currently available. Insensitivity to the SWM 5.07 has been studied extensively and is widely accepted as having a strong correlation with risk of neuropathic ulceration and amputation (19). In addition, at least one report has described a correlation between an abnormal response to the biothesiometer and an increased risk of neuropathic foot ulceration (20).

In view of the high correlation between sensory impairment associated with peripheral neuropathy, particularly DPN, and lower extremity ulcers, amputations, and falls (21,22), effective treatment options for this condition are a priority of the research community. Thus far, these efforts have yielded suboptimal results. Accordingly, a widely held belief in mainstream medicine is that the sensory impairment associated with DPN remains irreversible and progressive. Excellent ("tight") glucose control is medically accepted as a method to delay the onset and progression of DPN. Additionally, current standards of care include patient education, periodic foot examinations, and special diabetic footwear to reduce the incidence of foot wounds and amputations, which are highly correlated with DPN.

The only report of significant improvement in sensory impairment associated with DPN is based on a surgical intervention known as peripheral nerve decompression, wherein the four medial ankle tunnels related to the tibial nerve and its medial, lateral, plantar, and calcaneal branches are decompressed (23). Interestingly, patient follow-up postoperatively indicates a substantially reduced incidence of neuropathic foot ulcers and amputations, which are objectives of the US Surgeon General in "Healthy People 2010" (24).

CONCLUSION

The current data strongly suggest that ATS treatments, delivered in the manner described, significantly improve sensory impairment associated with peripheral neuropathy, at least temporarily. These results were consistent among patients of both sexes and various ages, irrespective of the cause of the sensory impairment or the duration of the diabetes. Therefore, these findings may be generalizable to the patient population at large. Importantly, sensory impairment associated with DPN, at least as measured by insensitivity to the SWM 5.07, is strongly correlated with the occurrence of neuropathic foot ulcers and amputations. On the basis of data published by Dellon (25), significant improvements in sensory impairment associated with DPN achieved by peripheral nerve decompression reduce the incidence of neuropathic foot ulcers and amputations. By inference, improvements in sensory impairment associated with DPN after treatment with ATS, because they appear to be as significant as those with surgical decompression, may likely have the same effect on the incidence of ulcers and amputations, if the observed clinical effect is durable. The durability of ATS treatments was not evaluated as part of our current study. We plan to reevaluate this group of patients with CPT testing to determine the durability of clinical effect observed both with ongoing treatments and after cessation of treatment.

ACKNOWLEDGMENT

We acknowledge the assistance of Lynn Camacho, RN, BSN, in gathering the data reported in this study and Thomas Burke, PhD, who furnished the StatView statistical package for analysis of these data. This study was partially funded by a grant from the MedAssist Group.

REFERENCES

1. **Oishi M, Mochizuki Y, Suzuki Y, et al.** Current perception threshold and sympathetic skin response in diabetic and alcoholic polyneuropathies. *Intern Med.* 2002;41:819-822.

2. **Sima AA, Laudadio C.** Design of controlled clinical trials for diabetic polyneuropathy. *Semin Neurol.* 1996;16:187-191.
3. **Cameron NE, Eaton SE, Cotter MA, Tesfaye S.** Vascular factors and metabolic interactions in the pathogenesis of diabetic neuropathy. *Diabetologia.* 2001;44: 1973-1988.
4. **Kochman AB, Carnegie DH, Burke TJ.** Symptomatic reversal of peripheral neuropathy in patients with diabetes. *J Am Podiatr Med Assoc.* 2002;92:125-130.
5. **Frykberg RG, Lavery LA, Pham H, Harvey C, Harkless L, Veves A.** Role of neuropathy and high foot pressures in diabetic foot ulceration. *Diabetes Care.* 1998; 21:1714-1719.
6. **Olmos PR, Cataland S, O'Dorisio TM, Casey CA, Smead WL, Simon SR.** The Semmes-Weinstein monofilament as a potential predictor of foot ulceration in patients with noninsulin-dependent diabetes. *Am J Med Sci.* 1995;309:76-82.
7. **Jiang YD, Chuang LM, Wu HP, Tai TY, Lin BJ.** Role of an outpatient clinic in screening chronic complications of diabetes: a model for diabetes managed care. *J Formos Med Assoc.* 1998;97:521-527.
8. **Mattingly GE, Fischer VW.** Peripheral neuropathy following prolonged exposure to streptozotocin-induced diabetes in rats: a teased nerve fiber study. *Acta Neuropathol (Berl).* 1983;59:133-138.
9. **Jensen TS, Bach FW, Kastrup J, Dejgaard A, Brennan J.** Vibratory and thermal thresholds in diabetics with and without clinical neuropathy [erratum in *Acta Neurol Scand.* 1992;85:159-160]. *Acta Neurol Scand.* 1991;84:326-333.
10. **Takekuma K, Ando F, Niino N, Shimokata H.** Prevalence of hyperesthesia detected by current perception threshold test in subjects with glucose metabolic impairments in a community. *Intern Med.* 2002;41:1124-1129.
11. **Stevens MJ, Feldman EL, Greene DA.** The aetiology of diabetic neuropathy: the combined roles of metabolic and vascular defects. *Diabet Med.* 1995;12:566-579.
12. **Cameron NE, Cotter MA.** Metabolic and vascular factors in the pathogenesis of diabetic neuropathy. *Diabetes.* 1997;46(Suppl 2):S31-S37.
13. **Pham HT, Economides PA, Veves A.** The role of endothelial function on the foot: microcirculation and wound healing in patients with diabetes. *Clin Podiatr Med Surg.* 1998;15:85-93.
14. **Veves A, Akbari CM, Primavera J, et al.** Endothelial dysfunction and the expression of endothelial nitric oxide synthetase in diabetic neuropathy, vascular disease, and foot ulceration. *Diabetes.* 1998;47:457-463.
15. **Arora S, Smakowski P, Frykberg RG, et al.** Differences in foot and forearm skin microcirculation in diabetic patients with and without neuropathy. *Diabetes Care.* 1998;21:1339-1344.
16. **Veves A, King GL.** Can VEGF reverse diabetic neuropathy in human subjects? *J Clin Invest.* 2001;107:1215-1218.
17. **Aszmann OC, Kress KM, Dellon AL.** Results of decompression of peripheral nerves in diabetics: a prospective, blinded study. *Plast Reconstr Surg.* 2000;106:816-822.
18. **Maegawa Y, Itoh T, Hosokawa T, Yaegashi K, Nishi M.** Effects of near-infrared low-level laser irradiation on microcirculation. *Lasers Surg Med.* 2000;27:427-437.
19. **Mayfield JA, Sugarman JR.** Use of the Semmes-Weinstein monofilament and other threshold tests for preventing foot ulceration and amputations in persons with diabetes. *J Fam Pract.* 2000;49(11 Suppl):S17-S27.
20. **Young MJ, Breddy JL, Veves A, Boulton AJ.** The prediction of neuropathic foot ulceration using vibration perception thresholds: a prospective study. *Diabetes Care.* 1994;17:557-560.
21. **Boyko EJ, Ahroni JH, Stensel V, Forsberg RC, Davignon DR, Smith DG.** A prospective study of risk factors for diabetic foot ulcer: the Seattle Diabetic Foot Study. *Diabetes Care.* 1999;22:1036-1042.
22. **Conner-Kerr T, Templeton MS.** Chronic fall risk among aged individuals with type 2 diabetes. *Ostomy Wound Manage.* 2002;48:28-34, 35.
23. **Barrett SL.** Restoring sensation in diabetic patients. *Podiatry Today.* 2002;15:38-44.
24. Healthy People 2010. Available at http://www.healthypeople.gov/publications/. Accessed February 12, 2004.
25. **Dellon AL.** Preventing foot ulceration and amputation by decompressing peripheral nerves in patients with diabetic neuropathy. *Ostomy Wound Manage.* 2002;48:36-45.