

Clinical trial

Transcutaneous electrical nerve stimulation for chronic post-herpetic neuralgia

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Introduction

Treatment of postherpetic neuralgia (PHN) remains a challenging problem for clinicians. Herpes zoster is a relatively common disease with an incidence of 5 per 1000 patients per year. Involvement of the ophthalmic branch of the trigeminal nerve occurs in about 20% of cases.¹ The typical clinical presentation of ophthalmic zoster is blisters and inflammation of the skin supplied by the first division of the trigeminal nerve. If the pain and inflammation remains in the skin after one month with persisting neuropathic pain, it is termed chronic PHN.

The risk of developing PHN is highest with increasing age and presents a major public health issue. Many

Abstract

Postherpetic neuralgia remains a therapeutic challenge for the clinician. Many modalities have been utilized with limited success. In this pilot randomized study of patients who were refractory to previous medicinal treatment, the patients were treated with transcutaneous nerve stimulation with a biofeedback capability. After every two treatments with the sham and true device, the patients were required to fill out a standard neuropathic pain scale score. The patients were allowed to select the other device after three consecutive treatments if they felt an inadequate decrease in their pain. The true device was chosen over the sham device by all patients. The majority of these patients treated by the true device reported a statistically significant decrease in pain scores ($P < 0.001$). Further investigation of this Food and Drug Administration, class 2 accepted, electronic device for relief of pain is warranted for patients with a history of recalcitrant postherpetic neuralgia.

treatment modalities have been considered with limited success. The different medicinal treatments include the off-label use of antidepressants, opioids, anti-epileptics, and topical anesthesia.² Side effects from medical treatment include nausea, sedation, postural hypotension, dizziness, and somnolence. Constipation and sedation from opioids make these drugs poorly tolerated in the elderly. Topical lidocaine patches have been utilized by some physicians to lessen the chronic painful stimuli on the skin.³

Biofeedback is defined by the National Library of Medicine, MEDLINE database, as a process that utilizes instrumentation to give a person immediate continuous signals of changes in his/her body. Biofeedback is a well-accepted therapeutic modality. Electronic devices are

often utilized in biofeedback therapy. The development of computer instrumentation allows a cybernetic loop between the body and the device. The body's electronics can be measured as a response to a signal sent from the instrument, and then the instrument can send back a signal designed to modify the body's abnormal signal. The resulting response signal can then be measured, and a new modifying signal returned with a continuous dialogue being established. Therefore, with modern biofeedback, the body's abnormal electronics can be modified. A team of physicians and scientists at Sochi University in Russia, led by Alexander Revenko, MD, a neurologist, and Alexander Karasev, an electronics expert, developed in the late 1970s, a computerized method of the treatment biofeedback that was compact, efficient, and non-invasive.⁴⁻⁶ Modern modification of these self-controlled electronic neuroadaptive regulation (SCENAR) devices, such as the Tennant Biomodulator (TBM), have been granted a Food and Drug Administration class II designation. At no time is the patient allowed to endure pain because the practitioner can instantly reduce the stimulus at any report of adverse sensation.

Transcutaneous electrical stimulation (TENS) units have been utilized by placing electronic patches over the affected area and stimulating the skin beneath the patch in an effort to reduce the pain.⁷ Relief is obtained when the unit is activated and is attached to the skin of the involved area with patch electrodes that are connected to the unit. Thus, the use of skin electrode patches would present a mobility problem if they were used for the skin of the face and scalp in the periorbital region. However, the different types of electronic stimulation with handheld devices, which includes biofeedback and metal electrodes, such as the SCENAR and TBM units can be applied directly to the affected skin area. The major difference between SCENAR and TBM devices and the traditional TENS units is that the former devices utilize microamps, not the milliamps utilized by the TENS units. Furthermore, the SCENAR and TBM units utilize square wave versus sine wave technology utilized by TENS units, and the former units stimulate ATP whereas TENS units decrease ATP.

In a previously published case report, all three patients responded well with SCENAR.⁸ In this paper, the treatment effect of this modality is evaluated based on a controlled, randomized, prospective pilot study, comparing the TBM unit with a sham device.

Materials and methods

Patient sample

The study was approved by both Hawaii Pacific Health IRB and the Western Institutional Review Board. Patients were selected based on previously established inadequate or unsuccessful

response to pharmacological agents and other types of treatment such as lidocaine and capsaicin gels. All patients had been previously diagnosed by a health professional with the diagnosis of PHN. Patients were excluded from the study if they were pregnant or had an indwelling electronic device, such as a pacemaker, or were using opioids. All enrolled patients signed an informed consent and were informed about the purpose of the study. They were also informed that they could decide not to take part in the study or that they could withdraw from the study at any time.

Treatments

Twenty patients were randomized to initial treatment by either the TBM device (treatment arm: $n = 10$) or an identical looking sham device (sham treatment arm: $n = 10$). Patients were scheduled to receive an initial three consecutive sessions with either the TBM device or a sham device applied to the affected skin for 15 minutes at 3-7-day intervals. The electronic biofeedback device, the TBM, emits a gentle electronic stimulation, which can be felt by the patient, and this stimulus can be controlled by the investigator to ensure that the stimulus is never intense enough to induce pain. The patient reports the level of intensity of the treatment to the investigator so that the latter can modulate the treatment. The sham device emitted an electrical stimulation of 3 mA, which was felt as a slight electrical sensation. After receiving three treatment sessions, patients could request treatment with the other device if they felt they did not have a sufficient response to the first device. Each patient could receive up to six sessions of active treatment. A standardized neuropathic pain scale score (NPSS) form grading the discomfort, pain deep or superficial, burning, numbness, itching, etc., was completed by the patients to compare the treatment effect. The NPSS was completed by each patient at baseline and after every two treatment sessions and at a follow-up time.

All patients were given a gift certificate worth \$10 at each office visit. All records were kept confidential. The patients received notice that the records could be reviewed by agents of the United States Food and Drug Administration, Hawaii Pacific Health IRB, and the Western Institutional Review Board.

Data analysis

Patients' demographic and baseline NPSS scores were summarized by descriptive statistics: means (standard deviations) for continuous variables, frequencies, and percentages for categorical variables, and compared between the two treatment arms: two-sample *t*-tests for continuous variables and Fisher's exact tests for categorical variables.

As the treatment was switched after three sessions for those patients initially randomized to the sham device and the NPSS scores were collected only every two sessions, we separately calculated changes and percentage changes of

NPSS scores between baseline and NPSS no. 2, and between baseline and NPSS no. 3 for each arm. The change and percentage change of NPSS scores were then compared between the two treatment arms using the two-sample *t*-test. The overall changes and percentage change of NPSS scores during the active treatment period (from baseline to NPSS no. 5 for the TBM device arm; from baseline to NPSS no. 6 for the sham-to-active arm) were compared using two paired sample *t*-tests. For individuals who missed the last visit (*n* = 4), the last observation carried forward approach was taken in the final analysis. As a sensitivity analysis, for the sham-to-active arm, the change and percentage change of NPSS scores were also calculated from NPSS no. 3 (the first NPSS measurement after switching to active treatment) to NPSS no. 6. A responder analysis was also performed.

A responder was designated as an individual who had at least a 15% decrease in the recorded pain score. The proportions of responders for the two treatment arms and the average percentage decline of pain score among responders were also calculated. A two-sided *P*-value of <0.05 was regarded as statistically significant.

Results

Ten patients received initial treatment of the TBM, and 10 patients received initial treatment with the sham device. However, every patient, initially treated by the sham device, chose to be treated by the TBM after three consecutive treatments with the sham device because of inadequate relief of their symptoms with the sham device. These patients, initially treated by the sham device, all received six sessions of active treatment with the TBM for nine consecutive sessions (Fig. 1). The baseline NPSS score

Table 1 Summary of patients' demographic and baseline NPSS scores

	Electronic biofeedback treatment (n = 10)	Sham control (n = 10)	P-value ^a
Age (years): mean (SD)	71.2 (10.4)	72.2 (15.6)	0.87
Female: n (%)	7 (70.0%)	5 (50.0%)	0.33
Ethnicity			
White	5 (50.0%)	4 (40.0%)	0.50
Oriental	5 (50.0%)	6 (60.0%)	
Baseline NPSS score: mean (SD)	64.9 (21.9)	44.2 (18.6)	0.035

NPSS, neuropathic pain scale score.

^aTwo sample *t*-tests for continuous variables and Fisher's exact tests for categorical variables.

was somewhat higher for the treatment arm at baseline (*P* = 0.035). The baseline NPSS pain scores for those patients treated initially by the TBM ranged from 31 to 108 with a mean score of 64.9 (SD 21.9). The NPSS pain score for those treated initially by the sham device ranged from 15 to 66 with a mean score of 44.2 (SD 18.6). No statistically significant differences were observed in age, gender, or ethnicity between the two study arms (Table 1).

From baseline to the second visit (NPSS no. 2), the average percentage reduction of NPSS score was -18.4% for the treatment arm, compared with 1.3%, though not statistically significant. Similar pattern was shown for the comparison from baseline to NPSS no. 3, a reduction of 29.8% for the treatment arm and a reduction of 12.2% for the sham device (Fig. 2).

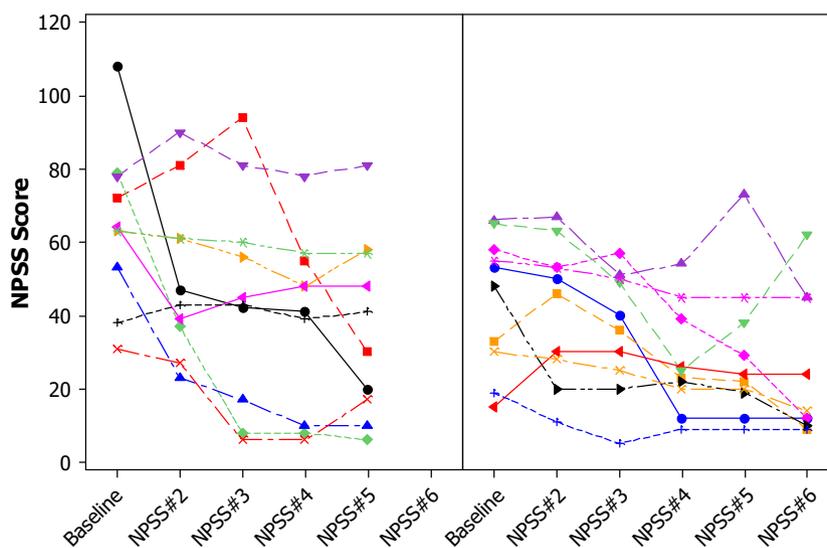


Figure 1 NPSS scores for individual patients in the two study arms (left panel: Tennant Biomodulator; Right panel: sham device to Tennant Biomodulator). NPSS, neuropathic pain scale score

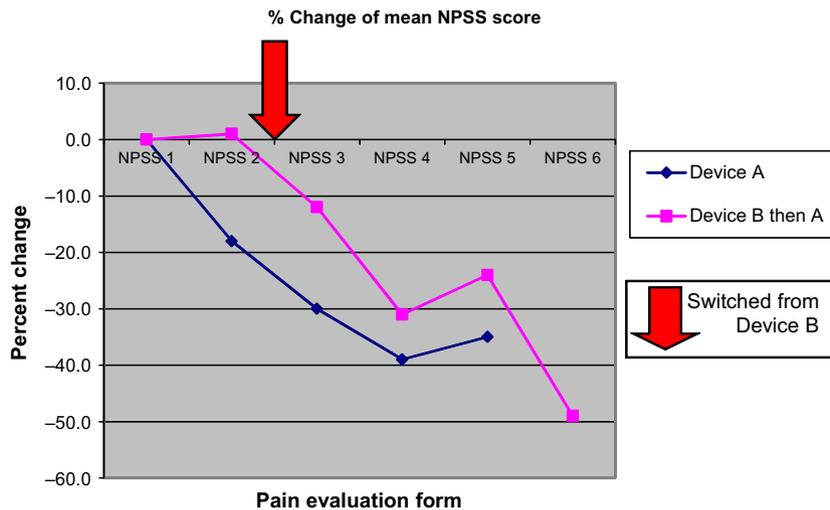


Figure 2 Percentage changes of NPSS score for the two study arms (device A: Tennant Biomodulator; device B: sham device). NPSS, neuropathic pain scale score

During the whole course of treatment, the NPSS decreased by 38.9% for the TBM arm ($P = 0.01$). The average percentage decrease for the arm initially assigned to sham treatment then to the TBM treatment was 40.9% ($P = 0.017$). When combined, the average percentage reduction is 39.9%, with a $P < 0.001$.

A total of 14 patients out of 20 (six originally assigned to the treatment arm and eight initially assigned to the sham device) experienced a decrease in symptoms of 15% or more, with an average reduction of 60.6% among these responders. Also of note was the fact that the intensity of the symptoms expressed by responders, as determined by the mean baseline pain scale number (54.9), was very similar to the initial mean baseline found in the non-responders (53.7).

Discussion

According to the developers of this mode of electronic biofeedback, the pathway for pain relief is said to result from producing regulatory neuropeptides by stimulation of the C-fibers, which comprise 85% of all the nerves of the body. These nerve fibers react most readily to electronic stimulation and are responsible for the production of the neuropeptides and other regulatory peptides. The neuropeptides, in turn, re-establish the body's natural physiological state and are responsible for muscle retraining and relaxation. The body apparently can become accustomed to a stable pathological state, which is caused by illness or injury. In the majority of the patients, as the device was moved over the skin, a prickly sensation was felt, followed by a relaxed state of well-being and a subsequent reduction of pain. A pathophysiologic hypothesis to explain the therapeutic process investigated is, perhaps, best supported by Woo *et al.*⁹ in their animal studies

relating pain to the pH (hence, voltage) of injured tissue. These investigators found that the pH (voltage) was significantly reduced in all tissues associated with pain behavior in the animals studied. When the tissue pH (voltage) returned to normal, pain behaviors were diminished. The inventors of the SCENAR and TBM believe that, when the electronic devices are applied to the injured skin, the voltage in the affected area is increased, thereby providing a therapeutic effect.¹⁰

Overall, 14 of the 20 patients who enrolled in the study reported 18–92% (with a mean of 60.6%) decrease in their symptoms during the study period. Responders, who reported at least a 15% decrease in their mean NPSS score, did not have a significant difference in the intensity of their symptoms before treatment by the electronic device, indicating that their responses were independent of baseline NPSS score. In the sensitivity analysis, for those in the sham-to-active arm, the NPSS no. 3 values (the first NPSS measurement after switching to active treatment) were used, instead of the baseline scores. The pattern for the change of NPSS scores was similar to those when baseline was used.

The limitations of the study were the small sample size and the relatively short follow-up time. As the device utilized in the study is new and the magnitude of its effect is unknown, a priori power was not determined for this pilot study. Due to the exploratory nature of this investigation, 10 patients per group were enrolled. This relatively small number of patients would have limited statistical power in detecting moderate effects. Based on the observed variability and sample size, the study would have 80% power to detect a difference of at least 3.4%. It is possible that more patients might have had a greater therapeutic response if more than six active treatments

had been allowed for the study. During more than five years of use of the TBM, there have been no reports of damage to tissues subjected to the electrical stimulation. However, long-term efficacy results beyond the study period were not available. The timing of the switching of treatment could have been planned better to corresponding to an NPSS measurement, which was measured after every two treatment sessions.

Nevertheless, considering that patients in the present study had failed all other modalities of treatment, the study results suggest that a larger and more definitive clinical trial investigating the transcutaneous electrical nerve stimulation with biofeedback capability for recalcitrant PHN is warranted.

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