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Is the use of Transcutaneous Electrical Nerve Stimulation Both Safe and Effective in Preventing and Treating Postherpetic Neuralgia?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not the use of TENS is safe and effective in preventing and treating PHN.

STUDY DESIGN: Two randomized controlled trials and one retrospective observational study that were published in peer-reviewed journals after 2006 in the English language were reviewed.

DATA SOURCES: Studies were found in the PubMed database and selected based on relevance to the research question and whether they evaluated patient oriented outcomes.

OUTCOMES MEASURED: Prevention of PHN, determined by absence or presence of symptoms, and reduction of pain due to PHN, using a visual analog scale (VAS).

RESULTS: In the first RCT, Barbarisi et al showed that TENS therapy along with pregabalin caused a statistically significant reduction in pain ($p < 0.02$) compared to pregabalin plus placebo device. Stepanovic et al studied the use of TENS in preventing PHN and found that it was significantly better than antiviral treatment ($p = 0.001$). In the retrospective observational study by Kolsek, 0% of patients treated with TENS therapy during acute HZ developed PHN, compared to 28.6% of patients treated with antivirals.

CONCLUSIONS: The use of TENS is both safe and effective in preventing and treating postherpetic neuralgia.

KEYWORDS: transcutaneous electrical nerve stimulation, postherpetic neuralgia

INTRODUCTION

Herpes Zoster (HZ) is a dermatologic condition caused by the reactivation of Varicella Zoster Virus (VZV). It affects approximately 30% of the population, leading to 1 million new cases diagnosed each year¹. The virus remains dormant in dorsal root ganglia following varicella infection, and is believed to reactivate due to reduced cellular immunity associated with immunocompromising states such as stress and increased age². HZ is a clinical diagnosis characterized by a vesicular eruption in a dermatomal distribution, most commonly on the trunk. It is a self-limiting, viral infection lasting up to a few weeks with relatively low incidences of morbidity and mortality. Up to 30% of patients, however, go on to develop post-herpetic neuralgia (PHN)^{3,4,5,6}.

PHN, the most common complication of HZ, is characterized by moderate to severe burning, tingling, and/or hyperesthesia in a dermatomal pattern that lasts months to years, and is occasionally lifelong. The pathophysiology of PHN is not completely understood but is believed to be multifactorial, involving the necrosis, fibrosis, and destruction of afferent nerve fibers to the spinal cord².

Many cases of HZ are treated with antivirals such as acyclovir, valacyclovir, and brivudine. Antiviral therapy has been shown to decrease severity and duration of HZ, but no treatment has been shown to decrease the incidence of PHN^{3,6}. The current first line treatments for PHN are tricyclic antidepressants like amitriptyline, and anti-seizure drugs like gabapentin and pregabalin⁷. Topical agents such as capsaicin cream and lidocaine are also frequently used for more mild cases or patients that do not want systemic therapy. Although the use of opioids for chronic pain is controversial, their efficacy in treating PHN has been shown in a small

number of trials and these agents are still commonly prescribed⁷. Less commonly used methods for refractory pain include glucocorticoid injections and botulinum toxin injections⁷.

The estimated annual health care cost of HZ in the United States is \$1.1 billion⁸. Patients who go on to develop PHN have health care costs that are 4 - 7 times higher than patients who do not develop the complication, costing up to \$11,147 per case⁹. The costs associated with HZ and subsequent PHN can partly be explained by the difficulty in treating neuropathic pain and the need for chronic treatment.

While pharmacologic therapies remain the mainstay of treatment for PHN, these drugs are not always effective in reducing pain and create a challenge for physicians and patients. A non-pharmacologic intervention, transcutaneous electrical nerve stimulation (TENS), has been shown to effectively reduce pain in various acute and chronic conditions^{3,7,10}. TENS is the process by which electrodes placed on the skin produce an electrical current that activates various receptors leading to pain reduction. This application has been shown to provide analgesia both peripherally and centrally by activating opioid, serotonin, muscarinic, and alpha-2 noradrenergic receptors^{3,10}. TENS may be safe and effective in decreasing pain caused by PHN, and possibly in preventing PHN altogether.

With the aging population, the number of patients experiencing HZ is expected to increase, leading to an increased number of patients with PHN. New modalities of pain relief that are both safe and effective will become increasingly important for the PA profession, and providers as a whole, as the number of patients requiring treatment increases.

OBJECTIVE

The objective of this systematic review is to determine whether or not the use of TENS is safe and effective in treating and preventing PHN.

METHODS

This paper evaluates two randomized controlled trials (RCTs) and one retrospective observational study. All three studies compared the use of TENS to a visually-matched placebo device, another traditional treatment modality, or no treatment. The primary outcomes measured were prevention of PHN and reduction of pain. Articles were searched through the PubMed database and selected based on relevance to the research question and whether or not patient-oriented outcomes were used. Keywords used included “transcutaneous electrical nerve stimulation” and “postherpetic neuralgia”. Articles published in English in peer-reviewed journals after 2006 were evaluated. The demographics and specific characteristics of each study are represented in Table 1.

Table 1. Demographics and characteristics of included studies.

<u>Study</u>	<u>Type</u>	<u># Pts</u>	<u>Age in years</u>	<u>Inclusion Criteria</u>	<u>Exclusion Criteria</u>	<u>W/D</u>	<u>Interventions</u>
Barbarisi, 2010	RCT	30	50-80	PHN > 3 mo; locations of pain at cervical, thoracic, lumbar, or sacral root ganglions; VAS score of at least 60 mm	Hypersensitivity to pregabalin; neoplastic, hematologic, hepatic, renal disease; immunodeficiency; occipital, trigeminal HZ; alcohol misuse w/in 2 y; serious psychological condition	0	Pregabalin (300mg and 600mg doses) + TENS therapy
Kolsek, 2012	Retrospective, observational	102	68.9 +/- 16.6	Patients in the electronic medical record of a health center in Slovenia with clinical diagnosis of HZ	Patients that moved away whose later records could not be analyzed; patients that were hospitalized; patients with ocular involvement	0	TENS therapy alone, antiviral therapy alone, TENS + antiviral
Stepanovic, 2016	RCT	222	69 +/- 17.31	Patients in a primary health care office that	Patients with HZ in the ocular or genital region;	0	TENS therapy alone, antiviral

				presented with clinical diagnosis of HZ	immunocompromised patients, patients with chronic diseases; patients with previous neuropathic pain		therapy alone, TENS + antiviral
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OUTCOMES MEASURED

The primary outcomes measured in all three studies were prevention of PHN in patients with HZ and reduction of pain due to PHN. In the study by Barbarisi et al, the primary measure of reduction of pain due to PHN was a change in baseline of a visual analog scale (VAS), “0” being no pain and “100 mm” being worst possible pain. Over the four week experiment patients filled out the VAS for pain at each visit. The authors also measured sleep interference due to pain using a questionnaire that patients completed at each visit. Treatment groups for this study included use of pregabalin (300mg dose) + TENS therapy, pregabalin (600mg dose) + TENS therapy, and two groups with each respective dose of pregabalin + TENS placebo.

In the study by Stepanovic et al, the primary outcome measured was prevention of PHN using TENS therapy. Patients with clinical diagnosis of HZ were treated either with TENS therapy alone, TENS + antiviral therapy, antiviral therapy alone, or no intervention. To determine incidence of PHN, the authors had patients record the presence or absence of the following symptoms over a 6 month period: spontaneous feelings of pain, allodynia, hyperalgesia, and/or paresthesia. The authors also analyzed adverse events between treatment groups.

In the retrospective observational study by Kolsek, the primary outcome measured was prevention of PHN. The author evaluated this outcome using medical records of patients treated for HZ in three outpatient family practices. The treatment groups included TENS therapy alone, antiviral therapy alone, TENS + antiviral therapy, and the control group included patients who

received no therapy or who received any of the therapies but presented to treatment after 72 hours of rash eruption. The author analyzed the use of analgesics among treatment groups, incidence of PHN, and adverse events related to any of the treatment types.

RESULTS

The study by Barbarisi et al was a randomized, placebo-controlled trial that included 30 patients receiving either pregabalin (300 or 600 mg) with TENS therapy or pregabalin (300 mg or 600 mg) with a visually matched TENS placebo device. The statistical analyses used by the authors include mean change in baseline and ANOVA. The patients receiving TENS therapy at either dose of pregabalin showed statistically significant reductions in pain compared to groups receiving respective doses of pregabalin and TENS placebo ($p < 0.02$ for both doses of pregabalin). The results of the study are shown in Table 2. Compliance to drug therapy was not reported, however compliance to TENS therapy was maintained as each patient received therapy on location at the test site.

Table 2. Summary of reduction in pain from baseline from Barbarisi et al.

Treatment	Reduction in Pain from Baseline
600 mg Pregabalin + TENS	40%
600 mg Pregabalin + Placebo	16%
300 mg Pregabalin + TENS	30%
300 mg Pregabalin + Placebo	10%

In the RCT by Stepanovic et al, the authors evaluated the efficacy of TENS therapy, antivirals, TENS therapy + antivirals, or no treatment on the prevention of PHN. To determine the effect of each treatment group on development of PHN, they performed a logistic regression, using presence of PHN and treatment type as the dependent and independent variables, respectively. They reported a statistically significant correlation between the treatment types and PHN ($p = 0.001$); the odds for developing PHN were significantly lower in patients treated with

TENS therapy alone, with a numbers needed to treat (NNT) of 4. The odds of developing PHN using any of the other treatments were not statistically significant. The results of this study are summarized in Table 3. The authors report that the only adverse events of the trial were bacterial skin infections and no serious complications were reported. There was no statistical difference in adverse events between treatment groups ($p = 0.128$). Compliance to drug therapy was not noted, but TENS therapy was given on location at the test site to maintain compliance.

Table 3. Summary of results of logistic regression on prediction of PHN using Odds Ratio (OR) from Stepanovic et al.

Treatment	OR (95% CI)	p	NNT
TENS therapy	0.15 (0.05; 0.47)	0.001	4

The article by Kolsek was a retrospective observational study that examined the medical records of 102 patients treated for HZ in outpatient family practices. A Chi squared test was used to analyze differences in prevalence of PHN between treatment groups. The rate of patients with PHN in the TENS therapy group was 0%, the antiviral group was 28.6%, antiviral + TENS therapy group was 20.8%, and the control group without therapy had a rate of 14.3%. TENS therapy alone had the greatest statistically significant decrease in rate of PHN with $p = 0.024$. Using this data, 4 patients would need to be treated with TENS therapy in order to prevent 1 patient from developing PHN (NNT=4), as compared to traditional antiviral therapy. The results of this study are summarized in Table 4. Adverse events were not reported numerically but the author claimed that the only complication included secondary bacterial infection and the difference between treatment groups was not significant. Compliance to drug therapy was not noted. The author also does not indicate whether TENS therapy was done in the office or at home, and again does not mention compliance.

Table 4. Summary of treatment effects of TENS therapy on preventing PHN from Kolsek study.

Relative Risk Reduction (RRR)	Absolute Risk Reduction (ARR)	NNT
0.4	28.6%	4

DISCUSSION

The treatment of PHN remains a difficult task for providers. Despite vaccination efforts, the incidence of HZ has increased within recent years, likely due to a shift in demographics and the aging population¹. With increases in HZ occurrence, the number of patients developing PHN is going to increase, with older adults having the greatest chance of developing the complication^{3,4,5}.

TENS therapy has been shown to be effective in reducing acute and chronic pain in some studies, yet its use in certain conditions remains controversial and meta analyses on its efficacy continue to have conflicting results^{7,10,11}. In the Barbarisi et al study analyzed in this systematic review, TENS therapy along with standard treatment methods was shown to significantly decrease pain due to PHN compared to standard treatment methods alone. These results may imply that multiple treatment modalities should be used when treating chronic pain. A shortcoming to this study was that the physician administering the TENS device or TENS placebo device was not blinded. The authors explain how blinding would be impossible as the administering physician needed to explain to patients that they would either experience an electrical tingling sensation or nothing at all. The sample size was also very small in this study, with each treatment group containing between 6 and 8 patients. It is also important to note that compliance to drug therapy was not reported in the study.

While antivirals decrease the duration and intensity of HZ, they have no effect on the prevalence of PHN^{3,4}. Vaccination has been shown to decrease incidence of HZ and therefore PHN⁶, but with the aging population the incidence of PHN continues to be up to 30%³. The use

of TENS therapy during HZ has been shown to decrease the incidence of PHN^{4,5,11}. In this systematic review, two studies assessing the efficacy of TENS therapy in reducing PHN were analyzed. In the RCT by Stepanovic et al, TENS therapy alone was shown to have a significant decrease on the incidence of PHN, when compared to antiviral therapy given alone or in addition to TENS therapy. The pathophysiology behind the combination of antivirals and TENS therapy not reducing PHN is unknown and needs to be investigated further, but these findings are consistent with other trials^{4,11}. The retrospective observational study by Kolsek showed that TENS therapy during HZ resulted in a 100% decrease in PHN incidence and was significantly better in preventing PHN than antivirals. The study has some limitations because it is retrospective and observational. One could speculate that patients receiving only TENS therapy had less severe cases of HZ, which has been linked to a decreased chance of developing PHN^{5,11}. Another limitation with this study is that the placebo effect could have played a major role. Patients in the treatment group receiving TENS therapy all came from the same practicing physician who the author states had always used TENS to treat HZ. If that was a common practice by that physician, then it is likely that he would have told patients the device decreases pain and has been shown to be effective, possibly influencing results. Both of these studies show that TENS therapy is more effective in reducing development of PHN compared to antivirals, yet they do not comment on drug compliance. Some of the antivirals used are dosed 3-5 times per day, which could easily have led to missed doses and affected outcomes.

Harmful side effects and adverse events due to TENS therapy have not been reported; the only contraindications to its use are implanted pacemakers and malignant skin lesions^{5,10}. The studies in this systematic review reported no adverse events due to TENS therapy and no

significant difference between secondary bacterial infections caused by HZ vesicles in treatment or control groups^{4,5}.

CONCLUSION

TENS therapy is safe, inexpensive, and easy for patients to use, leading to its growing popularity in treating many acute and chronic pain conditions. The studies analyzed in this systematic review provide evidence suggesting TENS therapy is safe and effective in treating and preventing PHN. TENS therapy alone has been shown to decrease the incidence of PHN, but the mechanism behind this is unclear^{4,5,10}. It is also unclear why the use of TENS therapy in combination with antivirals does not decrease the incidence of PHN. Both of these are areas of further research that could be investigated as TENS therapy becomes more commonly used.

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