

Safety and Effectiveness of Cranial Electrotherapy in the Treatment of Tension Headache

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SYNOPSIS

One hundred patients were enrolled in a multicenter double-blind study to evaluate the safety and effectiveness of the Pain Suppressor Unit, a cranial electrotherapy stimulator for the symptomatic treatment of tension headaches. Treatment consisted of extremely low level, high frequency current applied transcranially. Pain scores before and after 20 minute treatments of individual headaches as well as patient and physician global evaluations were the primary efficacy variables. Following use of the active unit, patients reported an average reduction in pain intensity of approximately 35%. Placebo patients reported a reduction of approximately 18%. The difference was statistically significant ($p=0.011$). The active unit was rated as moderately or highly effective in 40% by physicians, and in 36% by patients. Both physicians and patients scored the placebo unit moderately or highly effective for only 16%. The difference in ordered outcomes was statistically significant ($p=0.004$). Approximately 10% of patients in each group reported at least one minor adverse experience. Cranial electrotherapy stimulation is distinct from TENS, and is safe and often effective in ameliorating the pain intensity of tension headaches. It should be considered as an alternative to the chronic usage of analgesics.

(*Headache* 29:445-450, 1989)

INTRODUCTION

Recurring head pain is the most common pain ailment. It is estimated that up to 50 million people in the United States suffer from some form of headache. According to recent surveys, almost 70% of American families have at least one member who suffers from headache.¹

The primary headache disorders are migraine, cluster headache, and tension (muscle contraction) headache. In 1962 the Ad Hoc Committee on the Classification of Headache focused on symptom-specific types and considered migraine to be primar-

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Accepted for Publication: May 3, 1989.

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ily vascular in nature and distinct from other forms of head pain disorders.¹ However, this concept is not as widely held today and is gradually giving way to the view that tension headache and migraine may have a common underlying physiologic basis. The so called "central hypothesis" holds that the distinct symptomatic appearance of headache is reflective of a central disturbance of neurochemical/receptor function and related physiological events within the upper brain stem, limbic, and/or hypothalamic regions.¹ The term "mixed headache syndrome" refers to a condition in which features of both migraine and tension headache occur together. This observation and studies challenging the traditional linkage of headache symptoms to blood flow or muscle status have lent support to the central hypothesis. Evidence has been presented indicating a transformation of intermittent migraine into chronic daily headache:^{2,3} these headaches are often associated with analgesic abuse. The changing view of tension headache has been associated with a reevaluation of traditional treatment concepts which relied heavily of analgesic compounds including narcotics. Current prophylactic pharmacologic treatments reflect the influence of the central hypothesis. Tricyclic antidepressants are known to be centrally active analgesics and are commonly prescribed for headache sufferers.

Although the benefit of pharmacologic treatment for patients with tension headaches cannot be doubted, complications due to overuse of medications is a major problem. As a result, there has been a growing emphasis toward nonpharmacologic treatments such as biofeedback, counseling and physical therapeutic measures.⁴ A recent addition to the nonpharmacologic treatments of headache is the use of transcutaneous electrical nerve stimulation (TENS) applied to the cranium.^{5,6} While these studies reported a degree of effectiveness, TENS units carry a theoretical risk, as these devices often deliver substantial amounts of low-frequency electrical energy, averaging between 40-80 mA.¹² Aside from the potential tactile discomfort, the safety of

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4 mA. The pulse was repeated at a frequency of 15,000 Hz for 50 ms. The 50 ms pulse train had a repetition rate of 15 Hz. The signal is further described in Figure 1.

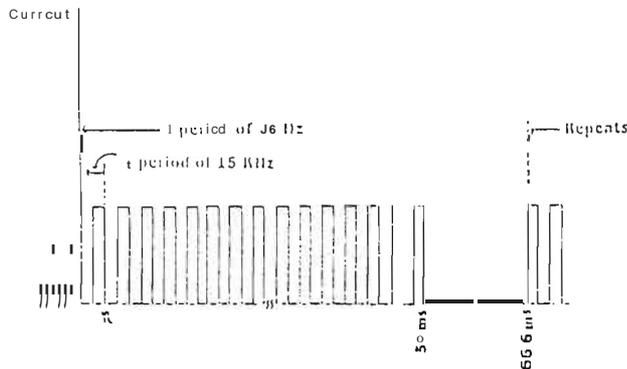


Fig. 1 – Electric current waveform of the Cranial Electrotherapy Stimulator manufactured by Pain Suppression Labs, Inc. Wayne, New Jersey 07470.

A perfectly blinded study when using a stimulating instrument as a therapeutic agent is not possible. The placebo unit ran for 70 seconds before shutting off but the current meter registered 1.0-4.0 mA for 20 minutes, the same as the active unit. Patients were told that the sensation initially experienced might disappear after about one minute or might last the full 20 minutes; in any case, the electrodes were to be maintained for the full 20 minutes. Although patients were informed that they might receive a placebo unit, they did not know that the unit turning off after 70 seconds of stimulation was to be the placebo unit.

Primary Efficacy Variables. Efficacy was based on the global evaluations of the cranial electrotherapy units by the patients and the investigators, and on the reduction in headache severity scores after treatment. The global evaluations were classified as "highly effective," "moderately effective," "minimally effective," and "not effective." Headache severity was rated by circling an integer score on an analog pain scale ranging from 0 (no pain) to 10 (maximum pain).

Statistical Methods. All hypothesis tests were performed using The Statistical Analysis System. All P-values were based on two-tailed tests. Global evaluations were compared between treatment groups using a categorical data procedure. The ordered nature of the responses listed above was accounted for by using the RESPONSE function with scores 3, 2, 1, and 0, respectively.

For each headache, the change from baseline in headache severity scores was calculated using the score prior to treatment and the last post-treatment score. Averages over multiple evaluable headaches were calculated to give a single pre-treatment and post-treatment severity score for each patient. Headaches were considered non-evaluable if one or more protocol violation was evident.

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Headache severity scores were analyzed using the following statistical models: 1) analyses of changes and of percent changes from baseline in headache severity scores, using a one-way analysis of variance with treatment as the factor and baseline scores as the covariate; 2) analyses of changes from baseline in headache severity scores, using a two-way analysis of variance with treatment and investigator as the factors.

Safety Evaluations. Tabulations were made for the prevalence of adverse events. The proportion of patients reporting adverse events were compared between treatment groups using Fisher's Exact tests.

RESULTS

One hundred and twelve patients (57 active and 55 placebo) used the unit during the study. Because of various protocol violations, twelve patients had no evaluable headaches. This reduced the number of evaluable patients to 100, 50 active and 50 placebo.

Patient Characteristics. There were no significant differences between treatment groups for distributions of sex, age or race. Ages ranged from 20 to 70 years with a mean age of 41 for patients in the placebo group and 42 for patients in the active group. Likewise there were no significant differences between treatment groups for diagnosis, average severity, or average number of headaches per month. A majority of the patients in the active group (52%) had headaches of 12-24 hours in average duration, while a majority of patients in the placebo group (54%) had headaches of less than 12 hours in duration. The distributions of average duration of headaches, categorized as less than 12 hours, 12-24 hours, and greater than 24 hours, were significantly different ($p = 0.004$).

Global Evaluations. Global evaluations of the effectiveness of the unit by the patients and investigators are summarized in Table 1. In the active group 36% of the patients evaluated the unit as "highly effective" or "moderately effective," whereas only 16% of patients in the placebo group so evaluated the unit. Sixty-three percent of the patients in the placebo group evaluated the unit as "not effective," compared to only 38% of the patients in the active group. There was a significant difference between treatment groups in the ordered outcomes for the patient global evaluations ($p = 0.006$). The investigator's evaluations were similar to the patients' evaluations.

Headache Severity Scores. Statistics for changes from pre-treatment to post-treatment in headache severity scores are given in Table 2. The mean severity score decreased by 2.1 following use of the active unit and by 1.2 following use of the placebo unit. This difference was statistically significant ($p = 0.016$). Analysis of percentage change from pre-treatment scores was also statistically significant, ($p = 0.011$); treatment with the active unit produced an

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Table 4
Summary of Premature Terminations

Reason for Termination	Number (%) of Patients	
	Active Unit	Placebo Unit
Adverse Event	2 (4%)	2 (4%)
Lack of Therapeutic Effect	3 (5%)	3 (5%)
Non-Compliance	1 (2%)	1 (2%)
Other	4 (7%)	1 (2%)
Total	10 (18%)	7 (13%)

uses analgesic medications. Pain relief in these patients is so strong that ingestion of analgesics in response to a headache may be reflexive. Reduction of analgesic medication is often a principal goal in the treatment of chronic headache patients. The use of a nonpharmacologic modality is a welcome addition to the current treatment approaches.

As shown in Table 3 there was not a significant difference in the incidence of adverse events between the treatment groups for any of the reported symptoms. A small percentage of patients, 3.5% (2/57), developed a slight skin irritation in response to applied current. This is a common observation for devices that couple electric fields to the skin via surface electrodes. In this study, sponge electrodes were moistened with ordinary tap water to provide a conductive bridge. Alternatively, a commercial conductive gel electrode could be used. These findings of safety are consistent with the extensive study by the National Research Council regarding cranial electrotherapy stimulators, in that report, which consisted of a review of low level cranial stimulation, no evidence of important side effects was found.

This cranial electrotherapy stimulator is not to be confused with TEMS. TENS is a low frequency, high current modality that provides pulses of current at frequencies of 200 Hz or less, with intensities that range into the hundreds of mA.¹² The Pain Suppressor, on the other hand, generates a high frequency carrier signal at low voltage (Figure 1). A capacitor has the characteristic of passmo current at high frequency, and the skin has this capacitive component." The high frequency of the Pain Suppressor allows the current to flow to deep tissues at relatively low voltages; there is a high efficiency of power deposition to deep tissues. TENS units, however, have a low efficiency of deep tissue stimulation since the low frequency output primarily meets the high resistance of the skin. Hence, high voltage is needed to drive current through the skin.

To determine the electric field and current density through the scalp and the skull the finite element method in a computer simulated model of cranial electrotherapy stimulation has been used to construct an approximate three dimensional spherical model of the human head.^{19,20} The model consisted of concentric spheres comprising the brain, cerebrospinal fluid (CSF), inner cortex of the skull, diploe,

outer cortex of the skull, subcutaneous tissue and skin. By simulating the moistened sponge electrodes on the model and solving Laplace's equations, the electric field and current density were determined in each tissue compartment.

In this simulated model with an applied current at the external electrode surface, solution of the equations showed: 1) relatively high electric fields in the cortical bone, 2) increased current density in the CSF, 3) increased current density in the outer surface of the brain that falls off toward the interior, and 4) a uniform electric field in the bulk of brain tissue. At a total current flow of 1 mA, the current density in the brain ranged from 5 to 18 μ A per cm.² The electric field in the brain ranged from 2.8 to 8 mV per cm.² The highest current densities and electric fields in the brain were concentrated at the cortical surface."

This is contrasted with procedures that stimulate the brain with direct current. Invasive procedures have been used to control severe and intractable pain by directly stimulating the periventricular and periaqueductal grey matter via permanently implanted electrodes."²¹ While the computer model indicates that these areas of the brain are stimulated by the noninvasive technique, the current levels are between one and two orders of magnitude less than those delivered by direct stimulation techniques.

Why and how extremely weak currents produce biological activity has been the subject of much conjecture since the finding that weak currents promote wound healing responses of both soft tissue and bone.^{25,26,27} From this work has emerged the concept of "frequency" and "amplitude" windows of therapeutic efficacy."²⁸ Apparently, low level currents on the order of 1-20 μ A per cm.² either direct current or modulated at extremely low frequencies of 0-100 Hz, interact with cell membranes in a manner that produces modifications in information transduction associated with the classical second messenger pathways, calcium channels and cyclic AMP.^{30,31,32} The pulse repetition rate (15 Hz) used in this study and the current density at the cortical surface as given by the computer model fall within these biologically active windows. As an alternative concept the responses seen in this study may be related to the gate theory of pain. According to this theory, sensation on the skin stimulates delta fibers which act to close the putative pain gate.³³ Whatever the mechanism further investigation of the relationship between mild cranial electrotherapy and neurotransmitter activity is warranted.

It appears that this noninvasive cranial electrotherapy stimulator is safe, and should be considered in the management of tension headache as an alternative to the chronic usage of analgesics

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