THE INTERNET JOURNAL OF ANESTHESIOLOGY
ISSN 1092-406X
2004 VOLUME 8 NUMBER 2

Title: The Effect of Cranial Electrotherapy Stimulation (CES) on Pain Associated with Fibromyalgia

Authors: Randall C. Cork, M.D., Ph.D., Department of Anesthesiology, LSU Health Sciences Center, Shreveport, LA
Patrick Wood, M.D., Department of Anesthesiology, LSU Health Sciences Center , Shreveport, LA
Norbert Ming M.D., Department of Anesthesiology, LSU Health Sciences Center, Shreveport, LA
Clifton Shepherd M.D., Department of Anesthesiology, LSU Health Sciences Center, Shreveport, LA
James Eddy M.D., Department of Anesthesiology, LSU Health Sciences Center, Shreveport, LA
Larry Price Ph.D., Texas State University, San Marcos, TX

Abstract
Subjective pain intensity was the primary measured variable in a double-blind crossover study examining the effect of cranial electrotherapy stimulation (CES) on the pain associated with fibromyalgia. Initially, 39 patients were randomly allocated to CES and 35 patients were allocated to a sham group. Measurements taken at baseline and after three weeks included pain intensity, McGill Pain Score, tenderpoint score, profile of mood states, and Oswestry Score. Three weeks after crossover, measurements were repeated. Significant CES effects were identified, revealing an improvement in pain intensity, McGill Score, tenderpoint score, and profile of mood states ($p<0.05$). However, no significant effect was observed on Oswestry Score, which is a score identifying functional effects of pain. This study reveals that CES could play a significant role in the treatment of pain associated with fibromyalgia; however, the long-term effects on disability remain to be studied.

Supported by a grant from the Department of Anesthesiology, LSU Health Sciences Center. No financial support was received from the makers of the Alpha-Stim®; however, Electromedical Products International, Inc. did loan the authors the Alpha-Stim® units necessary to do the study.

Introduction
In a nod to Lewis Carroll, Arthur Weinstein has referred to fibromyalgia as not so much “a grin without a cat,” but a “frown without a cat.” [1] In fact, so little is known about fibromyalgia that many indignant academicians question its existence. Unfortunately for us clinicians, the parade of patients presenting daily at our offices must be addressed. We have to do something. As a result, we are constantly looking for something new to do.

Cranial electrotherapy stimulation (CES) may be that something. It is a form of electrical stimulation that has already been approved by the FDA as a drug-free treatment for anxiety, depression, and insomnia, all of which have been identified as common comorbidities in patients with fibromyalgia. CES typically involves the passage of microcurrent levels of electrical stimulation across the head for from 20 minutes to an hour daily for a few days to a few weeks. Kirsch has published a review of over 150 human and animal studies regarding CES. [2] A recent series of meta-analyses on the effectiveness of CES has also been recently published. [3]

The purpose of this clinical study was to examine the effect of CES on a group of patients with a diagnosis of fibromyalgia. The primary variable was pain intensity, as measured by the patient using a numerical scale of 0 (no pain) to 5 (worst pain possible). Secondary measurements included tenderpoint score, McGill Pain Score, Profile of Mood States (POMS), and Oswestry Score.

Methods
After approval from the LSU Health Sciences Center—Shreveport IRB, patients 22-75 years of age presenting at the LSU Pain Clinic with a diagnosis of fibromyalgia were randomly assigned to either a Sham Group or a Cranial Electrotherapy Stimulation (CES) Group. The diagnosis of fibromyalgia was verified using the criteria set forth by the American College of Rheumatology. [4] Exclusion criteria included pregnancy and presence of implanted pacemakers, pumps, or stimulators, as well as the presence of superficial or internal ear infections. No change was made in the medical management of the patient during the study.

All patients were given a CES device that would provide either subsensation treatment or sham treatment. The Alpha-Stim CES device was used (Electromedical Products International, Inc., Mineral Wells, TX, http://www.alpha-stim.com/). Each device was preset to provide 1 hour of 100 µA, modified square-wave biphasic stimulation on a 50% duty cycle at 0.5 Hz, and to automatically turn off at the end of one hour. All treatment was given via electrodes clipped to the ear lobes (Figure 1). Location of electrodes on the ear lobes is illustrated in Figure 2. Sham treatment was provided by identical ear clip electrodes that did not pass current. All staff, the physicians, and the patient were blind to the treatment conditions. At the end of three weeks, the CES Group was unblinded, and the Sham Group was given the option to receive active therapy for an additional three weeks.

Figure 1: The Alpha-Stim 100 Cranial Electrotherapy Stimulator with ear clips. Study settings were at 0.5 Hz for 1 Hr. Sham ear clips did not pass current.

Figure 2: Location of electrode placement on earlobe. Patient is unaware of whether electrode is treatment or sham.

Initial measurements were taken at baseline, prior to commencement of the treatment period. These measurements included:

Pain Intensity: The patient was asked to write down a number between 0 and 5, where 0 represented no pain, and 5 represented the worst pain imaginable.

McGill Pain Score: The patient was asked to complete the Short-Form McGill Pain Questionnaire (SF-MPQ). [5] The SF-MPQ consists of the following 15 pain descriptors: Throbbing, shooting, stabbing, sharp, gnawing, cramping, burning, aching, heavy, tender, splitting, tiring, sickening, fearful, and punishing. Each of these pain descriptors are scored by the patient as none (0), mild (1), moderate (2), or severe (3), and then the total score is summed for the McGill Pain Score.

Tenderpoint Score: Tenderpoints [6] and sham points listed in Table 1 were palpated with 4 kg pressure. The patient was asked to rate the pain elicited at each point on a scale between 0 (no pain) and 10 (worst pain imaginable). The scores for all the points were added up, and the scores for the sham points were subtracted from the total to arrive at the Tenderpoint Score.

Profile of Mood States (POMS): The POMS [7], [8] (Educational and Industrial Testing Service, San Diego, CA) is a standardized paper and pencil psychological test measuring the following mood factors: tension/anxiety, depression/dejection, anger/hostility, energy/vigor, fatigue/inertia, and confusion/bewilderment. An overall total mood disturbance score is calculated as a POMS Score.

Oswestry Score: The Oswestry Disability Questionnaire [9] assesses functional impairment by scoring how much the activities of daily living are affected by disability. In this case, the disability is pain. Patients are asked to rate from 0 to 5 the magnitude of their pain and the impact of their pain on the following activities: Tying shoes and putting on socks, lifting, walking, sitting, standing, sleeping, sexual function, social life, and traveling. Points are summed to form the Oswestry Score.

Following the baseline tests, the subjects were taught how to use the CES unit, and they were instructed to use it every day for 1 hour over a 3-week period. At the end of 3 weeks, the subjects returned to the Pain Clinic, and all the above tests were repeated. At that time, the key to the blinding was broken, and the patients in the Sham Group were given the option to receive CES for an additional three weeks. Those who elected to do so returned to clinic after the three-week period and were re-tested.

Data were analyzed with repeated-measures analysis of variance, with least-significant-difference a posteriori testing. Significance was defined as $p<0.05$. The primary variable to be assessed was pain intensity (0-5). Assuming a standard deviation of 0.2, a difference of 0.1 in this measurement is detectable with a sample size of 35 in each group, resulting in a calculated power of 82.0%.

Results

A total of 74 patients were studied, 39 in the CES Group and 35 in the Sham Group. Following the unblinding at 3 weeks, 23 patients in the Sham Group elected to cross over to active treatment for three weeks. Of the 74 patients, 70 were female. Average age was 53 (min 22 yrs, max 75 yrs); average duration of symptoms was 7.3 years (min 1 yr, max 21 yrs).

All measurements are graphically depicted in the accompanying Figures 3-5, 7-8. There were no differences detected at baseline between the CES Group and the Sham Group for any of the measurements. The Pain Intensity Score, the Tenderpoint Score, and the POMS Score were all significantly less in the CES Group compared to the Sham Group at 3 weeks ($p<0.01$). For those patients in the Sham Group who elected to receive treatment with CES over the subsequent 3-week period, all measurements except the Oswestry Score were significantly improved over baseline ($p<0.001$).

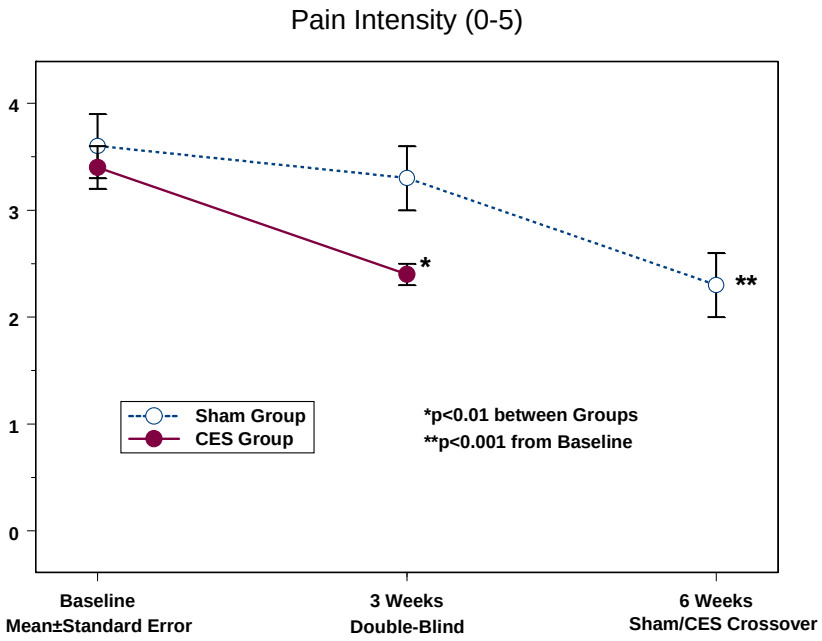

Figure 3: Pain intensity as a numerical scale reported by patients based on a scale of 0-5, where 0 represents no pain, and 5 represents the maximum pain imaginable. The pain intensity reported by the CES Group was significantly less at three weeks, compared to the Sham Group ($p<0.01$). However, after crossover, the Sham Group showed a significant decrease in pain intensity after receiving cranial electrotherapy stimulation (CES) for the subsequent three weeks ($p<0.001$). All values are means ± standard error of the mean (sem).

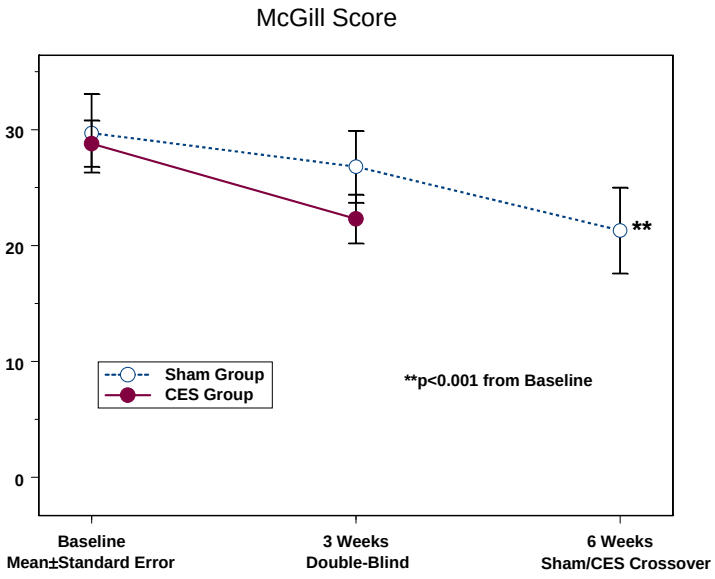

Figure 4: Pain as measured using the Short-Form McGill Pain Questionnaire.[5] The higher scores represent more pain. The decrease in pain scores reported by the CES Group after three weeks of CES did not achieve significant difference from the pain scores reported by the Sham Group. However, after crossover, the scores reported by the Sham Group after three weeks of subsequent CES were significantly decreased (p<0.001). All values are means ± sem.

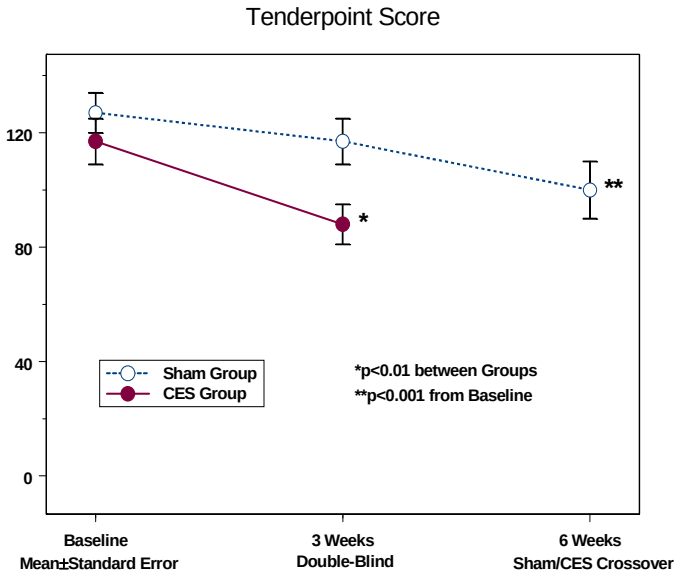

Figure 5: Tenderpoint self-reported pain score. Eighteen (18) tenderpoints and three sham points were identified for testing (Table 1).[4] Before the tenderpoints were palpated, the patient was given a sheet with the ten-point self-rating pain scale (0, none; 10, worst), and asked to rate overall pain level by placing a check beneath the number that represented the pain "right now." The tenderpoints, plus the sham tenderpoints, were then palpated sequentially and the patient asked to rate the pain during each palpation on a scale of 0 for no pain, up to 10 for excruciating pain. Four (4) kg of pressure was applied to each point. After the 18 points were palpated, the scores were added up, for a maximum total of 180. Scores reported from the sham points were subtracted from the total tenderpoint score. Results showed that the tenderpoint scores were significantly less in the CES Group at 3 weeks compared to the Sham Group (p<0.01), and after crossover, the Sham Group showed a significant decrease in tenderpoint score after receiving CES for the subsequent 3 weeks (p<0.001). All values are means ± sem.

Table 1: Tenderpoint Sites*

Occiput	Bilateral, at the suboccipital muscle insertions.
Low Cervical	Bilateral, at the anterior aspects of the intertransverse spaces at C5-C7.
Trapezius	Bilateral, at the midpoint of the upper border.
Sham Point	Bilateral, at midpoint of the biceps brachii muscle.
Supraspinatus	Bilateral, at origins, above the scapular spine near the medial border.
Second rib	Bilateral, at the second costochondral junctions, just lateral to the junctions on upper surfaces.
Lateral epicondyle	Bilateral, 2 cm distal to the epicondyle
Sham Point	Bilateral, abdomen 5 cm to left, then right, of umbilicus.
Gluteal	Bilateral, in the upper outer quadrants of buttocks in anterior fold of muscle.
Greater trochanter	Bilateral, posterior to the trochanteric prominence.
Knee	Bilateral, at the medial fat pad proximal to the joint line.
Sham Point	Bilateral, belly of gastrocnemius.

*From Romano TJ [6]. A rheumatologist's perspective on pain management. In: Weiner RS, editor. Pain management; A practical guide for clinicians. 5th ed. Boca Raton: St. Lucie Press; 1998. p. 361.

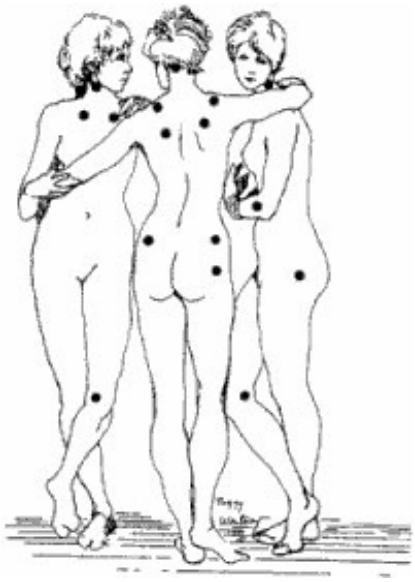

Figure 6: Tenderpoint locations for the 1990 classification criteria for fibromyalgia from the American College of Rheumatology [4] (after The Three Graces, by Baron Jean-Baptiste Regnault, 1793, Louvre Museum, Paris). See Table 1 for details of tenderpoint site locations.

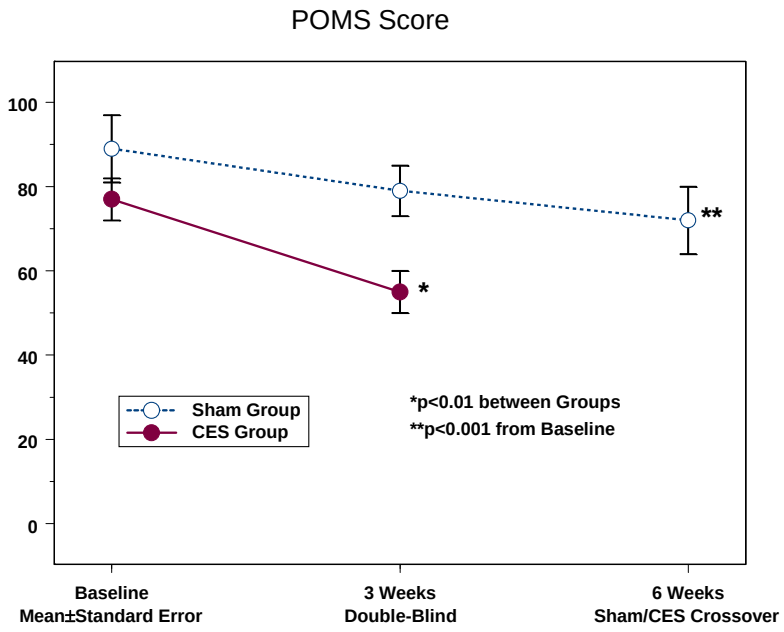

Figure 7: Patient mood as measured by the Profile of Mode States (POMS).[7,8] The higher scores represent more anxiety. The anxiety reported by the CES Group after three weeks of CES was significantly less than the anxiety reported by the Sham Group after three weeks of sham treatment (p<0.01). However, after crossover and three weeks of subsequent CES treatment, the Sham Group reported a significant decrease in anxiety levels from their baseline scores (p<0.001). All values are means ± sem.

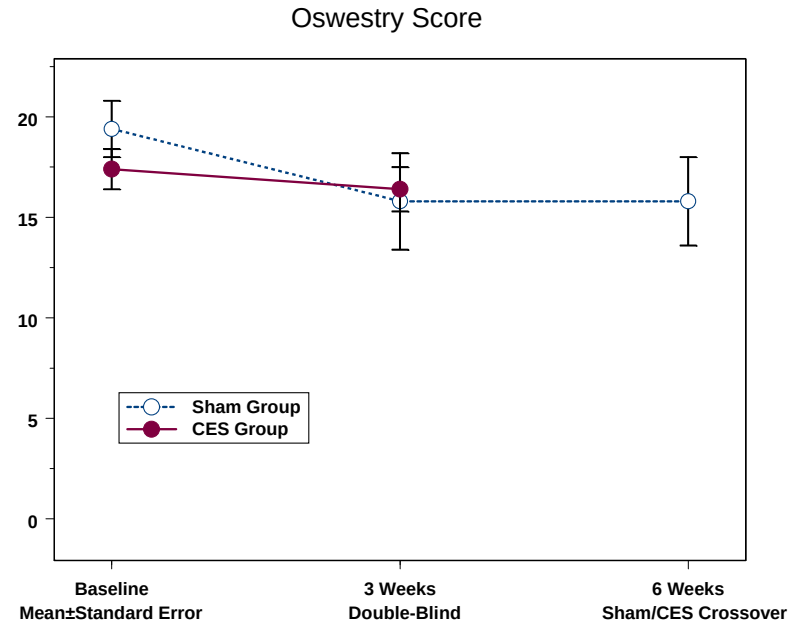

Figure 8: The Oswestry Score is a measure of physical disability which is used as an index of the functional effect that pain has on a patient's daily activities. [9] The Oswestry Score did not change significantly over 3 weeks for the CES Group or over 6 weeks for the Sham Group.

Discussion

We have demonstrated that active treatment with CES results in significant improvement in a number of clinical parameters associated with fibromyalgia, including subjective pain intensity, McGill Pain score, tenderpoint score and self-reported anxiety (per POMS score). The results of our investigation appear to be most encouraging, given the refractory nature of fibromyalgia pain to conventional pain management. Taken together, one might conclude that CES was indeed able to favorably alter the patient's clinical state, while failure to improve Oswestry scores, a measure of subjective disability, may reflect more of a trait quality in this sample of individuals on referral to a tertiary care pain management program. The Oswestry Scale was originally used to quantitate disability, [5] rather than as a functional assessment of pain, so one might reasonably conclude that longer follow-up would be necessary to see changes in the Oswestry scores.

The suggestion that CES may be efficacious in the treatment of fibromyalgia begs the question by what mechanism? It could be just a matter of improved sleep patterns, which CES has been shown to induce. [3] However, low frequency, repetitive stimulation may hold the key to understanding our success. Specifically, studies using sub-dissociative doses of the non-competitive n-methyl-d-aspartate (NMDA) receptor antagonist ketamine have demonstrated the pain of fibromyalgia to be uniquely related to hyperactivity of this subtype glutamate receptor in a majority of fibromyalgia patients. [10] Likewise, fibromyalgia pain has been theoretically linked to transformation of NMDA receptor function specifically within the hippocampal formation [11], wherein they are known to participate in the modulation of tonic pain. [12] Whereas high frequency (i.e. tetanic) stimulation of hippocampal NMDA receptors produces long-term potentiation, low frequency stimulation has been demonstrated to down-regulate NMDA receptor function, resulting in long-term depression. [13, 14] Thus, the efficacy of CES in alleviating fibromyalgia pain may be related, at least in part, to an alteration in the functional parameters of supraspinal NMDA receptors that hypothetically contribute to the experience of chronic widespread pain.

The repetitive nature of the stimulus may hold the key to understanding the success of CES in the treatment of chronic pain. Repetitive stimulation has been long associated with wind-up, neuroplasticity, and central sensitization. Many of these same processes are mediated by the NMDA receptor. Could it be that the subsensory or low-sensory stimulation of CES interferes with the adverse neuroplastic and NMDA changes associated with neuropathic pain? Is there a neuropathic Gate Control Theory? As poorly defined or accepted as fibromyalgia be, it could hold the secret to a new area of study involving neuropathic pain.

Conclusion

CES appears to be an effective, well-tolerated treatment for the treatment of fibromyalgia. Those involved in the treatment of fibromyalgia should include it in their clinical armamentarium, given the demonstrated safety of this non-invasive modality.

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