Using Cranial Electrotherapy Stimulation to Treat Pain Associated with Spinal Cord Injury

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Abstract

Treatments for chronic pain in persons with spinal cord injury (SCI) have been less than effective. Cranial electrotherapy stimulation (CES), a non-invasive technique that delivers a micro-current to the brain via ear clip electrodes, has been shown to be effective in treating several neurological and psychiatric disorders. The present study examined the effects of one-hour CES or sham-CES treatment (randomly assigned) over 21 days on pain intensity and interference with activities in 38 males with SCI. The CES group \( n = 18 \) reported significantly greater decrease in daily pain intensity compared to the sham-CES group \( n = 20 \); mean change: CES = -0.73, Sham = -0.08; \( p = 0.034 \). Additionally, the CES group had significantly decreased reported pain interference (-14.6 pre- vs. post-treatment; \( p = 0.004 \), in contrast to the non-significant effect in the sham-CES group (-4.7, \( p = 0.238 \)). These results suggest that CES appears to be an effective treatment for chronic pain in persons with SCI.

Key Words

Adults
Cranial
Cranial Electrotherapy Stimulation
Electric Stimulation Therapy
Male
Musculoskeletal
Neuropathic
Pain
Spinal Cord Injuries
Veterans

Abbreviations

ASIA – American Spinal Injury Association
BPI – Brief Pain Inventory
CES – Cranial Electrotherapy Stimulation
Cohen’s \( d \) – an indicator of effect size
DSM-IVTR - Diagnostic and Statistical Manual of Mental Disorders (4th edition, text revision)
MEDVAMC – Michael E. DeBakey Veterans Affairs Medical Center
\( n \) – number
\( p \) - probability
QEEG – Quantitative Electroencephalographic
RA – Research Assistant
SCI – Spinal Cord Injury
VA – Veterans Affairs
Introduction

Chronic pain following spinal cord injury (SCI) is frequently a significant issue that can affect the clinical outcome of post-injury rehabilitation and ultimately the overall quality of life in numerous domains (e.g., physical, psychological, social, and occupational). At least two-thirds of persons with SCI suffer from frequent pain [1-3]. To date, the majority of studies of SCI pain have been conducted during initial rehabilitation or within the first few years after injury. However, the majority of persons with SCI report chronic pain that persists, and is characteristically progressively severe for many years following SCI [1]. Several temporal and circumstantially-related patterns of SCI pain are notable (e.g., patient age, delayed rehabilitation, and localization of spinal insult), both in regard to possible pathophysiologic mechanisms involved and for potential implications for types of treatment and/or management [4-10]. Irrespective of such provocative or exacerbating factors, chronic pain after SCI has been shown to impose an additional handicap for a given degree of SCI-related disability [2,11,12]. Despite numerous experimental and clinical attempts at controlling chronic pain in persons with SCI, the vast majority of these treatments have been largely ineffective. Ragnarsson noted that this persistent refractoriness greatly reduces the resultant quality of life [13].

Cranial Electrotherapy Stimulation (CES). CES is a non-invasive technique used to treat a variety of conditions. The analgesic action of sub-perceptive levels of CES has been demonstrated in various clinical pain models [14,15]. Extracellular recording techniques indicated that CES modifies noxious stimuli-evoked responses in regions of the rat brain involved in nociceptive processing [16,17]. In humans, the mechanism of action of CES is not fully understood, however, it has been shown to stabilize neurotransmitter turnover [18], stimulate the production of the growth hormone IGF-1 [19], and facilitate normalization of monoamine levels following experimentally-induced noxious stress [20]. Additionally, it has been shown that CES can enhance anesthetic effects in humans: CES increased the potency of nitrous oxide (N₂O) by approximately 37% [21], and CES reduced the required analgesic dose of fentanyl by an average of 33% in patients undergoing urologic surgery [22]. CES has also been shown to have anxiolytic [23,24] and mood-enhancing effects [25] in humans. CES has been demonstrated to effectively decrease spinal [26], headache [27-29], dental [30,31], and muscle pain and spasms [32-34], as well as controlling several conditions that are often associated with pain (e.g., anxiety, depression, insomnia, and generalized stress) [35]. A recent double-blind, placebo-controlled study of fibromyalgia showed that CES was as effective as pharmacotherapy in reducing pain, and unlike pharmacotherapy, did not incur the risk of adverse side effects or the potential for polypharmacy [36]. In addition to pain reduction, CES also significantly improved sleep, feelings of well-being, and the reported quality of life of the patients with fibromyalgia. Donaldson reported that CES modified the specific quantitative electroencephalographic (QEEG) “signatures” associated with the condition which, when altered, may have been partly responsible for, or reflective of, a significant decrease in pain and associated symptoms [37].

One of the advantages of CES is the apparent absence of adverse side effects. Prior to 1990, there were a few reports of mild burns at the electrode site [38], transient blurring of vision when electrodes were placed over the eyes [39-44], slight dizziness [32], headache [45,46], giddiness [45], and tooth pain [45]. Such side effects appear to be related to the use of higher voltages and the placement of electrodes on the eyes. It is important to note that current iterations of CES consistently use lower voltage delivery and the method of placing electrodes...
over the eyes was discontinued nearly 30 years ago. More recently, Smith reported that one of 23 (4.3%) psychiatric outpatients cried during treatment and one (4.3%) reported skin irritation behind the ears when electrode gel began drying out [47]. In two post-marketing surveys (1995 and 1998), 47 physicians reported the results of CES use by 500 patients for a variety of conditions [48]. Six (1.2%) patients reported dizziness and two (0.4%) reported nausea, both of which normally occur if the current is set too high. Three reported skin irritation (0.6%), and 1 each (0.2%) reported anger, a metallic taste, a heavy feeling, and intensified tinnitus. Several studies conducted during the 1990s, with a combined total of 259 participants, reported no side-effects that could reasonably be attributed to the use of CES [24,25,49,50].

Given the demonstrated success of CES in treating fibromyalgia, a centrally-mediated pain typically triggered by physical trauma (as is central neuropathic pain in persons with SCI), it is hypothesized that CES could be effective in reducing chronic pain after SCI and lower the burden of long-term pharmacologic management.

A study by Capel and colleagues found that CES decreased the intensity of pain (of mixed etiology) and medication use in persons with SCI who received active CES treatment as compared to sham-CES treated controls [51]. In the first arm of the study, 14 of the participants received active CES and 13 had sham CES for two hours twice a day for four days. The active CES group reported less pain during and immediately after receiving CES and reported that they used less pain medication. After a wash-out period of eight weeks, both groups received active CES for two hours twice a day for four days. The group who initially had sham-CES showed significant improvement when they received active CES in the second arm of the study. Such results, while certainly encouraging, are somewhat limited in that the mixed etiology of pain in the investigation leaves questions about the mechanistic basis of effect(s) yet unaddressed. Furthermore, their study used very small amounts of current (12 microamperes), CES was administered for a relatively large amount of time per day (4 hours), and had a very short intervention period (4 days), leaving questions about the optimum current, duration of daily treatment, and number of days of treatment unanswered. In apparent recognition of these limitations, the authors concluded that larger studies of the effectiveness of CES for treating specific types of chronic pain in persons with SCI are needed.

Thus, given the potential of such findings, together with the paucity of similar data on CES-based pain therapeutics in SCI, the present pilot study was undertaken to assess the efficacy of CES on the intensity and specific behavioral correlates of musculoskeletal and neuropathic pain associated with SCI, in a sample of veterans who had received care at a Veterans Affairs Spinal Cord Injury Center. In addition, this study explored the feasibility and logistics of conducting the study with the treatments being self-administered daily in the home environment over a 21-day period. This procedure is particularly important given the mobility limitations resulting from SCI, and the need to provide adequate pain relief in the non-inpatient care setting.

**Method**

**Participants:**

Forty (40) veterans who were six months to 60 years post-SCI, with chronic musculoskeletal or neuropathic pain were recruited from the Michael E. DeBakey Veterans Affairs Medical Center (MEDVAMC) SCI Care Line in Houston, Texas. The inclusion criteria were (a) diagnosis of SCI with chronic pain of at least 3 months duration and of moderate to severe intensity (6 or above on a numeric scale of 0 to 10); (b) at least 6 months post injury; (c)
signed IRB approved informed consent form; (d) ability and willingness to comply with instructions, treatment regimen, and other requirements of the study; and (e) ability to travel to the medical center at least twice and possibly three times, depending on group assignment. Exclusion criteria were (a) a documented history of noncompliance with past treatment or research studies (e.g., missed follow-up appointments and not taking medications as directed); (b) evidence of substance abuse (e.g., confirmed violation of medical orders, inappropriate dose escalation, procurement against medical advice, and/or current DSM-IV/IVTR diagnosis of substance abuse disorder), and (d) history of severe cognitive and/or mental disorder that might interfere with the treatment regimen. Overall attrition was limited to two participants.

**Experimental Design:**

The study was conducted as a double-blind, sham-controlled design with random assignment of participants to either an active CES or sham CES treatment group. The investigators, research assistant (RA), and subjects were blinded to treatment type until the end of the initial phase of the study.

**CES Equipment:**

The CES equipment used in this study was the Alpha-Stim 100 (Electromedical Products International, Inc., Mineral Wells, TX.), which is a prescription medical technology that is FDA approved for the management of pain, anxiety, depression, and insomnia. The device is illustrated in Figure 1.

![Figure 1](image)

Alpha-Stim technology has been commercially available on the medical market since 1981 and has been the subject of over 50 studies to date. The device uses microcurrent electrical therapy and although a slight tingling sensation is sometimes felt under the electrodes, observed/reported treatment effect(s) are not contingent upon this liminal sensory input, as many patients report complete absence of sensory stimulation with Alpha-Stim 100 treatment. The therapy is applied through ear clip electrodes that are easy to apply. The CES devices for the study were provided by the manufacturer.
Half of the CES units delivered active CES and half provided sham CES. Participants were unable to determine whether they were receiving active CES or sham, as the amount of electrical stimulation was set at a sub-threshold level and could not be changed by the participants. The manufacturer also provided a third set of CES units to be used in an Open-Label phase for those originally in the Sham CES group. These units were the same as those available on the market; thus, the level of stimulation could be adjusted by the user from 100 microamperes to 500 microamperes. The manufacturer provided training to the research staff on the proper use of the CES units.

Procedure:

Participants were recruited by telephone from a list of patients with SCI who were on the registry at the MEDVAMC. Persons who agreed to participate met with the RA who explained the study, obtained informed consent, and explained the financial compensation to assist with travel to the medical center (i.e., $25 per data collection point). The RA also conducted a structured interview that included an initial questionnaire packet described below. Participants were instructed in the self-administration of CES and use of the daily pre- and post-session pain rating form. The participants were then randomly assigned to either the active or sham treatment groups. Participants in both groups were provided with a CES unit to take home and were instructed to self-administer the treatment daily for 21 consecutive days. Participants who had the Active units received one hour per day of 100 microamperes sub-threshold CES. The RA contacted the participants by phone on a regular basis, generally weekly, to answer questions and to ensure that study instructions were followed.

After completing the initial 21-day trial, the participants returned to the clinic and a post-intervention interview was conducted that included completion of a post-intervention questionnaire packet. Then the unit number was checked against a list (maintained by someone not directly involved in the study) to determine if the unit had been programmed to deliver active or sham treatment. If the latter, the participant was offered the opportunity to participate in an Open-Label trial with an active CES unit. Those who chose to participate in the Open-Label phase were given the same instruction to self-administer the treatment one hour per day and to record their pain ratings immediately before and after each daily treatment session for another 21 days. Although these Open-Label units allowed the participants to adjust the level of current intensity at their own discretion, they were not required to record the intensity used. After the 21 days of the Open-Label phase, the participants returned to the MEDVAMC to complete another packet of questionnaires and return the CES device.

Measures:

Demographic and Injury-Related Information was obtained by self-report. These included age, race/ethnicity, educational status, marital status, date of SCI, and etiology of the SCI.

Level and Completeness of SCI were obtained from medical records. This included the American Spinal Injury Association (ASIA) Impairment Scale grade, which indicates degree of completeness [52].

Type of Pain - A physiatrist caring for persons with SCI determined whether the chronic pain was neuropathic or musculoskeletal during a brief examination. Siddall and colleagues have proposed a 3-tiered taxonomy for post-SCI pain [53,54]. The first tier categorizes pain as nociceptive or neuropathic. These categorizations are based upon accepted operational definitions of pain that reflect distinct peripheral and/or central mechanisms [55]. Nociceptive
pain is classified as being of musculoskeletal and/or visceral origin. Neuropathic pain is classified according to site of occurrence/experience relative to the level of SCI.

Daily Pain Rating Sheets were used to maintain a record of pain intensity immediately before and immediately after each daily one-hour treatment session. A numeric 0 to 10 rating scale was used, with 0 indicating “no pain” and 10 indicating “pain as bad as you can imagine.”

Pain intensity was assessed by the Brief Pain Inventory (BPI) Pain Intensity subscale [56]. Similar to the daily pain estimates, the BPI asks patients to rate their pain on 0-10 numeric scales “at its worst in the past 24 hours,” “at its least in the past 24 hours,” “on average,” and “right now.” Each rating scale is bounded by the words “no pain” at the 0 level and “pain as bad as you can imagine” at the 10 level.

Originally developed to assess cancer pain [56], the BPI has been recently validated for evaluating non-malignant chronic pain [57]. However, while the BPI has been used with persons diagnosed with chronic low back and amputation pain [58-61], we are aware of no reports of the use of the BPI in patients with SCI. In the present study, Cronbach’s alpha was 0.91 at pre-intervention and 0.92 at post-intervention for the BPI Pain Intensity scale.

Pain Interference was assessed using a version of the Pain Interference scale of the BPI that has been modified for persons with physical disability [62]. This modified scale has 10 items rated on a 0-10 numeric scale. Participants were asked to rate the degree to which in the past week pain had interfered with ten quality of life domains, including general activity, mood, mobility, work, relations with other people, sleep, enjoyment of life, self-care, recreational activities, and social activities. Each item scale is bounded by “does not interfere” and “interferes completely.” There are data to support the reliability and validity of the BPI for assessing pain interference in patients with cancer [56,63], and preliminary evidence supports the reliability of the modified BPI Interference scale for assessing pain interference in patients with pain secondary to physical disability [62,64,65]. Cronbach’s alpha for the present study was 0.95 at pre-intervention and 0.96 at post-intervention for the BPI Pain Interference scale.

Data Analyses:

Descriptive statistics (means, standard deviations, and ranges for continuous variables, and number and percent for categorical variables) were obtained for each demographic and injury-related variable.

Daily Pain Ratings – For each participant an average pre-session pain rating (across the 21 daily sessions) and an average post-session pain rating were calculated. The difference between the pre-session average pain rating and the post-session average pain rating was calculated, yielding one mean change score per person. A two-sample t-test was performed to determine if the average change score for the Active group was significantly different from the average change score for the Sham group. Additionally, within each group (Active, Sham and Open-Label), paired t-tests were performed to determine whether there was a significant change in pain ratings from pre- to post-session.

BPI Pain Intensity and Pain Interference – For each data collection point (Pre-Intervention, Post-Intervention, Post-Open-Label), the four BPI pain intensity items were summed to form a Composite Pain Intensity score and the 10 pain interference items were summed to produce a Composite Pain Interference score. Change scores were calculated for each variable from Pre- to Post-Intervention for all 38 participants and from Post-Intervention to Post-Open-Label for the 17 persons who participated in the Open-Label phase.

Two-group t-tests were conducted to determine whether Pre-Post change in each variable for the Active group was significantly different from change for the Sham group. Additionally,
paired *t*-tests were performed separately for each group (Active, Sham, and Open-Label) to determine whether there were significant changes within each group in the item and total scores from pre- to post-21-day intervention.

Exploratory analyses (*t*-tests, ANOVA, and Pearson correlations) were performed to assess whether (a) etiology of SCI (traumatic or non-traumatic), (b) level and completeness of injury (Tetraplegia with ASIA grades of A, B, or C; Paraplegia with ASIA grades of A, B, or C; or Tetraplegia or Paraplegia with an ASIA grade of D), (c) type of pain (musculoskeletal or neuropathic), and/or (d) baseline levels of each measure were related to the amount of change in pain intensity or pain interference.

**Results**

Thirty-eight participants completed the study; 18 were randomly assigned to the Active group and 20 to the Sham group. The characteristics of the two groups are shown in Table 1. When participants in the Sham group were subsequently provided an opportunity to participate in the open-label trial, 17 (85%) agreed to do so.

<table>
<thead>
<tr>
<th>Group</th>
<th>Sham CES</th>
<th>Active CES</th>
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<tbody>
<tr>
<td>Number</td>
<td>20</td>
<td>18</td>
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<table>
<thead>
<tr>
<th>Group</th>
<th>Mean (SD) Range</th>
<th>Mean (SD) Range</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>56.6 (10.9) 42-82</td>
<td>56.0 (8.3) 38-74</td>
</tr>
<tr>
<td>Time Since Onset of SCI (years)</td>
<td>19.7 (16.0) &lt;1-60</td>
<td>20.1 (10.3) 2-41</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gender</th>
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<th>Percent</th>
<th>Number</th>
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<td>20</td>
<td>100</td>
<td>18</td>
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<th>Percent</th>
<th>Number</th>
<th>Percent</th>
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<td>White (not Hispanic)</td>
<td>13</td>
<td>65</td>
<td>12</td>
<td>67</td>
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<tr>
<td>African-American</td>
<td>4</td>
<td>20</td>
<td>5</td>
<td>28</td>
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<tr>
<td>Hispanic</td>
<td>3</td>
<td>15</td>
<td>1</td>
<td>6</td>
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<th>Number</th>
<th>Percent</th>
<th>Number</th>
<th>Percent</th>
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<tr>
<td>High School or Less</td>
<td>7</td>
<td>35</td>
<td>4</td>
<td>22</td>
</tr>
<tr>
<td>Some College or More</td>
<td>13</td>
<td>65</td>
<td>14</td>
<td>78</td>
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<th>Percent</th>
<th>Number</th>
<th>Percent</th>
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<tr>
<td>Married</td>
<td>10</td>
<td>50</td>
<td>8</td>
<td>44</td>
</tr>
<tr>
<td>With Significant Other</td>
<td>1</td>
<td>5</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Neither</td>
<td>9</td>
<td>45</td>
<td>9</td>
<td>50</td>
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<table>
<thead>
<tr>
<th>Etiology of SCI</th>
<th>Number</th>
<th>Percent</th>
<th>Number</th>
<th>Percent</th>
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<tbody>
<tr>
<td>Traumatic</td>
<td>18</td>
<td>90</td>
<td>15</td>
<td>83</td>
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<tr>
<td>Non-traumatic</td>
<td>2</td>
<td>10</td>
<td>3</td>
<td>17</td>
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<th>Level and Completeness of SCI</th>
<th>Number</th>
<th>Percent</th>
<th>Number</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetraplegia (ASIA A, B, or C)</td>
<td>4</td>
<td>20</td>
<td>4</td>
<td>22</td>
</tr>
<tr>
<td>Paraplegia (ASIA A, B, or C)</td>
<td>10</td>
<td>50</td>
<td>6</td>
<td>33</td>
</tr>
<tr>
<td>All ASIA D</td>
<td>6</td>
<td>30</td>
<td>8</td>
<td>44</td>
</tr>
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<table>
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<tr>
<th>Type of Pain</th>
<th>Number</th>
<th>Percent</th>
<th>Number</th>
<th>Percent</th>
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</thead>
<tbody>
<tr>
<td>Neuropathic</td>
<td>11</td>
<td>55</td>
<td>12</td>
<td>67</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>9</td>
<td>45</td>
<td>6</td>
<td>33</td>
</tr>
</tbody>
</table>

*Percentages may not sum to 100% due to rounding.

Note: There were no significant differences between the Sham and Active groups on any of the characteristics listed in this table. Small cells were combined for chi square analyses of race/ethnicity and marital status (White/Non-white; With spouse or partner/Not with spouse or partner).
Daily pain ratings:
The Active and Sham groups did not differ significantly with regard to the average before session pain rating (Active mean = 6.46, Sham mean = 6.08). The two groups also did not differ significantly with regard to the average after session pain rating (Active mean = 5.73, Sham mean = 6.00). However, the results of a two-sample \( t \)-test indicated that the average change in pain intensity from before to after each daily session was significantly larger for the Active group (mean = -0.73) than for the Sham group (mean = -0.08, \( p = .034 \)). The effect size of the treatment was medium to large (Cohen’s \( d = .759 \)) as defined by Cohen [66]. Furthermore, the results of paired \( t \)-tests within each group indicated that participants who received the sham CES did not show a significant reduction in their self-reported pain (\( p = 0.337 \)), whereas participants who received the active CES did show significant pain reduction (\( p = 0.016 \)). In other words, the sham CES group’s average daily after-session rating was 98.7 percent of the before-session rating, whereas the active CES group’s after-session rating was 88.7 percent of the before-session score. Finally, when 17 of the Sham participants subsequently participated in an Open-Label use of CES, they reported a significant reduction after the daily CES sessions (\( p = 0.003 \)). These findings are summarized in Table 2.

Table 2: Average Daily Pain Ratings over the 21 Days of CES Treatment

<table>
<thead>
<tr>
<th>Treatment Condition</th>
<th>N</th>
<th>Before Mean (SD)</th>
<th>After Mean (SD)</th>
<th>Changea Mean (SD)</th>
<th>t-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Range</td>
<td>Range</td>
<td>Range</td>
<td></td>
</tr>
<tr>
<td>Active CES</td>
<td>18</td>
<td>6.46 (1.95)</td>
<td>5.73 (2.56)</td>
<td>-.73 (1.15)</td>
<td>2.69*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.94-10.00</td>
<td>1.24-10.00</td>
<td>-.14 to 0.00</td>
<td></td>
</tr>
<tr>
<td>Sham CES</td>
<td>20</td>
<td>6.08 (2.42)</td>
<td>6.00 (2.41)</td>
<td>-0.08 (0.38)</td>
<td>0.98</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.93-10.00</td>
<td>1.60-10.00</td>
<td>-1.20 to +0.67</td>
<td></td>
</tr>
<tr>
<td>Open-label CES</td>
<td>17</td>
<td>5.97 (2.35)</td>
<td>5.51 (2.51)</td>
<td>-.46 (0.54)</td>
<td>3.47**</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.95-10.00</td>
<td>0.95-10.00</td>
<td>-1.48 to +0.19</td>
<td></td>
</tr>
</tbody>
</table>

a Mean After-Session Rating minus Mean Before-Session Rating (negative change scores indicate decreased pain intensity)

** \( p < .01 \), * \( p < .05 \)

Pain ratings before and after the daily treatment sessions for the Active and Sham groups are shown in Figures 2 and 3, respectively. Only 17 of the 20 individuals originally assigned to the Sham group participated in the Open-Label phase. Displayed in Figure 4 are the mean pain ratings before and after daily treatment sessions for the 17 participants who were in both the Sham and Open-Label phases.
The Brief Pain Inventory:

Pain Intensity – Two-sample t-tests revealed no significant differences between the Active and Sham groups in the degree of change in any of the BPI pain intensity items or the Composite Pain Intensity score. However, paired t-tests within treatment groups revealed that among the four pain intensity measures in the BPI, the Worst Pain subscale appeared to be the most sensitive to CES treatment because it decreased the most. However, none of the changes in BPI pain intensity measures was statistically significant for any of the three groups.

Pain Interference - Two-sample t-tests revealed no significant difference between the Active and Sham groups with regard to change from pre- to post-intervention in any of the BPI pain interference items or the Composite Pain Interference score. However, in paired t-tests, for the Active group, there were significant changes in seven of the 10 individual pain interference items reflecting small to moderate effect sizes—general activity ($d = .665$), self-care ($d = .580$), sleep ($d = .532$), social activities ($d = .509$), normal work ($d = .450$), enjoyment of life ($d = .421$), and recreational activities ($d = .375$). A paired t-test within the active CES group revealed that the BPI Composite Pain Interference score decreased significantly (mean change = -14.6, $p = .004$, Cohen’s $d = .500$). For the Sham group, none of the individual items or the Composite Pain Interference score (mean change = -4.7, $p = 0.238$) changed significantly, however, during the Open-Label phase, interference with sleep decreased significantly ($d = .398$). Displayed in Figures 5-8 are the findings for the three pain interference items with effect sizes greater than .50 and for the Composite Pain Interference score. Although the Active group showed a significant reduction in Composite Pain Interference score from pre to post treatment, the change scores between the two groups were not significantly different, partly due to the fact that both groups showed a decrease in the Composite Pain Interference score from pre to post intervention. In other words, the slope for the Active group was significant and the slope for the Sham group was not significant, however the two slopes were not significantly different from each other.

![Figure 5](image-url)
Figure 6

Interference with General Activity

Figure 7

Interference with Social Activities

Figure 8

Interference with Enjoyment of Life
Exploratory analyses of the effectiveness of CES were performed only on the data from the group who initially received active CES (n = 18). Relationships of effectiveness with etiology of SCI, level and completeness of SCI, type of pain, and initial pain ratings were examined.

Etiology of SCI – There were only three participants in the active CES group who had non-traumatic SCI. The mean change in daily pain ratings from before to after CES sessions was -1.04 for the three persons with non-traumatic injuries and -0.67 for the 15 with traumatic injuries. Decrease in pain intensity, as measure by the BPI, also favored the non-traumatic participants for improvement in the individual items, as well as the Composite Pain Intensity score (-2.33 vs. -1.93). Decrease in pain interference was also greater for the non-traumatic group for 5 of the 10 interference items, particularly the only two items that decreased significantly--enjoyment of life (-5.33 vs. -0.73, p < .0001) and social activities (-4.57 vs. -1.20, p = .030)--as well as the interference composite score (-21.33 vs. -13.20), which was not significant.

Level and Completeness of Injury – The mean difference between the daily before and after ratings was greater for those with less impairment from the SCI. Persons (n = 4) with tetraplegia with ASIA grades of A, B, or C had the smallest decrease in pain (mean = -.22), persons (n = 6) with paraplegia with ASIA grades of A, B, or C had a mean change of -.46, and persons with an ASIA grade of D (n = 8) had a mean change of -1.19. The same pattern in which persons with tetraplegia A, B, or C had the smallest change and persons with ASIA D had the largest was found for the average pain and worst pain items of the BPI. However, when change in pain interference was examined, persons with paraplegia with grades of A, B, or C fared the best for 9 of the 10 individual items and the Composite Pain Interference score.

Type of Pain – Six of the Active group had musculoskeletal pain and 12 had neuropathic pain. Change in the before-and-after session daily pain intensity ratings was larger for the neuropathic group than for the musculoskeletal group (-.81 vs. -.57), however, due to the small number of participants in each group, this difference was not statistically significant. The findings for pain intensity as measured by the BPI were mixed. Two of the four items (worst pain and pain now) and the Composite Pain Intensity score favored musculoskeletal pain and two items (average pain and least pain) favored neuropathic pain. For pain interference, musculoskeletal pain improved more than neuropathic pain for eight of the 10 items and the Composite Pain Interference score (-19.50 vs. -12.08), but the differences were not significant.

Relation of Change in Pain Ratings to Level of Initial Pain Ratings – Examination of the relationship between the mean before-session score and the mean daily change score revealed that there was greater change in pain during the sessions for persons who had less intense pain before the session, particularly those whose mean before-session pain rating was 7 or less. However, in examining the relationships between the initial BPI scores for pain intensity and the change in pain intensity, persons with higher initial pain intensity had greater improvement in pain intensity during the 3-week study period. A similar pattern of relationships was found for the pain interference items and the Composite Interference score. Persons with higher initial scores improved more during the three-week period.

Discussion

This study extended the knowledge base regarding the effectiveness of CES on pain in persons with SCI. We established that persons with SCI can and will use the device at home.
over a three-week period. This period of use (21 days) is longer than in other studies and this difference may be important. Some persons may need a longer trial period before experiencing any effects of the treatment. The technology of the specific CES device used in this study is quite different than the devices used in other studies. The results of this pilot study indicated that participants who were given active CES reported significant pain reduction, on average, after each of the 21 daily sessions but those receiving sham CES did not (Figures 2 and 3), yielding a medium to large effect size. In separate paired t-tests, a significant difference was demonstrated between the before-session and after-session pain ratings for the Active group but not for the Sham group. Furthermore, when 17 participants who were originally in the Sham group participated in the subsequent open-label phase, there was a significant difference between the pre- versus post-treatment ratings (Figure 4). The reduction in pain in this study was not as great as in the study by Capel et al. in terms of pain intensity as a percent of baseline. In the first arm of their study, the final day’s pain rating was about 50 percent of baseline for the active treatment group, whereas our study found only an 11.3 percent change.

A number of possible factors may allow the relatively small size of the change in the average daily pain ratings to be viewed in perspective. First, there was considerably more variability in change scores among the Active group members than among the Sham group members (standard deviation of 1.15 for active vs. 0.38 for sham, and a range of 4.14 for active vs. 1.87 for sham). Second, the dose was set at a sub-threshold 100 microamperes to maintain the double blind design. It is possible that higher doses would result in greater improvement in pain; however, to date, no study examined the dose-response effect of CES on pain.

Post-hoc exploratory examination of the daily pain rating data suggested that persons with non-traumatic injuries, lower level and/or less complete injuries, neuropathic pain, and mild to moderate pain intensity may get more immediate benefit from CES than persons with traumatic injuries, higher and/or more complete injuries, musculoskeletal pain, and more severe pain. Thus, the size of change in pain ratings is likely to increase when specific subgroups of persons with SCI are targeted for this treatment. Additional studies are required to identify those patients who are more likely to benefit from CES, and investigate the possible mechanistic basis of such effects. Studies are also needed to determine the duration of pain relief after each session. Figure 2 suggests that improvements in pain dissipated substantially by the time of the next day’s session. However, there is no known reason that CES treatment could not be used indefinitely on a daily basis.

The findings of paired t-tests within groups revealed that the observed reductions in the individual and composite BPI pain intensity scores were not significant. However, the results showed that the interference composite score and several of the individual interference items decreased significantly for the Active group but not for the Sham group from before to after the 21-day intervention.

Thus, these data indicate that CES was effective in reducing pain intensity immediately after each treatment session, but its long-term effects in pain reduction were not statistically supported. Furthermore, exploratory analyses indicated that which groups tended to get the most benefit from CES differed depending on which outcome measure was examined--average daily decrease in pain intensity, three-week decrease in pain intensity, or three-week decrease in pain interference. Short-term relief of pain intensity was better in persons with less severe pain while longer-term relief of pain intensity and interference was better in persons with more severe pain. Such differences in effect may possibly be due to the small sample size. Future research should
replicate the findings using a larger sample size and more closely examine the issue of long-term effect of this treatment. 

The fact that active CES significantly altered short-term pain intensity and long-term pain interference but not long-term pain intensity, should not compromise the importance of the findings. Other studies have shown that (a) pain interference plays a central role in mediating the relationship between negative emotions (such as depression) and disability [67], (b) pain interference mediates the effect of pain severity on depression [67], and (c) perceived control over pain interference with daily activities is more strongly associated with functioning than is perceived control over pain intensity [68]. The relationship of pain intensity, pain interference, depression, and disability should be examined carefully in future studies of the effects of CES treatment.

One important limitation of the present study is that the participants were all male veterans receiving care at a Veterans Affairs healthcare facility. Generalizing the findings to female patients and other groups of persons with SCI outside of the VA population should be done with caution due to the somewhat unique socio-demographic factors inherent to this patient group and their type(s) and access to longitudinal care. Furthermore, this study did not address a number of important factors including: (a) the impact of CES on psychological distress and quality of life, (b) possible reduction in analgesic consumption, and (c) the amenability of patients to use the device on a long-term basis if it were available. Finally, while many statistical tests were performed, thus, increasing the probability of chance findings, the preliminary nature of this study and the use of post-hoc analysis of many variables was justifiable so as to better inform or suggest domains of inquiry for future studies. In conclusion, the findings of this study, if replicated with larger samples, support the use of CES as a practical and effective treatment for particular types of SCI-induced pain.

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