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An Expanded Trial of Scrambler Therapy in the Treatment of Cancer Pain Syndromes And Chronic Chemotherapy-Induced Peripheral Neuropathy

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Abstract

Background—Neuropathic pain is common among cancer patients and often difficult to treat. This study used Scrambler Therapy, a patient specific electrocutaneous nerve stimulation device, to treat cancer patient with pain.

Methods—Patients received Scrambler Therapy for ten sessions (one daily) over a two- week period. The primary outcome was change in pain numeric rating scale (NRS) at 1 month; secondary outcomes were changes in the Brief Pain Inventory and European Organization for Treatment and Cancer QLC-CIPN-20 over time.

Results—39 patients, mean age 56.5, 16 men and 23 women, were treated over an 18 month period for an average of 9.3 days each. The “now” pain scores reduced from 6.6 before treatment to 4.5 at 14 days, 4.6, 4.8 and 4.6 at 1, 2 and 3 months. ($p<0.001$) Clinically important and statistically significant improvements were seen in average, least, and worst pain; BPI interference with life scores, and motor and sensory scales on the EORTC CIPN-20. No adverse effects were observed.

Conclusions—In this single arm trial, Scrambler therapy appeared to relieve cancer associated chronic neuropathic pain both acutely and chronically, and provided sustained improvements in many indicators of quality of life.

Keywords

Chronic neuropathic pain; chemotherapy induced peripheral neuropathy; Analgesics; refractory pain; Scrambler Therapy; Electroanalgesia

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Introduction

Neuropathic pain is common in cancer patients and often difficult to effectively treat[1]. While conventional treatments such as opioids, neuroleptics, and other drugs help, all have side effects and limited effectiveness[2].

Scrambler therapy is a novel approach to pain control that attempts to relieve pain by providing “non pain” information via cutaneous nerves to block the effect of pain information. Scrambler therapy has relieved refractory chronic pain in several uncontrolled clinical trials: 11 cancer patients with abdominal pain[3]; 226 patients with neuropathic pain including failed back surgery, brachial plexus neuropathy, and others[4]; refractory chemotherapy induced neuropathic pain[56]; a wide spectrum on cancer-related pain[7]; and post-herpetic neuropathy[8], spinal cord stenosis, and failed back syndrome[9]. Other small series show a >50 % reduction in refractory post –herpetic pain[10], cancer pain[11], and back pain[12]. In a large series of complicated pain patients, including spinal pain, neuralgia, chronic regional pain syndrome, and multisite pain, D’Amato and colleagues reported a significant reduction in pain scores across all diagnostic groups[13]. In a pilot randomized trial[14], 52 patients with chronic neuropathic pain (spinal cord stenosis, failed back syndrome, post-herpetic neuropathy) were randomized to Scrambler therapy or treatment following standard pharmacology guidelines[15]; at one month, the Scrambler therapy group had a 91% decrease in pain, compared to the standard therapy group with a 28% decrease.

The purpose of this study was to continue our original observations in a more diverse group of patients with cancer pain syndromes as we became more experienced with the treatment, evaluate if there was chronic pain relief in addition to acute pain relief, and evaluate the impact of pain relief on quality of life.

Materials and Methods

Study Population

Patients were eligible if they had CIPN neuropathy from neurotoxic chemotherapy (including taxanes-such as paclitaxel or docetaxel, or platinum-based compounds such as carboplatin or cis-platinum or oxaliplatin, or vinca alkaloids such as vincristine, vinblastine, or vinorelbine, or proteosome inhibitors such as bortezimib). They were also eligible if they had other chronic pain syndromes including chemotherapy induced peripheral neuropathy with predominant numbness but not pain; post mastectomy pain; post-surgical pain; post-herpetic neuropathy; Post-radiation pain; or others such as vertebral compression, fracture, miscellaneous. Pain or symptoms of peripheral neuropathy had to be greater than 1 month's duration. The pain must have been stable for at least 2 weeks, with the patient reporting an average daily pain rating of > 5 out of 10, using the pain numerical rating scale (NRS: 0 is no pain and 10 is worst pain possible); or numbness that bothered the patient at least “a little bit” on the CIPN-20. Patients had to be at least 18 years of age, have a life expectancy > 3 months, and an ECOG Performance Status of 0, 1, or 2. The Institutional Review Board approved the study, all patients gave informed consent, and the trial was listed nationally (MC10CC, NCI-2011-00339, 11-000675, NCT01347723).

Standardized Scrambler Treatment

The Scrambler Therapy was done as previously described[5]. Briefly, each Scrambler Therapy patient was given a 45-minute daily treatment for 10 consecutive days, Monday thru Friday. The stimulus was increased to the maximum intensity individually bearable by the patient that did not cause any additional pain or discomfort. The Scrambler therapy group maintained their starting drug treatment with no changes.

Data and statistical considerations

The clinical demographic characteristics were summarized by basic descriptive statistics. A repeated measure of analysis of variance was used to test if there are any changes over time on NRS pain scores, BPI scores, EORTC CIPN-20 scores, and morphine oral equivalent doses (MOEDs), respectively. Pair-wise comparisons between the time points were tested and the Tukey's HSD procedure was used to adjust for the multiple comparisons to control the overall type I error of 5%. SAS 9.2 was used for all analyses.

Results

There were 16 men and 23 women with a mean age 56.5 years. There were 28 Caucasian-Americans and 11 African-Americans, who underwent an average of 9.3 days of treatment each. The cause of pain was CIPN in 33, post-mastectomy pain in 3, post herpetic neuropathy in 2, and radiation related pain in 1 person.

Full results are shown in table 1. Results are shown for the whole group. When we analysed the 33 CIPN patients separately, there were no differences between them and the entire group. (Data not shown, available on request.)

The primary endpoint results, the least squared means of the Numeric Rating Scale for "pain now" immediately before and after each session are shown in Figure 1. The NRS change over time was significant (p-value of the overall testing = 0.0006), and the change between day 30 and baseline, the primary endpoint, was significant (adjusted p-value by the Tukey's HSD procedure = 0.0070).

The secondary endpoints all showed significant improvement. The least squared means of BPI pain score from Question 5 (What is your pain now?) are shown in Figure 2. The difference between day 30 and baseline was statistically significant (adjusted p-value = 0.0049) and the change over time was significant (p-value = 0.0002).

The sensory component of the EORTC CIPN-20 also improved as shown in Figure 3, as did the motor component, shown in Figure 4. For the sensory component, the change over the entire time period was significant (p-value <0.0001), and the difference between day 30 and baseline was significant with the adjusted p-value = 0.0007. For the motor component, the change over time was statistically significant (p-value = 0.0019), and compared with baseline motor component, days 14, 30, and 60 have significant lower motor component with the adjusted p-values = 0.0143, 0.1035, and 0.0094, respectively. The use of opiates did not change appreciably, as shown in Figure 5 (p-value = 0.45).

We saw across the board improvements in all the components of the BPI "interference with normal life" that were sustained, in mood, sleep, relationships, etc. A typical curve is shown in Figure 6, "How much did pain interfere with your ability to walk?" The difference was significant, p = 0.0003 at the 30 day time point from baseline.

Discussion

In this trial Scrambler Therapy appeared to reduce pain, both acutely and chronically. It substantially reduced the interference of pain with normal life in every scale measured. The substantial reduction in pain scores from baseline to the primary endpoint at one month, 30%, meets the IMMPACT recommendations for a moderately important improvement[16,17,18] The reduction in CIPN pain scores is more than the 10% reported with the only drug proven to have efficacy, duloxetine[19]. While we did not formally study quality of life in this pilot trial, the changes in function as assessed by the CIPN-20 and BPI were all encouraging and long lasting. As in previous trials, we saw no side effects.

There are limitations to this study. First, there was no control group so some of the change could be due to placebo, regression to the mean over time, and recovery. In the randomized controlled trial of duloxetine versus placebo in CIPN patients such as treated here, the placebo group changed only by 0.1–0.2 (of 1.0 points on the 10 point scale) during the first and second six week periods of testing[22]. Our patients had rapid, stepwise relief over 14 days, then persistent relief that is larger than the effect heretofore observed with placebo. Second, this was not a homogenous group of patients so the effects could be disparate. For instance, in the duloxetine study, the drug helped patients with oxaliplatin-induced neuropathy but had no effect on taxane-induced neuropathy[22]. Our study was not of sufficient size to report meaningful differences in any subgroup.

There are strengths to this study, in addition to the limitations. The patient reported outcomes are all standard, reproducible, and valid. The magnitude of the pain relief effect is large, persistent, and consistent with the size of the pain relief in the other uncontrolled Scrambler therapy studies and in the one randomized pilot trial.

In conclusion, the pain relief obtained in this trial encourages further development of both treatment and knowledge regarding Scrambler Therapy. This knowledge will provide a better understanding of the mechanisms of action and new opportunities for the treatment of all forms of pain. It also provides more knowledge of effect size for further randomized placebo or sham controlled trials.

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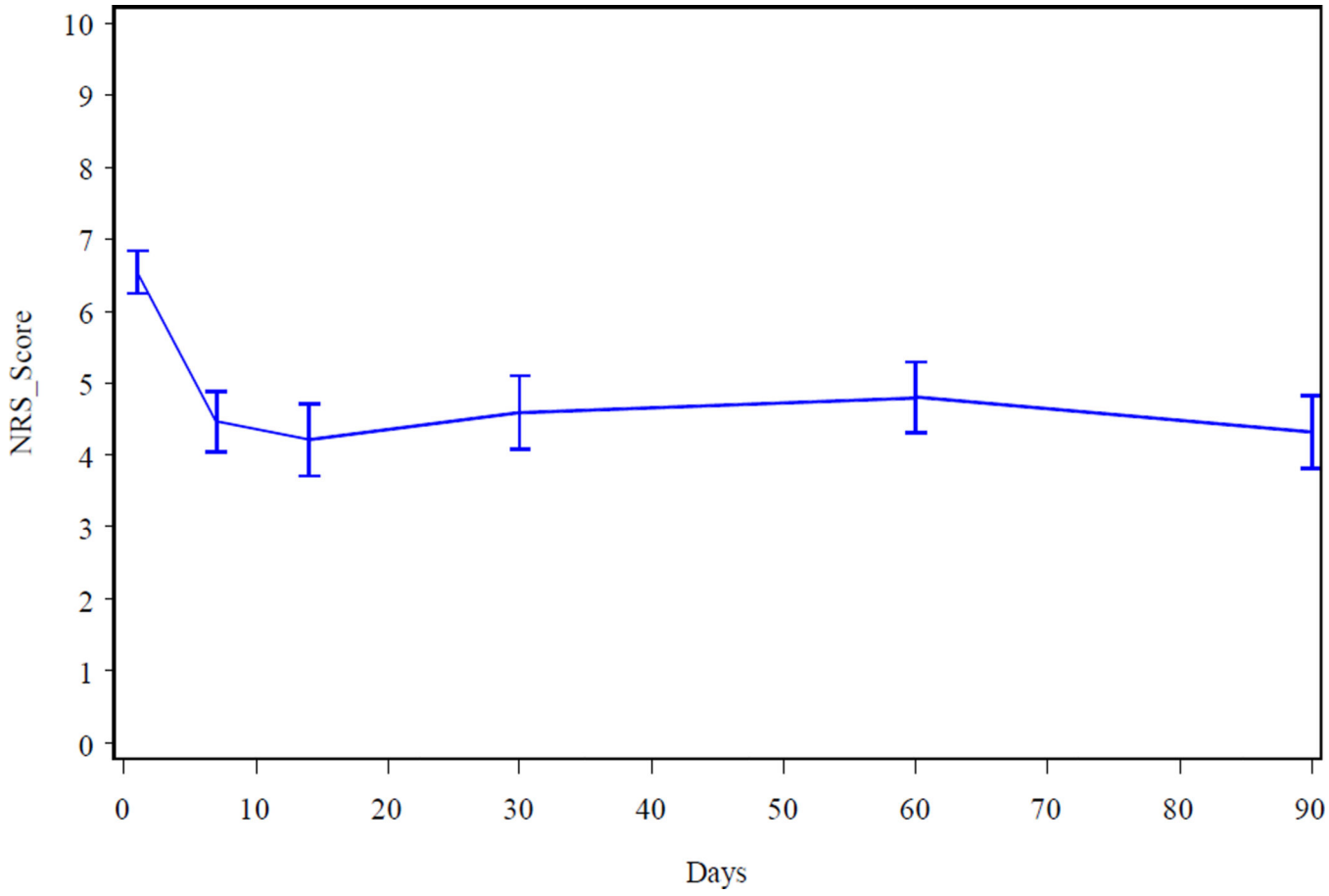

Figure 1.
Effect on Numeric Rating Scale, Pain

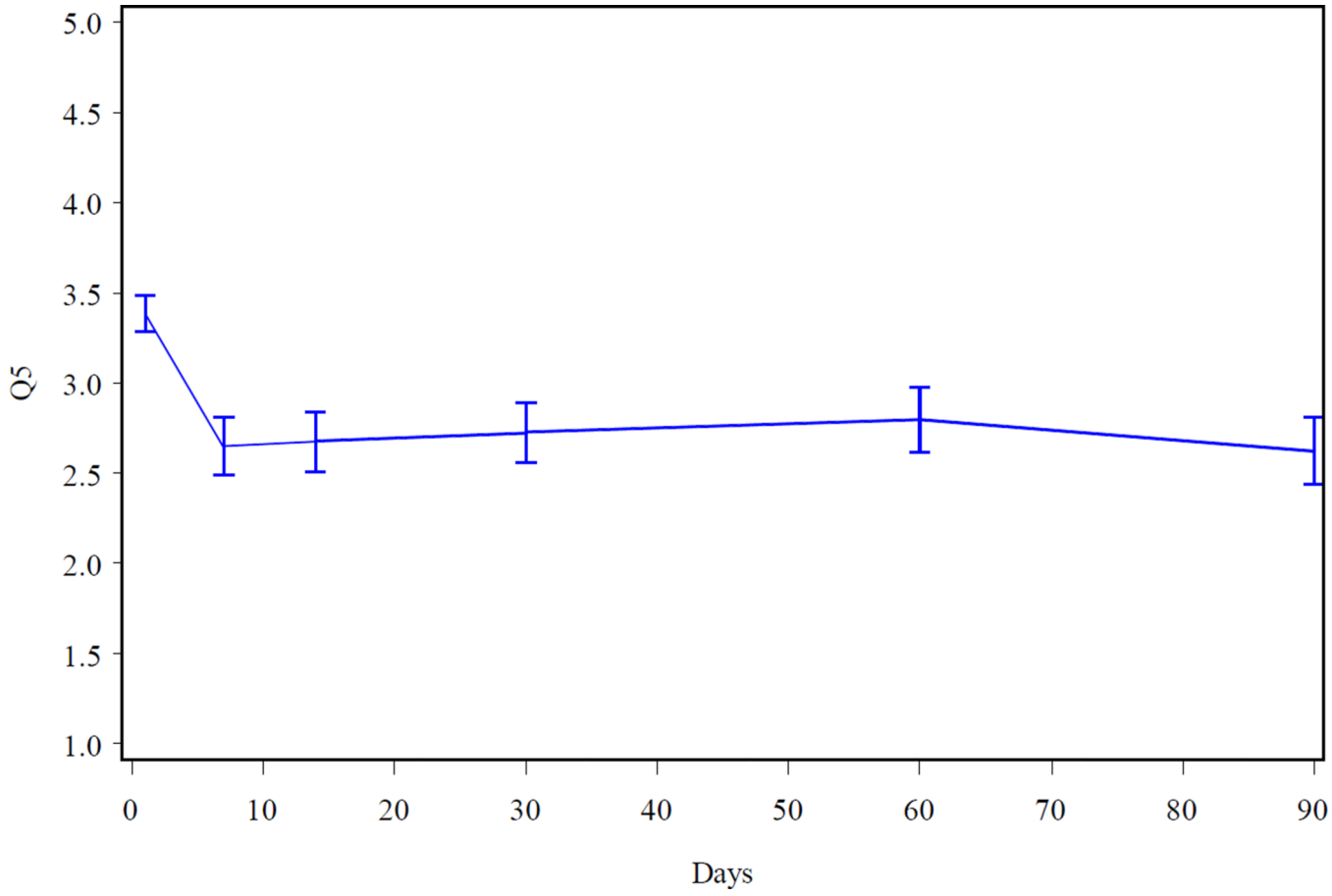

Figure 2.
Effect on BPI question 5, What is your pain now?

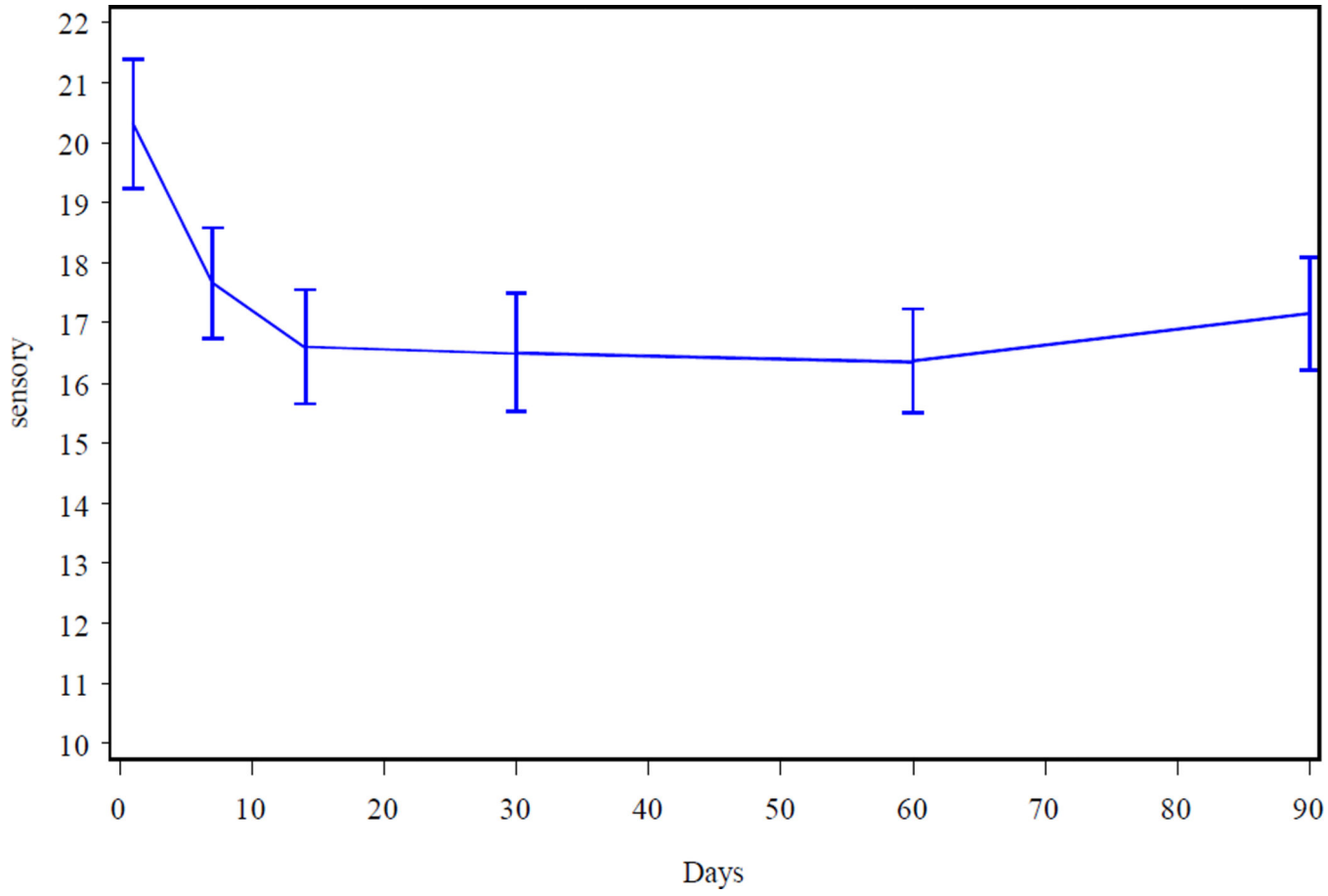

Figure 3.
Effect of Scrambler Therapy on sensory components of the CIPN-20

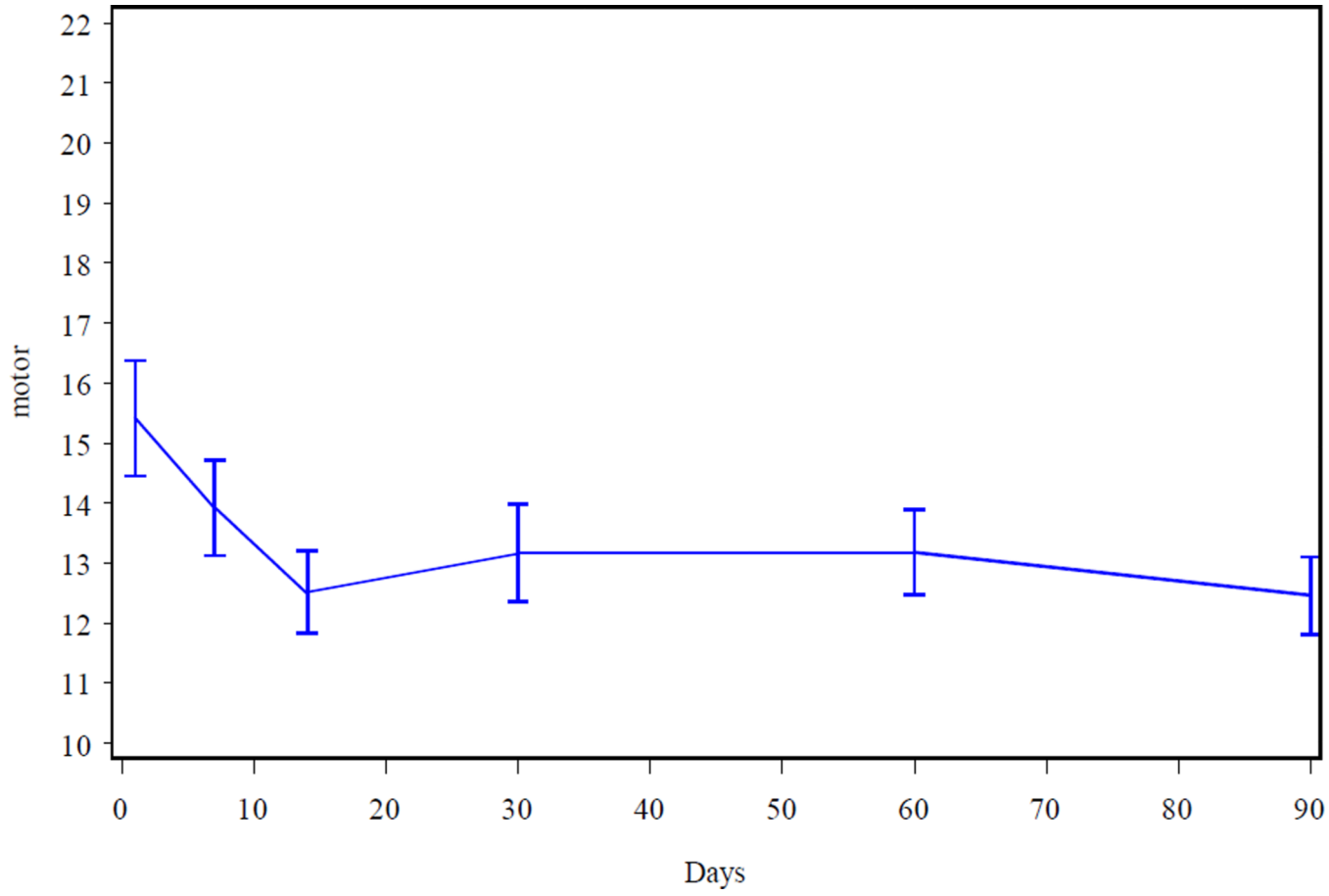

Figure 4.
Effect of Scrambler Therapy on motor components of the CIPN-20

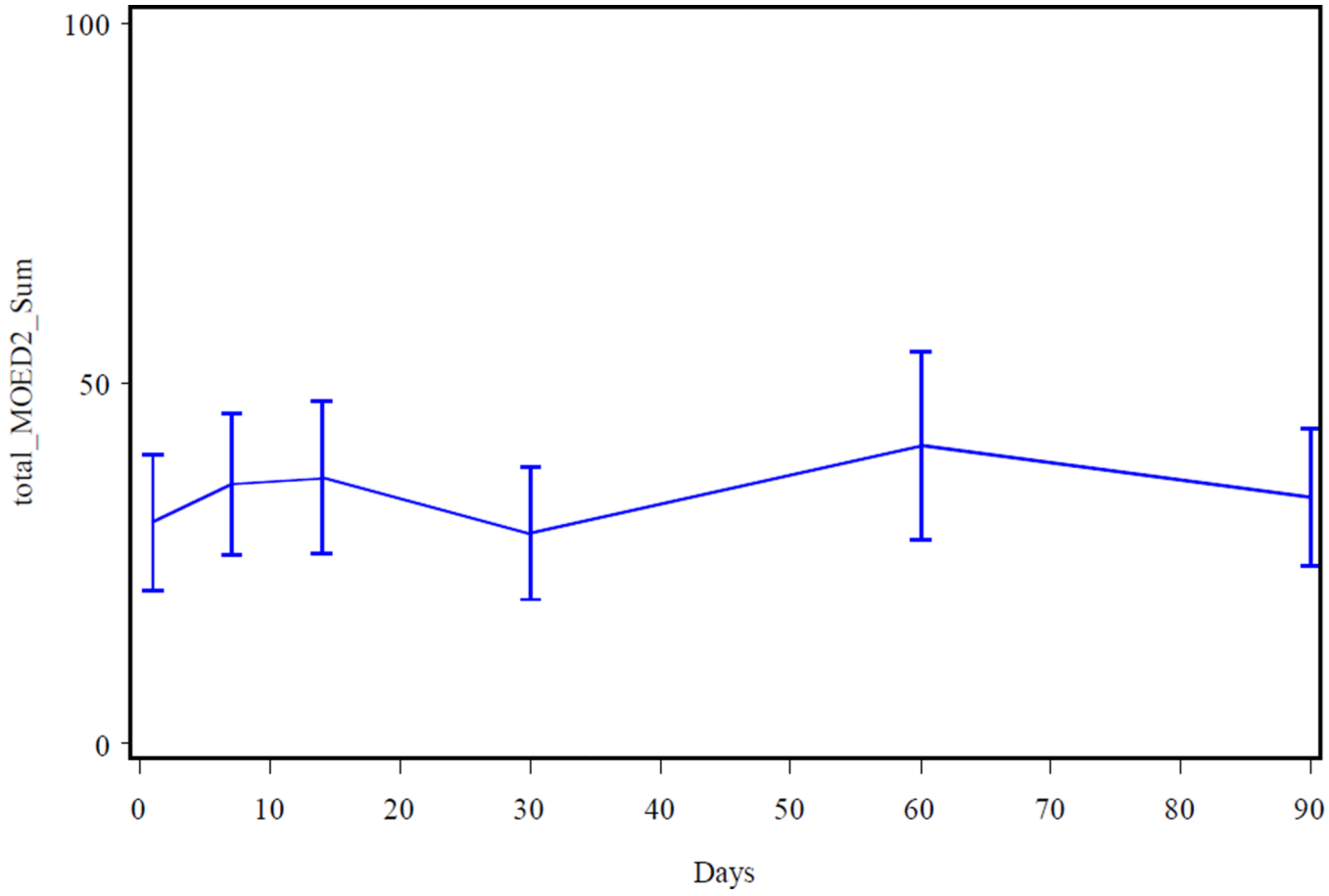

Figure 5.
Use of opiates during the trial, showing no significant differences

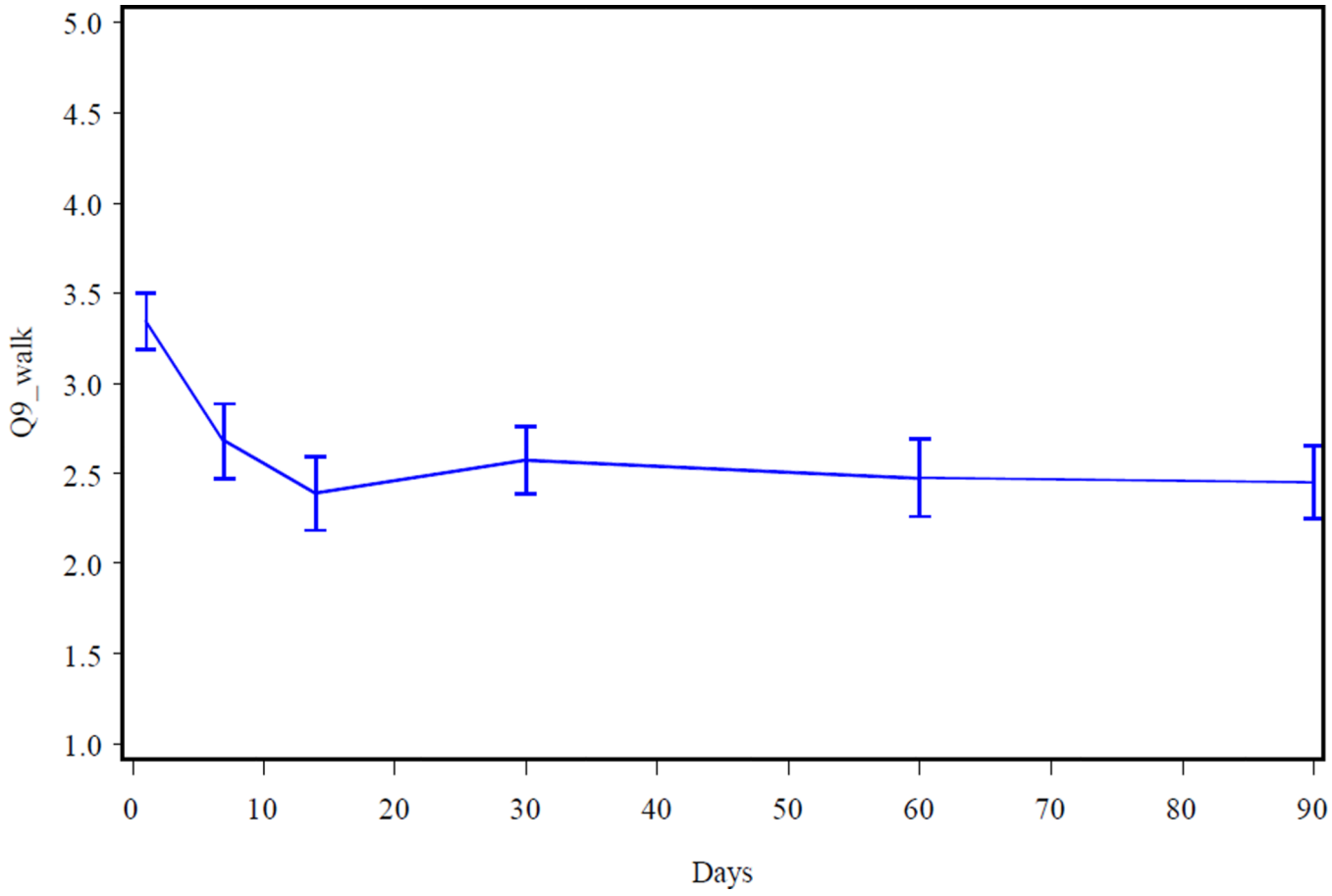

Figure 6.
How much did pain interfere with your ability to walk? (as representative of all the BPI interference questions)

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Table 1

Summary results of least squared means and/or p-values of comparing each time point with baseline

	Baseline	**14 days p-value***	**1 month p-value***	**2 months p-value***	**3 months p-value***
Numeric Rating Scale Pain (NRS)	6.5385	4.2142 0.0005	4.5901, −30% 0.0070	4.7984 0.0090	4.3204 0.0020
BPI Q2 pain at its worst	3.7692	3.0138 0.0069	3.1722 0.0165	3.1129 0.0043	3.2035 0.0892
BPI Q3 pain at its least	2.4615	2.0766 0.3823	2.2541 0.7913	2.3847 0.9977	2.2462 0.8987
BPI Q4 pain on average	3.3333	2.7733 0.0672	2.8535 0.0617	2.8319 0.0296	2.8739 0.1773
BPI Q5 pain right now	3.3846	2.6765 0.0033	2.7254 0.0049	2.7980 0.0093	2.6271 0.0014
BPI 9. Circle the word that describes how, during the past 24 hours, pain has interfered with your _____. (only P values are shown)					
General activity		0.0022	0.0501	0.0689	0.0150
Mood		0.0009	0.0013	0.0131	0.0014
Walking ability		<.0001	0.0003	0.0009	<.0001
Relations with other people		0.0011	0.0537	0.0194	0.0109
Sleep		0.0207	0.0287	0.0017	0.0043
Enjoyment of life		<.0001	<.0001	0.0002	<.0001
EORTC CIPN-20					
Sensory	20.3124	16.5985 0.0006	16.5019 0.0007	16.3696 <.0001	17.1601 0.0005
Motor	15.4088	12.5068 0.0143	13.1628 0.1035	13.1682 0.0094	12.4578 0.0038

* We compared baseline Day 1 to day 14, 30, 60, 90 with the Differences of Least Squares Means Tukey-Kramer Adjustment.