PAIN® 154 (2013) 2178–2184

PAIN®

www.elsevier.com/locate/pain

Longstanding neuropathic pain after spinal cord injury is refractory to transcranial direct current stimulation: A randomized controlled trial

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

ARTICLE INFO

Article history:
Received 20 February 2013
Received in revised form 20 June 2013
Accepted 28 June 2013

Keywords:
Below-level neuropathic pain
Clinical trial
Neuropathic pain
Randomised controlled trial
Spinal cord injury
Transcranial direct current stimulation

ABSTRACT

Neuropathic pain remains one of the most difficult consequences of spinal cord injury (SCI) to manage. It is a major cause of suffering and adds to the physical, emotional, and societal impact of the injury. Despite the use of the best available treatments, two thirds of people experiencing neuropathic pain after SCI do not achieve satisfactory pain relief. This study was undertaken in response to a recent clinical trial reporting short-term, clinically significant reductions in neuropathic SCI pain with primary motor cortex transcranial direct current stimulation (tDCS). In this investigation, we aimed to build on this previous clinical trial by extending the assessment period to determine the short-, medium-, and long-term efficacy of tDCS for the treatment of neuropathic pain after SCI. We found that, contrary to previous reports, after 5 tDCS treatment periods, mean pain intensity and unpleasantness rating were not significantly different from initial assessment. That is, in this trial tDCS did not provide any pain relief in subjects with neuropathic SCI pain (n = 10). A similar lack of effect was also seen after sham treatment. Because the injury duration in this study was significantly greater than that of previous investigations, it is possible that tDCS is an effective analgesic only in individuals with relatively recent injuries and pain. Future investigations comparing a range of injury durations are required if we are to determine whether this is indeed the case.

1. Introduction

Although loss of mobility is often considered the most serious consequence of spinal cord injury (SCI), people with SCI consistently rate pain as one of the most difficult problems associated with their injury [31]. It not only is a cause of suffering, but also has a direct bearing on the ability of the spinally injured person to participate in rehabilitation and to regain their optimal level of activity [1,31]. Although a wide range of treatment options is used for SCI pain, evidence from clinical trials indicates that satisfactory relief (50% pain reduction) is at best obtained in only one third of individuals [8].

A wide range of neuromodulatory techniques has been used in recent years to target supraspinal pain mechanisms associated with persistent pain. Cortical targets have been of particular interest due to their accessibility to noninvasive methods [19], for example, techniques such as transcranial magnetic stimulation and transcranial direct current stimulation (tDCS) [4,19]. Of particular relevance to SCI neuropathic pain, a noninvasive electrical stimulation trial published in 2006 demonstrated profound analgesic effects [9]. This randomized controlled trial using a 5-day course of tDCS reported a >50% reduction in neuropathic SCI pain intensity in the majority of subjects tested (63%) for the duration of follow-up [9]. Although subjects were only evaluated for 16 days, the large reductions in this notoriously treatment-resistant pain suggested that tDCS may be an extremely effective option for individuals with neuropathic SCI pain.

In light of this, given the initial substantial benefit of tDCS on pain intensity, we decided to replicate this study and use a substantially longer follow-up period to determine the length of analgesic effect and therapeutic value as a long-term treatment. The aim of this study therefore was to determine the short-, medium-, and long-term efficacy of tDCS for the treatment of neuropathic pain after SCI.

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0304-3959/$36.00
http://dx.doi.org/10.1016/j.pain.2013.06.045

2. Methods

2.1. Study participants

Ten subjects with complete thoracic SCI and neuropathic pain were recruited for the study (mean age ± SD = 56.1 ± 14.9, 8 male) (Table 1). Neuropathic pain was defined as pain arising within an area of altered sensation below the neurological level of SCI. History, examination, and past records were examined to exclude other causes. The International Spinal Cord Injury Pain Classification was used to define type of pain [6]. Subjects were required to have had pain for more than 6 months and be 3 or greater on an 11-point numeric rating scale (0 = no pain; 10 = most intense pain imaginable). The mean duration of injury was 21.3 ± 13.8 years, and the mean duration of pain was 15.8 ± 11.3 years. Ethics approval was obtained from the local institutional ethics committee, and all subjects gave informed consent to participate in the study.

2.2. Study design

A randomized crossover design was used so that all subjects participated in an active treatment (transcranial direct current stimulation) and sham treatment period. Both the subjects and the response assessor were blinded to the randomization sequence. The assessments of pain and other pain-related variables occurred at initial assessment, before and after each period of intervention, and at follow-up (4 weeks and 6 months). Subjects were not requested to cease medications before the trial. However, stable use was required. The randomized crossover designed is shown in Fig. 1 (Consort E-Flowchart [24]).

2.3. Interventions

2.3.1. tDCS treatment

Both the active and the sham treatments used were identical to those described previously by Fregni et al. [9]. For each active treatment, one 20-minute session was delivered each day for 5 consecutive days. A 4-week period occurred between each treatment type (active and sham). Direct current was applied to the scalp using a saline-soaked pair of surface sponge electrodes (35 cm^2, 5 × 7 cm) and delivered by a commercial tDCS unit with a maximum output of 10 mA. During active tDCS treatment, subjects received anodal stimulation of the primary motor cortex (M1), in which the anode electrode was placed over C3 or C4 (using an electroencephalogram 10/20 system) and the cathode electrode over the contralateral supraorbital area. The electrode placement was determined using a standard electroencephalogram head cap. This electrode position enhances the excitability of M1 [28]. Stimulation was applied to the dominant hemisphere (left for right-handed subjects, right for left-handed subjects). Of note, all patients had bilateral neuropathic pain. A constant current of 2-mA intensity was applied for 20 minutes (30-second ramp on, 8-second ramp off). During this stimulation protocol, subjects commonly report an itching sensation at both electrodes at the beginning of the stimulation. This stimulation protocol has been shown to be safe in healthy volunteers [16].

2.3.2. Sham intervention

For sham stimulation, the electrodes were placed in the same positions as for anodal M1 stimulation; however, constant current 2 mA was only delivered for 10 seconds (30-second ramp on, 8-second ramp off). During active tDCS treatment, subjects typically report tingling sensations under the electrodes, which rapidly fade [27]. Our sham intervention was therefore designed to provide an initial period of tingling so similar sensations were perceived during active and sham tDCS protocols. This sham protocol has been used by previous investigators [9,11].

2.4. Assessments

Subjects completed several questionnaires and underwent physical examination. The neurological level of injury was determined using the American Spinal Injury Association Impairment Scale [23]. Questionnaires recorded SCI duration, level, completeness, injury type, handedness, and level of disability. Pain duration, severity (numerical rating scale and verbal rating scale), location, and quality were assessed by interview and the Neuropathic Pain Scale [10]. State depression was evaluated by use of the Beck Depression Inventory (BDI) [3]. Pain unpleasantness was assessed in the

Table 1
Subject demographics.

Number	Age	Gender	Neurological level of injury	Injury duration (years)	Duration persistent pain (years)	Etiology	Analgesic medication
1	57	F	T8	46	4*	Transverse myelitis	Nil
2	45	M	T7	10	10	MVA	Oxycodone SR 20 mg twice per day Methadone 20 mg twice per day Morphine 20 to 60 mg per day Amitriptyline 100 mg at night
3	26	M	T10	3	1	MVA	Gabapentin 600 mg 3 times per day
4	66	M	T9	10	9.5	MVA	Pregabalin 150 mg twice per day
5	76	M	T12	28	27	MVA	Gabapentin 400 mg divided over 1 day
6	50	M	T3	33	33	Gunshot injury	Nil
7	59	M	T9	33	30.5	MVA	Nil
8	70	M	T10	8	8	MVA	Nil
9	67	F	T10	18	16	Fall	Pregabalin 150 mg 3 times per day
10	45	M	T4	24	19	MVA	Amitriptyline 100 mg at night Tramadol SR 300 mg per day Clonazepam 2 mg at night
Mean ± SD	56.1 ± 14.9			21.3 ± 13.8	15.8 ± 11.3		

* This patient described evoked neuropathic pain below the neurological level of injury since onset (46 years). F = female; M = male; MVA = motor vehicle accident; SR = sustained release.