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Effects of Transcranial Direct Current Stimulation (tDCS) on Chronic Pain in Spinal Cord Injured Patients

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Abstract

Introduction: Pain following spinal cord injury (SCI) is notoriously difficult to manage and often refractory to treatment. Novel approaches, such as non-invasive brain stimulation, targeting central mechanisms associated with chronic pain, have shown early promise as a safe treatment in various patient groups, including spinal cord injury. To date the number of small clinical trials using non-invasive brain stimulation to treat chronic pain in SCI have produced mixed results (1). We report here the findings of a UK based trial examining the effects of anodal Transcranial Direct Current Stimulation (tDCS) administration on pain in spinal injury patients.

Methods: Sixteen spinal injury patients from the National Spinal Injury Centre, Stoke Mandeville Hospital, Aylesbury, UK participated in a single centre, double blind randomized control trial. Patients were randomly allocated to either the active (n=8) or sham (n=8) treatment groups. tDCS was administered by electrodes with anode placement over the dominant M1 and the cathode electrode over the contralateral supra-orbit scalp area. Subjects received either active (2mA anodal current) or sham tDCS for 20 minutes daily treatment for 5 consecutive days with the dose based on previously reported chronic pain studies in spinal cord injury patients. A mixed ANOVA was used to evaluate both tDCS treatment and time effects on validated assessment measures for pain and depression up to 2 weeks following treatment intervention.

Results: No adverse effects of the treatment were observed in this study, nor were there any significant differences between groups in rating perception of stimulation. While treatment appeared to have reduced group pain scores on a visual analogue scale (VAS), there were no statistically significant differences between active and sham treatment groups when re-examined at the two week follow up.

Conclusions: There was a reduction in self-assessed VAS pain score in our small group of SCI patients during treatment in both the sham and active tDCS and at two weeks post treatment. However, our study appears to indicate only a placebo-like effect of tDCS on chronic pain in SCI and no effect attributable to the active anodal stimulation over motor cortex. We also did not observe any significant effects over time or treatment on neuropathic pain when assessed with validated measures. We observed trends of non-significant reduction in some of self-assessed pain scores of measures, however, these are inconclusive. Studies of clinical efficacy of pain treatment by tDCS in spinal cord injury should therefore be conducted on a larger scale, and with a longer follow up period to address the limited evidence available.

Keywords: Spinal cord injury; Pain; Neurostimulation; tDCS

Introduction

Pain is a common secondary complication following spinal cord injury (SCI) affecting the bio-psycho-social aspect of patient's life [1]. In addition to loss of mobility, chronic pain is one of the most serious consequences of SCI, and the most persistent symptom associated with spinal cord injury [2]. Pain also directly contributes to disability by limiting participation in rehabilitation and return to work [3]. Pain may be continuous or it can worsen following SCI, and it has also been observed that patients reporting neuropathic pain 3-6 months following SCI are likely to continue experiencing it at 3-5 years. In addition, pain has a broad impact on physical, emotional, cognitive and social functioning that needs to be evaluated and addressed in any management plan [4]. Achieving optimal pain relief relies on an accurate identification of the type of pain present [5] as it has been increasingly recognised that pain following SCI may be due to a complex combination of changes at various levels of the nervous system [6].

In a high percentage of cases, pain following SCI is refractory to treatment approaches which include: drug interventions (i.e. anticonvulsants, analgesics, opioids, anti-inflammatory,

antidepressants), surgical approaches, and physiotherapy. However, despite various treatments, evidence from clinical trials indicates that satisfactory pain relief (50% pain reduction or more) is at best obtained in only one third of individuals [7]. In conclusion, pain in SCI patients is complex, the mechanism is poorly understood and it is further complicated by the psychosocial impact of the nature of injury. Treatment and management modalities do not work in isolation and need to be combined with pharmacological treatments, physical therapy and psychological input in specialist centers. More research needs to be conducted in novel experimental therapies with emphasis on improving patient's quality of life after SCI [8]. Non-invasive brain stimulation (NIBS) techniques have shown early promise in treating chronic pain, and moreover it has shown to be well tolerated and safe [2], [8]. The proposed mechanism of action suggests that, like direct cortical stimulation of motor cortex, may involve alteration of subcortical circuits associated with persistent pain [9]. Based on success with these methods in pain trials, it has been suggested that NIBS may act by modulating neuroplasticity of central pain mechanisms [10], [11]. Among the NIBS techniques used to treat pain, both repetitive Transcranial Magnetic Stimulation (rTMS) and Transcranial Direct Current Stimulation (tDCS), have been trialed and earlier results have been the impetus for possible therapeutic treatment approaches for chronic pain following spinal cord injury [12]. Studies have shown that both methods may be effective in pain relief [11], but tDCS have key advantages over rTMS and that has made it a more attractive application for pain relief. Compared to TMS, tDCS equipment is less expensive, much more portable, and commercially available devices which could enable potential self-administration in an outpatient setting. tDCS applies continuous weak electrical current on the scalp and acts through inducing changes in the electrical properties of the neuronal membrane that can result in depolarisation (anodal) or hyperpolarisation (cathodal) of the stimulated area. Since some studies monitoring excitability changes in human motor cortex have demonstrated that changes in excitability outlast the application duration for several minutes to hours, possible synaptic effects may also be involved. Thus, application of tDCS over the motor cortex (M1) may modulate pain perception through indirect effects on pain modulating areas such as thalamic and subthalamic nuclei [13].

In a RCT study by Fregni et al. [11], one week of daily 2mA tDCS treatment over dominant M1 in SCI patient showed a significant reduction of pain for active treatment only. Although subjects were only evaluated for 16 days, the significant reductions in this treatment-resistant pain individuals suggested that tDCS may be an effective option for management of neuropathic pain in SCI patients [11]. In contrast a more recent study using a small cohort of patients utilizing a cross over design showed that tDCS did not provide any pain relief in subjects with neuropathic SCI pain out to 6 months post treatment [2]. In this additional feasibility study, we examined the possible therapeutic effects of 5 days anodal tDCS treatment on chronic pain in a small group of SCI patients admitted to spinal injury wards undergoing rehabilitation.

Methods

This study was a single centre, double blind, randomized, sham-controlled trial located at the national spinal injury centre (NSIC) at Stoke Mandeville Hospital (Aylesbury, UK). Inpatients were recruited from spinal injury wards and randomly assigned to either groups. At the outset of the study, sample size calculation, based on a Fregni study [12], anticipated 16 or more subjects per treatment groups. Participants were enrolled between August 2012 and May 2014 with the following inclusion criteria: moderate/severe pain assessed with the visual analogue scale (VAS) scoring pain perception of 4 or higher (moderate-severe intensity) and stable over 1 week at baseline, and on a stable pain treatment (medication and rehabilitation). Those excluded from the study were: affected from other neurological or neuropsychiatric diseases, including epilepsy, with a history of severe head injury, a history of unmanaged substance abuse and acute dermatological condition affecting the scalp. Group allocation was done sequentially by enrolment through an allocation list generated using online software (www.random.org). The study complied with the ethical standards of the Helsinki declaration was approved by local research ethics committee (Health Research Authority National Research Ethics, Bristol REC Centre, Bristol BS1 2NT UK). Participants provided written consent.

Table 1 Baseline data for SCI patients in the study. American spinal injury association (ASIA) classification (A-D); injury: traumatic (T), transverse myelitis (TM), visual analog scale (VAS); The Leeds Assessment of Neuropathic Symptoms and Signs (LANSS)] Pain Scale; The McGill Pain Questionnaire (MGPPQ): Beck depression inventory (BDI).

Patient	Treatment	Hand	Age	Gender	Months post injury	AIS	Injury Level	Type of Injury	VAS pain	LANSS	MGPPQ	BDI
S1 [5]	sham	L	28	M	125	B	C5	T	8	19	59	35
S2 [7]	sham	R	33	M	9	B	C6	T	5	17	6	18
S3 [8]	sham	L	40	M	12	A	C8	T	3	12	34	6
S4 [11]	sham	R	51	M	7	A	C4	T	8	19	40	29

S5 [12]	sham	L	38	M	23	A	T4	T	7	19	53	27
S6 [13]	sham	L	33	M	72	A	C4	T	8	11	51	32
S7 [14]	sham	R	52	M	302	A	T10	T	9	5	57	4
S8 [16]	sham	R	42	F	3	D	T4	TM	5	17	12	2
A1[1]	active	R	33		12.5	A	T11	T	4	7	24	4
A2 [3]	active	R	61	M	4	C	C6	T	6	15	27	7
A3 [4]	active	R	60	M	5	C	C5	T	6	9	36	22
A4 [6]	active	R	47	M	5	D	C4	T	5	5	8	7
A5 [9]	active	R	29	M	4	D	T4	T	6	23	43	47
A6 [15]	active	R	28	F	156	A	T4	T	5	6	6	20
A7 [17]	active	R	57	F	4	D	C4	TM	7	-	24	1
A8 [18]	active	R	67	M	5	D	T2	T	6	12	48	11

The study was structured in 3 phases following the initial recruitment: one week baseline, 5 days of daily treatment with tDCS, and a 2 week follow up. In addition to daily assessment of VAS pain, several other self-assessments were undertaken by each participant, as well as other outcome measures obtained by a blinded clinical assessor. Moreover, during the treatment week, participant's vital signs (temperature, pulse rate, saturation and blood pressure) were monitored before and after the intervention but none of the participants exhibited any adverse effects that would warrant exclusion from further tDCS treatment. During the post-treatment follow up period, all assessments were obtained daily for the first 5 days, and then weekly for up to 2 weeks post treatment, including a weekly full clinical assessment of all outcome measures.

tDCS

Sham or anodal tDCS was applied by means of a programmable battery-operated constant current unit, (model- Neuroconn DC stimulator Plus®, Rogue Resolutions, Wales UK). Stimulation was applied through carbon rubber electrodes inserted into sponge pockets (both 5x7 cm) soaked in isotonic saline and coated with conductive ultrasound gel to reduce scalp/hair impedance (<10kOHms). The anode (positive) electrode was centred over C3 or C4 (of the dominant hemisphere) which was first measured and marked on the head with indelible pen. Identification of M1 anode electrode placement was from Cz (vertex of 10-20 International System of Electroencephalography) in compliance with tDCS electrode placement guidelines, and typically 3-5 cm lateral to midline. The cathode was positioned over the contralateral frontal supra-orbit. Electrodes were fixed securely and comfortably to the scalp with two elastic bandages. The tDCS stimulation was delivered for 5 consecutive days on a ward setting, while patients were either sitting upright in bed or in a wheelchair, between 9am and 5pm, accommodating the stimulation with the patient's timetable of daily routine rehabilitation activities at the National Spinal Injury Centre.

For the real stimulation, 2mA current intensity was applied for 20 minutes, with a ramp duration at onset/offset of 20 seconds, (current density of 0.057mA/cm², total daily charge of 68.6mC/cm²). Our rationale for location, electrode size, orientation and current strength was based on relevant earlier pain study which also used 2mA current targeting the dominant primary motor cortical area [11]. For sham stimulation, 2mA current was maintained for 30 seconds following the same onset/offset rise time, (current density of 0.057mA/cm², total daily charge = 1.7mC/cm²). Thus for the sham treatment, this duration was longer than previous sham stimulation duration parameters, but well below minimum duration reported to produce M1 excitability after effects [13].

Previous studies have identified that the use of short duration (10-20 s) of the target current is a suitable method of sham application, given that the perception of the electrically induced sensation of tingling and itchiness during application are rapidly habituating, so that it is difficult to identify sham or active conditions based on this sensation [13]. While we were aware of recent concerns about the sham integrity of 2mA current (14), our study was a replication of pain relief and determined not to use a weaker intensity, but we monitored possible detection by patients as described later. To ensure both operator and patient blinding, we utilised the study mode of the stimulation device, which required a 5 digit numerical code to be entered each day to initiate application. The set of unique numerical codes were pre-allocated according to the randomised treatment list by an independent researcher who was not involved in this study. During this mode of operation, only a countdown of stimulation duration was shown on the LCD display irrespective of type of stimulation. Thus, double blinding included, the operator, patients, and the clinician involved with assessments and was maintained throughout the statistical analysis. We also monitored daily reported sensations associated with the treatment and evaluated this using Likert scales (0-3 rating of sensation). In addition, at the end of the week, patients were also asked to rate how certain they were of the type of treatment received using a 5 point

Likert scale: [(1) certain sham, (2) might be sham, – (3) unsure either way – (4) might be active, (5) certain active].

Table 2 Baseline assessments for the two treatment groups. Means and standard deviations are shown for the two treatment groups as well as independent t-tests results for comparison.

	Sham	2mA tDCS	Mean Difference	T statistic	P Value
Age in years	39.6 (8.6)	47.8 (15.8)	-8.125	-1.28	0.221
Time from injury (mo.)	69.1 (103.2)	24.4 (53.3)	44.7	1.09	0.295
VAS pain (1-10)	6.4 (1.7)	5.3 (1.4)	1.087	1.4	0.183
BDI (1-63)	19.1 (13.5)	14.8 (14.9)	4.25	0.6	0.56
BRF Pain Severity [0-10]	6.5 (1.8)	4.47 (0.92)	1.99	2.76	0.015*
BRF Pain intensity (0-10)	5.6 (2.2)	3.2 (1.78)	0.812	2.39	0.032*
MGPQ (0-76)	37.3 (21.4)	27.0 (15.1)	13.4	1.34	0.202
LANSS (0-24)	14.8 (5.1)	11.0 (6.4)	3.88	1.29	0.212

VAS: visual analogue scale; BDI: Beck's depression inventory; BRF Brief pain inventory; MGPQ: McGill pain questionnaire; LANSS: Lans assessment for neuropathic symptoms and signs

Outcome measures

Pain and depression measures used were the following self-assessed and combined patient and clinician assessments, which have been previously validated: VAS (10 cm Visual Analogue Scale), Leeds Assessment for Neuropathic Symptoms and Signs (LANSS, range 0-24), Mc Gill Pain Questionnaire (range 0 to 78, the higher the score the higher the pain), Brief Pain Inventory (BPI)-severity (range 0 to 10) and intensity (range 0 to 10), Clinical Global Impression of Change CGI-C scores range from 1 (very much improved) to 7 (very much worse), Patient Global Impression of change (PGIC) scale (range 1 no changes after the treatment to 7 a great deal better after treatment), and Beck Depression Inventory (BDI) (range 0 to 63 with score 0-13 no depression, 14-19 mild depression, 20-29 moderate depression, 30-63 severe depression).

Statistical analysis

Data were analysed using SPSS (Statistical Package for Social Science for windows version 20, IBM). Following the main statistical analysis of the study, identification of the two treatment group allocations was revealed. One participant (A7) in the anodal tDCS treatment group was not given the LANSS Neuropathic pain for the study at baseline, and for others there were some missed assessments at various time points during the follow up monitoring period, which represented about 20% of the complete data set. Normality of the data was assessed using the Shapiro-Wilks test and therefore parametric statistics was determined appropriate here. Evaluation of Likert scale assessment of perception, type of sensation, and treatment detection was done by nonparametric tests. In order to compare baseline characteristics between the two study groups we used independent samples t-tests for patient characteristics and

assessment pain scores. A mixed factors ANOVA was used to examine the interaction effect of tDCS treatment (between groups factor) and time (within factor). Levene's test for equality of variance and Mauchly's sphericity test were also undertaken and where necessary sphericity adjustment to the degrees of freedom using Greenhouse-Geisser adjustments are reported. Statistics reported here include the exact p value and partial eta squared (η^2) for F tests in SPSS. Significance was set at $p < 0.05$, and post hoc comparisons between group were undertaken using a Sidak correction. The analysis was undertaken on raw assessment scores across baseline, treatment days and up to 2 weeks post treatment. Group mean and standard deviations and 95% Confidence intervals (CI) are reported in the text.

Results

Of the 18 patients recruited for this study two dropped out in the early stages, one completing 5 days of treatment, and the other after the first day of treatment. Therefore, data are provided on 16 subjects, 8 in each treatment group. The majority of the participants in this study with only three females (sham (1) and active (2) participants. Baseline characteristics of participants are shown in table 1. Differences in the composition of patients according to ASIA Impairment Scale (AIS) classification are also noted: Sham treatment group, 5 complete (AIS A), 3 incomplete (AIS B and D), and for the active treatment group, 2 complete, and 6 incomplete (AIS B, C and D). In terms of injury, both groups mainly consisted of those who had traumatic injury, and one in each group was diagnosed with transverse myelitis. Baseline comparisons between the two groups are shown in table 2. T-tests revealed no significant differences between treatment group allocation for age, time since injury, and most of the assessments, except

for significant higher BPI pain intensity and severity scores for the sham treatment group.

All patients tolerated the daily application of tDCS, with no adverse effects reported during the week of administration, or in the follow up period. Patients described the stimulation, irrespective of treatment, as a mild tingling sensation without pain, under one or both of the electrodes. There were no

significant differences for ratings of stimulation sensation between groups, (see Table 3). The median detection of treatment type by the participants, obtained on the last day of administration, were 3.0 for the sham and 4.0 for the active, which were not significantly different ($U= 17.55$, $p =0.203$) $t(14)=1.37$; $p=0.19$).

Table 3 Perception and Detection of tDCS treatment: Group Median Ratings of perception on last day of treatment on types of sensation under one or both electrodes (0- no sensation to 3- strong sensation). Assessment treatment identification as sham or active using: (1) definitely sham, (2) might be sham, (3) unsure, (4) might be active, (5) definitely active. Mann Whitney U test for nonparametric two samples shown.

Perception of stimulation	Sham tDCS Median	2mA Anodal Median	Mann Whitney U	P value
Itchiness (0-3)	1.5	1	17.5	0.175
Burning (0-3)	1	1	20.0	0.351
Tingling (0-3)	1	1	24.0	0.053
Pain (0-3)	1	1	2.05	0.063
Detection of type of tDCS treatment (1-5)	3	4	17.55	0.203

VAS pain

Figure 1 illustrates the VAS pain scores for the two treatment groups over the time course of the study. The baseline average VAS pain score was 6.4 (CI 5.2 to 7.6) for the sham group and 5.3 (CI 4.1 to 6.5) for the active group, respectively. The ANOVA revealed no significant differences between treatment groups, $F(1,14)= 0.96$, $p=0.34$, $\eta^2=0.064$, but a significant effect of time, $F(5,5)= 5.41$, $p=0.001$, $\eta^2=0.28$; while there was no significant interaction effect, $F(5,5)= 1.13$, $p=0.352$, $\eta^2=0.075$. In post hoc comparisons, for the main effect of time, there was a significant mean difference between baseline and two weeks post treatment, (1.75 (CI: 0.25 to 3.2); $p=0.016$). At two weeks post treatment, the mean VAS pain scores was 4.4 (CI 2.4 to 6.5) for sham group and 3.8 (CI 1.76 to 5.8) for active group respectively, as showed in **Figure 1**.

Leeds assessment for neuropathic symptoms and signs (LANSS)

LANSS neuropathic pain scores at baseline for the sham (15.4 CI 10.4 to 20.5) and active group (11.0 CI 5.4 to 16.3) were similar to the LANSS scores at two weeks post treatment: the sham group (15.6 CI 8.7 to 22.5) and active group (9.0 CI 1.56 to 16.5), respectively. The ANOVA revealed no significant treatment effect, $F(1,11)= 1.72$, $p=0.22$, $\eta^2=0.14$, as well as no significant effect of time $F(3,33)=0.24$, $p=0.87$, $\eta^2=0.02$, or interaction of treatment x time, $F(3,33)= 0.33$, $p=0.81$, $\eta^2=0.03$.

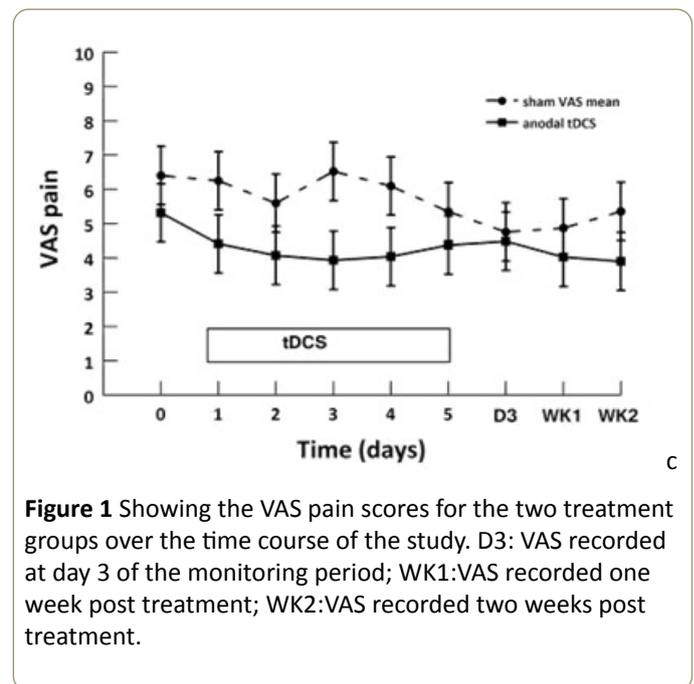


Figure 1 Showing the VAS pain scores for the two treatment groups over the time course of the study. D3: VAS recorded at day 3 of the monitoring period; WK1:VAS recorded one week post treatment; WK2:VAS recorded two weeks post treatment.

The McGill pain questionnaire

The mean McGill pain questionnaire (MCPQ) score at baseline was 37.3 (CI 22.4 to 52.2) for the sham group, and 27.0 (CI 13.0 to 41.0) for the active group, respectively. While at post 2 weeks, these scores were 38.3 (CI 22.6 to 53.9) for the sham group, and 23.6 (CI 9.0 to 38.3) for the active group. There was no significant effect of type of treatment on scores on the McGill Pain Questionnaire, $F(1,13)=2.54$, $p=0.135$, $\eta^2=0.16$, nor a significant effect of time $F(2,26)=0.96$, $p=0.40$,

$\eta^2=0.07$, but the interaction of treatment \times time was statistically significant, $F(2,26)=3.58$, $p=0.042$, $\eta^2=0.22$

The brief pain inventory (BPI)

Severity

As noted at baseline, the brief pain inventory (BPI) score for severity was 6.5 (CI 5.3 to 7.8) for the sham group and 4.5 (CI 3.3 to 5.6) for the active group were significantly different ($t=2.77$, $p=0.015$). While at post two weeks, this score was 5 (CI 3.2 to 6.8) for the sham group and 4.3 (CI 2.6 to 6.0) for the active group. The ANOVA revealed no significant effect here: for treatment, $F(1,13)=1.88$, $p=0.19$, $\eta^2=0.13$, however, a significant effect of time $F(2,26)=3.89$, $p=0.033$, $\eta^2=0.23$, but a non-significant interaction of treatment \times time $F(2,26)=2.56$, $p=0.10$, $\eta^2=0.16$.

Intensity

At baseline the BPI score for intensity, for the sham group was 5.3 (CI 3.6 to 6.8) and 3.74 (CI 1.4 to 6.1) for the active group were significantly different ($t=2.39$, $p=0.039$). While at post two weeks, these were lower, with the sham group score of 3.7 (CI 1.4 to 6.1) and 3.0 (CI 0.83 to 5.2) for the active group. The ANOVA showed no significant effects of treatment, $F(1,13)=1.36$, $p=0.26$, $\eta^2=0.09$, time, $F(2,26)=1.58$, $p=0.22$, $\eta^2=0.11$, or interaction of treatment \times time, $F(2,26)=0.84$, $p=0.44$, $\eta^2=0.06$.

Clinical global impression of change (CGIC)

The clinician's impression of change in the pain using the CGIC was assessed at the end of the 5 days treatment with a mean of 2.7 (CI 1.9 to 3.6) for the sham group and 3.2 (CI 2.6 to 3.1) for the active group. At reassessment, two weeks later, these scores were 2.9 (CI 2.0 to 3.7) for the sham group and 2.4 (CI 1.8 to 3.1) for the active group respectively. The ANOVA for treatment, $F(1,12)=0.68$, $p=0.42$, $\eta^2=0.05$, and time $F(1,12)=0.012$, $p=0.74$, $\eta^2=0.01$, were not significant, however, there was a significant interaction of treatment \times time $F(1,12)=5.65$, $p=0.035$, $\eta^2=0.32$.

Patient Global Impression of change (PGIC)

For the self-assessed patient impression of change (PGIC) the mean score was 3.1 (CI 1.4 to 4.8) for the sham, and 3.3 (CI 1.6 to 4.9) for the active group and hence were not significantly different at baseline. While at post two weeks, this was 3.13 (CI 1.4 to 4.8) for the sham, and 3.2 (CI 1.6 to 4.9) for the active group respectively. The ANOVA showed no significant effect of treatment, $F(1,12)=0.18$, $p=0.66$, $\eta^2=0.02$, or time $F(1,12)=0.48$, $p=0.5$, $\eta^2=0.04$, or interaction of treatment \times time $F(1,12)=0.12$, $p=0.74$, $\eta^2=0.01$.

Becks depression inventory (BDI)

We also evaluated the mean BDI depression scores, which was 17.3 (CI 5.6 to 29) for the sham group and 14.9 (CI 4.0 to 25.8) for the active group and were not significantly different at baseline. At post two weeks these were 13.6 (CI 2.7 to 24.4)

for the sham group and 15.1 (CI 5.0 to 25.3) for the active group respectively. The ANOVA revealed no significant effects of treatment, $F(1,13)=0.026$, $p=0.87$, $\eta^2=0.002$, or time $F(2,26)=3.012$, $p=0.067$, $\eta^2=0.19$, but a significant interaction of treatment \times time $F(2,26)=4.91$, $p=0.016$, $\eta^2=0.27$.

Discussion

The overall aim of this study was to examine whether 2 mA daily treatment with anodal tDCS produced a clinical significant reduction in chronic pain following SCI. Our findings did not show a treatment dependent difference in the main measure of self-reported VAS pain and other measures obtained post treatment in general. There was a reduction of 2 points on the VAS for the sham group and 1.5 points for the active group at two weeks post treatment observed in both groups sampled in this study. However, we noted some significant interaction effects with a small reduction in MGPCQ scores for the active treatment, as well as small increase in both CGIC and PGIC.

Anodal tDCS of the motor cortex has been reported to increase the pain threshold and to provide relief from neuropathic pain [14]. One of the studies we used as reference for our experimental protocol was that of Fregni et al. [11] which evaluated a follow up period following 5 days of anodal tDCS for up to post 16 days. This study gave a strong indication that tDCS may be an effective treatment for central pain due to traumatic SCI, showing a reduction in mean pain of 37% at 16 days, post treatment for the active treatment only. In our study, we found that there was a significant reduction in VAS pain measures over the time of the study, but of only 31% (sham) and 28% (active) treatment, respectively. There was a non-significant reduction in pain ratings after 5 days of trial but similar for both the sham and active treatments.

Wrigley et al. [2] examined changes in neuropathic pain scores following 5 days of similar dosage for up to one year, and did not find a statistically significant reduction in overall pain intensity in patients with neuropathic pain following SCI. They suggested that the reason for the lack of tDCS efficacy was the prolonged period since injury onset in their patients, since a negative correlation between pain intensity changes after tDCS treatment and duration of SCI had already been noted by the Fregni et al. [11]. Wrigley et al. [2] suggested the possibility that central changes resulting from neuropathic SCI pain had become consolidated, so that tDCS could not modulate the central pain related system.

In our study, the time from injury varied from patient to patient, with some as short as 3 months and some as long as 325 months, but overall there was no group difference at baseline, despite, the sham group average time from injury was 69 months while for the active group this was 24 months. This difference in the time from the injury between the groups resulted from the randomization process but in order to examine this impact on findings, other studies should consider shorter times since injuries for future evaluations of this form of treatment. Our results albeit of a small sample here, do show that pain perception was diminished in both groups

overall, therefore, the time from injury should not be correlated with the reduction of pain in our patients unlike the Fregni et al. [11] and Wringley et al. [2] trials.

Additionally, we noted a reduction in self-reported pain measures (VAS) during the active period for both the sham and the active treatment. That finding could be linked to the placebo effect associated with the tDCS administration. It is worth considering, therefore, the impact of placebo treatments and their potential effects in pain relief since its impact may be particularly important for non-invasive brain stimulation (NIBS) studies. In our trial, there was no differences between the two groups in terms of detection of the type of treatment. Of note in this regard, is a recent study which investigated the placebo effects of tDCS on depression demonstrating that tDCS reinforces brain networks activated by the expectation of therapeutic benefit, in other words, tDCS fortifies the placebo response to which it may, in part, contribute. Therefore, the investigators suggested that tDCS and placebo pills should be combined to increase the patients' expectation on efficacy for pain, as it is well known that the analgesia induced placebo pills effects are associated with activity in the insula, cingulate, and thalamus, which are regions believed to be polarized by tDCS montages commonly used in pain trials [15].

A recent trial by Yoon et al. [16], which studied the brain metabolism changes after tDCS stimulation over the motor cortex in patients suffering from pain after SCI, showed a statistically significant decrease in pain ratings after the active tDCS.

A study by Soler et al. [17] suggested that the analgesic effect of tDCS differed according to the subtype of spontaneous pain, and those findings were confirmed by Fregni et al. (2006) trial.

The precise mechanism responsible for the active effects of the tDCS remain unknown, but it has been reported that tDCS over M1 induces activity changes in a number of brain regions, and that the unilateral M1 tDCS evokes significant activity changes in both the underlying M1 as well as M1 on the contralateral side of the brain. It is possible that those analgesic effects are possible through the tDCS influence on activity within regions such as the somatosensory thalamus.

In our study, we decided to refer to validated safety protocols [16] which included the use of relatively large wet sponges (25 cm² to 35 cm²) and currents of 1 mA to 2 mA applied for duration of 20 min. For purpose of further studies, it might be useful to review those safety parameter in order to systematically elucidate the impact of the stimulation current settings, currently limited from safety purposes, on the analgesic outcomes looking, for example, at longer stimulation periods as well as thinking to use higher intensity and/or to apply it for longer interval of time each session, furthermore aspects related to electrode position and stimulation polarity could be revised. or it could be useful to review the stimulation protocols with regard to specific patient population.

The study by Yoon et al. [17] evaluated the underlying neural mechanisms of tDCS using [18] FDG-PET imaging, they found an increased metabolism in the medulla and decreased metabolism in the left dorsolateral prefrontal cortex (DLPFC) after active tDCS compared with sham tDCS. The left DLPFC changes were negatively correlated with pain relief. These results suggested that the analgesic effects of tDCS are associated with attentional modulation of pain perception through the DLPFC and medulla. Moreover, the increase in metabolism after active tDCS in the subgenual anterior cingulate cortex (sAAC) and insula suggest that tDCS modulates emotional components of the pain system.

The mechanism of tDCS is still not very well known, a work by Fritsch et al. [19] has shown that tDCS works on brain plasticity also by creating changes in the brain derived neurotrophic factor (BDNF) which has been associated with pain processing. In view of that we think that further studies looking at the relation between neurophysiology, biological markers and tDCS could be useful to improve our understanding on the tDCS effects on brain areas and furthermore for the optimisation the current stimulation protocols.

Our trial protocol overcame one of the Fregni et al. [11] study limitations since while in the before mentioned study subjects were allowed to change their medication regimen, we kept medications unchanged for all trial duration, which represented a challenge for the study.

Moreover, a study by Liebetanz et al. showed how antiepileptic medication and particularly carbamazepine interfere with the capability of motor cortex to react with sustained excitability changes to tDCS [20]. That is interesting to consider since, as mentioned, in our protocol we decided to continue the standard pain medications that the subjects were taking at the time of the trial. Since carbamazepine is one of the first line medication for neuropathic pain and the most of the subjects involved in our trial were on this treatment, we might hypothesize that a reduction in cortical effect after tDCS stimulation might be considered as a result of reduced excitability associated to long term neuroactive medication use in our population.

Another issue we faced has been linked to the hypothesis that the response to the tDCS stimulation could be variable in relation to the characteristic of the SCI lesion [12]. In facts, the links between pain and other variables such as level of injury, aetiology, completeness of SCI and psychosocial issues have not been extensively studied and an attempt at try to identify the SCI patients that show more improvements after the active treatment could be important to optimize future clinical trials. In our study we found clinical differences between the two groups which are related to the randomization, our sample population was randomized in a way that in the Sham group 6 participants out of 8 were complete SCI (AIS A), while in the Active group only 2 out of 7 were AIS A. Studies have suggested that variables such as advanced age at the time of injury, nature, onset intensity, bullet injury as a cause of trauma, early onset of pain in the weeks following the injury and associated symptoms (fatigue, infection, spasticity,

constipation, urinary retention, joint pain, mood changes) are negative prognostic factors, whereas symptoms typically associated with neuropathic pain such as dysesthesia, paroxysmal pain, location of SCI in thoracic and lumbar segments and sublesional pain are associated with positive response to brain stimulation, on the other hand completeness or incompleteness of the lesion has a neutral link with the response to the tDCS treatment [12].

Some strong points of our study protocol are that it has been designed and conducted in a double blinded manner and this is important since pain is a subjective variable and its evaluation as well as perception undergoes a significant placebo effect which is partially avoided with a double-blind trial method. Furthermore, it emerged that patient couldn't guess if they received the active or the sham treatment, in fact no significant differences emerged when patients were questioned about that during the trial. This finding confirms that tDCS can be used efficaciously in double blinded studies.

After the brain stimulation, no one showed adverse effects, neither in the short term nor after the follow ups, therefore the safety of tDCS have been confirmed by our study.

Conclusion

In conclusion, it does appear to be a reduction in some pain measures particularly during the active phase (5 consecutive days of 20 mA tDCS stimulation), but comparisons between sham and active treatment group indicate that this could be a partial placebo type effect, as the group differences are not significant.

Our data show that in individuals with longstanding neuropathic SCI pain, tDCS focused over M1 does not provide pain relief, our results are similar to the study by Wringley et al. [2] and differ from the Fregni et al. study [11] which inspired our study design.

In conclusion, even if anodal tDCS is a non-invasive, low risk neuro stimulation technique to treat one of the most bothersome among the consequences of SCI, such as chronic pain is, we still need to prove its real efficacy and we are yet not ready to prescribe it as an active for chronic pain.

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