



A preliminary study of transcranial direct current stimulation for the treatment of refractory chronic pelvic pain

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Background

The modulatory effects of transcranial direct current stimulation (tDCS) appear beneficial for different chronic pain syndromes; however, it is unclear whether this method can be used to treat refractory chronic pelvic pain.

Objective

The objective of this preliminary study was to determine the efficacy and safety of tDCS for the management of refractory chronic pelvic pain.

Methods

Seven patients with chronic pelvic pain having failed standard medical or surgical therapy underwent a crossover, double-blind sham controlled tDCS treatment protocol consisting of 1 mA applied for 20 minutes on two consecutive days with 2 weeks of follow-up symptom recording. Symptoms were recorded using multiple scoring systems, including visual analog scales for different pains, as well as organ-specific symptom scales. Comparison between active and sham treatment was performed by using paired *t* tests.

Results

Overall and pelvic pain scores were significantly lower after active compared with sham treatment, as were disability and traumatic stress scores. No patient discontinued the study because of side effects, which were infrequent.

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Conclusions

Active tDCS treatment induces a modest pain reduction in refractory chronic pelvic pain patients as compared with sham tDCS treatment. These results can guide the design and implementation of further studies investigating this method of neuromodulation for the treatment of refractory chronic pelvic pain.

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Chronic pelvic pain afflicts approximately 10% of women and results in billions of dollars in direct and indirect costs.¹⁻³ Chronic pelvic pain patients often receive more than one pain-related diagnosis,^{4,5} and these include pain of gynecologic origin, interstitial cystitis (IC), irritable bowel syndrome (IBS), fibromyalgia (FMS), levator ani syndrome, and vulvodynia.⁶ Multimodal therapy is the rule rather than the exception.⁷ Many of the treatments result in only symptom palliation, with relapses and repeat surgery being common.⁸ One explanation for this finding is the hypothesis that chronic pelvic pain is related to a dysfunction in pain-related neural networks, including the limbic system.⁹ Therefore, management of pelvic organs alone is unable to effect long-lasting resolution of the limbic dysfunction.

At the central level, pain leads to plastic changes in an extensive neural network that includes the spinal dorsal horn, limbic system, and cortical structures such as the somatosensory and prefrontal cortex.¹⁰ On the basis of earlier animal studies, transcranial direct current stimulation (tDCS) has been shown to alter brain activity in a reliable and significant way.¹¹ The tDCS is based on the application of a weak direct current to the scalp that flows between two relatively large anode and cathode electrodes. Some studies have shown that the efficacy of tDCS depends on parameters such as electrode position and current strength.¹² Application of tDCS for 13 minutes to the motor cortex can modulate cortical excitability for several hours.¹³

In addition to the encouraging results from tDCS studies on chronic pain, including spinal cord injury and fibromyalgia,^{14,15} it is unknown whether chronic pelvic pain can be affected by this technique. On the basis of the pathophysiology of chronic pelvic pain that is similar to other chronic pain syndromes, we hypothesize that active tDCS would result in greater pain improvement compared with sham tDCS. We therefore conducted a small, preliminary clinical trial to assess initial efficacy of this method for the treatment of chronic pelvic pain. In addition, the duration and extent of side effects from tDCS application were investigated. A pilot study is critical for providing information for future study design including sample size calculation and the inclusion or exclusion of different symptom scores for researchers of other laboratories.

Methods and Materials

This is a single-center, phase-II, double-blind, sham-controlled, crossover clinical trial to prospectively investigate

the efficacy of tDCS treatment in reducing chronic pelvic pain in a cohort of patients with refractory chronic pelvic pain. Conduct of this study was performed according to an institutional review board-approved investigational protocol at Summa Health System. Seven patients were randomly assigned to receive either active or sham tDCS at the first, 2-day treatment session. After a 2-week symptom recording interval, each patient then crossed over to the alternative 2-day treatment, which was in turn followed by a second 2-week recording period. Only the person administering tDCS was unblinded to the treatment assignment during the study. All other personnel in the study, including the investigators, study coordinators, participants, and their families, and all primary medical caregivers, were blinded.

Patients received a diagnosis of chronic pelvic pain as defined by the American College of Obstetricians and Gynecologists.¹⁶ Gynecologic pain was kept stable due to either a hysterectomy or the presence of continuous medical ovarian suppression. All patients had stable, continuing pain despite thorough evaluation and maximal medical or surgical management of concomitant pain disorders, including IC, IBS, and myofascial pain syndrome. Patients taking stable narcotics were included.

Direct current was transferred by a saline-soaked pair of surface sponge electrodes (35 cm²) and delivered by a specially developed, battery-driven, constant current stimulator. The dominant hemisphere was stimulated because all patients had midline pelvic pain. During each session, the anode was placed on the primary motor cortex (C3 or C4 according to the 10/20 EEG international system) and the cathode was placed over the contralateral supraorbital area. During active treatment, 1 mA of direct current was applied for 20 minutes. For sham treatment, the same montage was used; however, current was applied only for 30 seconds, as in a previously described protocol of sham stimulation.¹⁷

Daily symptom evaluations included visual analog scales (VAS) (0-10) for overall pain, pelvic pain, back pain, migraine pain, bladder pain, bowel pain, abdomen pain, and pain with intercourse. This scale has been widely used in studies that evaluate pain as an outcome. Its reliability and validity have been demonstrated¹⁸ and it has been used to evaluate the different aspects of chronic pelvic pain.¹⁹ Disability was measured using a previously validated 11-point scale.²⁰

Other symptom scales included the 20 point interstitial cystitis symptom index (ICSI),²¹ the five minor IBS

criteria,²² and the Regional Pain Scale for FMS,²³ which ranges from 0-111. Further evaluation included the International Personality Item Pool scales for depression (range: 0-30) and anxiety (range 0-25),²⁴ the posttraumatic stress disorder (PTSD) symptom scale (range: 0-51),²⁵ and a sleep questionnaire with a range of 0-27.²⁶ Other scales included a measure of tDCS side effects arranged in several categories with a severity scale and a scale to relate the side effect to the tDCS treatment.

Only symptom scores and side effects from the first week of treatment were compared; scores from the second week after either active or sham treatment failed to demonstrate any significant differences. Scores of continuous variables after active and sham treatments were compared using paired *t* tests when normally distributed and Wilcoxon signed ranks tests when not normally distributed. As this was a pilot, exploratory study, we did not define a main outcome for analysis; we were interested in exploring multiple potential changes, and therefore did not correct the significance levels of the tests to correct for multiple comparisons. The results of this study will need to be confirmed by subsequent research.

Results

Seven patients with a mean age of 38 years (range: 24-36 years) participated in the study. All patients had a previous history of abuse, gynecologic pain, and IC. All patients were either in natural menopause or undergoing medical or

surgical induction of amenorrhea. All but one patient had myofascial pain syndrome in addition to the other pain generators listed. Patients had an average 80 months of pain, had seen an average of four previous physicians, had undergone an average of three previous surgeries, and were unable to perform normal duties for an average of 6 days a month. All patients were neurologically intact; three were on stable doses of chronic narcotic pain medication. Four patients ended up allocated to receive sham treatment first.

Symptom scores

Table 1 demonstrates the overall change in paired scores between sham and active treatment for each symptom studied. Overall and pelvic pain VAS (scores decreased significantly as compared with sham stimulation. The VAS for pain or potential pain with sexual activity (dyspareunia) increased slightly when comparing active vs sham stimulation, as did sleep scores. Disability as measured by the RM-11 also decreased significantly after active treatment.

Side effects

No patient discontinued the trial because of side effects of the treatment, active or sham. Of all the side effect possibilities, there were only 14 total instances of any degree of side effect definitely related to the treatment (0.8%). These side effects occurred after both active and sham treatment in a distribution that was not significantly

Table 1 Changes in symptom scores between sham and active treatment

	Sham Mean	Active Mean	Difference Mean	Percent change	95.0% LCL of mean	95.0% UCL of mean	<i>P</i> value, two-tailed
VASo	5.9	5.0	-0.94	-16	-1.78	-0.11	.028
VASpp	5.9	5.1	-0.80	-14	-1.63	-0.03	.038
VAS back	5.3	5.0	-0.23	-4	-0.85	0.39	ns
VAS migraine	1.8	1.7	-0.11	-6	-0.88	0.65	ns
VAS bladder	5.7	4.9	-0.80	-14	-1.81	0.21	ns
VAS bowel	3.5	2.9	-0.63	-18	-1.14	-0.12	.01
VAS abdomen	4.9	4.8	-0.07	-1	-0.58	0.44	ns
VAS sex	5.5	5.8	0.30	6	0.06	0.55	.01
ICSI	10.6	10.0	-0.54	-5	-1.36	0.27	ns
IBS total	2.8	2.7	-0.11	-4	-0.51	0.28	ns
RM11	6.7	5.8	-0.83	-12	-1.93	-0.27	.023
FMS total	30.0	26.9	-3.14	-10	-6.80	0.52	ns
IPIP A	14.5	14.9	0.37	3	-0.41	1.16	ns
IPIP D	18.9	19.4	0.49	3	-1.03	2.00	ns
Sleep	6.4	7.7	1.29	20	0.18	2.40	.01
PSS	20.0	18.8	-1.29	-6	-3.90	1.33	ns

LCL = lower confidence level; UCL = upper confidence level; VAS = visual analog scale; VASo = overall; VASpp = pelvic pain; ICSI = interstitial cystitis symptom index; IBS = irritable bowel syndrome; RM11 = 11-point disability scale; FMS = fibromyalgia scale; IPIP A = International Personality Item Pool anxiety; IPIP D = International Personality Item Pool depression; PSS = posttraumatic stress scale. The mean difference with its upper and lower 95% confidence levels (95% LCL and UCL), and *P* value of a two-tailed paired test (*t* test for normally distributed data, otherwise a paired Wilcoxon signed rank test) are shown for each symptom score. VAS scores for each symptom range from 0 (no pain) to 10 (maximum pain); ICSI (range 0-20); IBS (range 0-5); FMS (range 0-111); IPIP A and D (range 0-25) and (range: 0-30); Sleep scale (range 0-27 worst); PSS (range: 0-51).

different (Pearson's chi square = 2.561 [$P = .1095$] Risk Ratio [RR] = 2.49; 95% confidence interval [CI]: 0.7829 < RR < 7.9291). Of the definite, reported side effects, 79% occurred in two subjects, and only four subjects reported any severe side effects.

No patient demonstrated any degree of skin injury; fair-skinned individuals had mild, transient erythema under the supraorbital pad site. No patient reported seizure activity, hearing loss, difficulty thinking, trouble concentrating, or mood swings. Sham treatment resulted in one instance of dizziness, one of sleepiness, and one patient thought it caused her to ovulate. Active treatment resulted in two instances of sleepiness and one instance of numbness over the supraorbital application site.

Table 2 displays the number of side effects reported after active or sham treatment, arranged by side effect, and by severity. Reports of no or mild side effects after active or sham treatment were equivalent, and moderate or severe side effects definitely related to the treatment were very rare.

Discussion

In this pilot study, tDCS was well tolerated and moderately effective in decreasing symptom scores from chronic pelvic pain. A regimen of 2 days of treatment, followed by 2 weeks of symptom recording was chosen to decrease the possibility that there would be a lingering effect from the active treatment for those patients randomly assigned to receive that arm first. Although shorter than the usual number of days of active tDCS used in other treatment protocols, this was a pilot study designed to avoid crossover effects and to evaluate a wide range of symptom scores in different organ systems that might potentially be impacted by this technique.

Because pain is an inherently subjective complaint, many different scores have been proposed to measure the patient's experience, and in this study, multiple measures of symptom change were used. Because multiple measures were used, the actual statistical significance of each individual test should be reduced to compensate for the mathematical error introduced with multiple comparisons. Because this is an exploratory pilot study, the objective was to determine use of the technique in this patient population

Table 2 Side effects reported after active and sham tDCS treatment

Side effect	None/mild		Severe/moderate	
	Active	Sham	Active	Sham
Headache	27	24	3	1
Neck pain	24	20	2	0
Scalp pain	26	23	1	0
Scalp burning	19	24	5	0

The total number of potential responses is 35 per category of side effect; some patients did not fill out all side effects, and there were some side effects that were remotely or only possibly related to the treatment.

and to provide guidance for selecting symptom measures for future studies. As a pilot study, a lack of power may be expected; however, several measures did demonstrate a significant improvement with active treatment. These changes provide treatment response characteristics that can be used to determine the power and sample size necessary for future studies.

The changes in symptom scores overall (Table 1) demonstrated significant decreases in some VAS scores but not others. Overall and pelvic pain showed to be sensitive measures as they demonstrated significant changes to the short course of active (but not sham) tDCS, which was the objective of this study. The decrease in disability scores provides a useful measure of the impact of any changes in perceived pain, and validates that a decrease in pain scores can translate into an improvement in functionality.

The slight increase in the measure of VAS with intercourse may not be an actual worsening of symptoms, because patients are asked what they would anticipate their pain to be, and most of them are not sexually active. Sleep scores also worsened after active treatment, but this failed to create disability for the patient, which calls into question the significance of this finding. In addition, a recent study showed that tDCS improves sleep pattern as indexed by polysomnography in patients with fibromyalgia who received M1 tDCS over the primary motor cortex.²⁷

Side effects were limited and occurred equally after both active and sham treatments. Most importantly, no patient discontinued the study because of side effects. Symptoms were generally limited to the site of application of the tDCS contacts, and some of these may be improved with further refinement of the application process.

The results of this study are in agreement with results of previous trials showing that tDCS induces significant improvements in pain in patients with chronic refractory pain. Chronic pain is associated with a dysfunction in pain-related neural networks.²⁸ The rationale for motor cortex stimulation is based on evidence showing significant thalamic dysfunction in chronic pain and also on studies showing that motor cortex stimulation changes thalamic activity significantly.²⁹ Two previous studies also showed improvements in pain scores with tDCS in fibromyalgia¹⁵ and spinal cord injury.¹⁴

In conclusion, the results of this study encourage future trials that assess the role of tDCS in the management of chronic pelvic pain and that are useful for planning the clinical trial design. In addition, these results support the notion that tDCS can induce therapeutic gains in chronic pain syndromes that are refractory to medical treatments.

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