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Anodal stimulation of primary motor cortex in elderly women with fibromyalgia: A randomized, double-blind, placebo-controlled trial

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It is thought that an excessive motor cortical facilitation is involved in the physiopathology of chronic pain in fibromyalgia. Studies have shown that transcranial direct current stimulation (tDCS) changes motor cortex excitability according to the stimulation polarity. Based on these effects, it is conceivable to hypothesize that tDCS, which can modulate brain activity, may induce pain relief in patients with fibromyalgia. Fifty older women with fibromyalgia were included in this randomized, double-blind, single-center placebo-controlled trial study. Patients received sham stimulation or real tDCS with the anode centered over the primary motor cortex (M1) and the cathode over the contralateral supraorbital area (2 mA for 20 minutes for 10 sessions). Pain intensity was evaluated using the visual analog scale for pain. Assessments were done before treatment and 30 days after the last session of stimulations. The mean age of participants was 58.20 years (SD = 7.80) with an age range from 55 to 74 years.Results showed no statistically significant baseline difference among patients in demographics and clinical characteristics. Comparing visual pain analogue between the sham and treatment groups revealed a statistically significant difference (p *value* < 0.001) for VAS immediately after intervention and 1 month post intervention between the sham and treatment groups. Analysis of data also showed a significant reduction in pain immediately after intervention and one month post-intervention in the treatment group compared to the sham group. Anodal tDCS is an effective non-invasive technique for pain reduction in elderly women with FM. The clinical improvements observed in the current study may have considerable impacts on pain experienced by elderly women with FM.

Keywords: Fibromyalgia, Pain, Transcranial direct current stimulation

Introduction

Fibromyalgia (FM) is a widespread musculoskeletal chronic pain syndrome characterized by neuropathic tenderness, sleep disorders, mood dysfunction, anxiety, and fatigue [1]. Epidemiological studies have revealed that the prevalence of FM in the general population ranges between 2%–%7 with the rate increasing with age [2]. The mean age for diagnosis is 47 years, and the female-male ratio is 9:1 [3]. Data from the available literature suggests that FM may have a considerable effect on patient's quality of life, usually caused by serious emotional distress [4], which can be very costly for the health system of a country.

The relevant literature suggests that an excessive motor cortical facilitation is involved in the physiopathology of FM which has been correlated with a higher level of trait anxiety, and a lower pain threshold [5-7]. It is thought that the chronic sensation of pain in FM results from changes in brain sensory processing due to central sensitization and abnormal information across the afferent pathways to the brain [8].

Despite extensive studies, the pathogenesis of pain associated with FM is not fully understood. However, an unbalance between nociception and normal physiologic pain control has become a generally accepted pathophysiologic model of FM [9]. According to this model, there is an overall decline in the inhibitory pathways related to pain, allowing, therefore, low intensity or non-nociceptive stimuli to be processed in pre-cortical and cortical areas related to the pain. Another area that has been found to have an important role in the maintenance and relief of chronic pain is the primary motor cortex (M1). Recently, a comprehensive review found that other pain syndromes have an increased activation in this area and increased response to nociceptive sensory stimuli, indicating its interaction with other pain-related modulating areas [10]. Some authors have also reported that the baseline characteristics of primary motor cortex or M1 are altered in FM patients [11], and activity patterns in response to induced pain are abnormally increased [12]. It has been proven that brain

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stimulation techniques, for example transcranial direct current stimulation (tDCS), modify the excitability of the M1 and change the pain level in FM [13-15]. Actually, tDCS as a noninvasive brain stimulation technique seems to be an effective method for reducing pain in FM patients [13, 16]. This technique is safe and painless with few complications that delivers a weak direct current stimulation (usually up to 2 mA) over the scalp, neuromodulating cortical areas by decreasing or increasing the neuronal firing threshold [17]. In fact, tDCS over the dorsolateral prefrontal cortex (DLPFC) increased the pain threshold [17] and relieved chronic pain in FM patients [18, 19].

Most studies in this field have focused on FM in the general population, while little attention has been given to FM symptoms occurring in elderly adults. Therefore, the current study investigated the effects of 10 sessions of M1 tDCS on pain intensity in older women with FM.

Materials and Methods

Participants

Fifty women (mean age of 58.20 ± 7.80 years, age range from 55 to 74 years) with refractory FM (diagnosed according to the ACR 1990 criteria) were included in this randomized (random number table), double-blind, single-center, placebo-controlled trial study. Medication in all patients did not change during the 8 weeks before the start of the study, during the study, or in the follow-up period. Inclusion criteria comprised (1) females aged above 55 years; (2) mean pain score of at least 4 on the visual analog scale (VAS) preceding the clinical trial; (3) no history of neuropsychiatric or other chronic pain disorder; (4) no history of substance abuse or dependence except for nicotine; (5) no history of brain surgery, tumor, or intracranial metal implantation or seizure. Written informed consent was obtained from all participants before the study. After each session, patients were asked to report any complications. The study was performed in accordance with the Declaration of Helsinki, and the methods used in this study were approved by the Ethics Committee of Iran University of Medical Sciences, Tehran, Iran (IR.IUMS-.REC.1394.9211497002).

Study design

Patients were divided into 2 intervention groups: anodal stimulation of M1 and sham stimulation. Participants were blinded to the intervention groups as was the therapist who performed the analysis. A baseline assessment of pain intensity was performed before stimulation sessions. Subjects then underwent 10 sessions of active or sham stimulation over a period of 3 weeks. Clinical assessments were performed again after the last stimulation session. Subjects then participated in follow-up assessment at 30 days after the final tDCS treatment session.

Questionnaires assessing the clinical characteristics

The visual analogue scale (VAS) was applied in the current study to assess the intensity of pain. This scale is a validated questionnaire instrument with items rated from 0 to 10. VAS measurements were performed before and after the sessions and one month after the intervention and the active and sham stimulation groups were compared with each other. A higher score reflected a greater level of pain, and a lower score reflected a lower level of pain. VAS has been validated in the Iranian population [20]. Patients were asked to mark the number that best reflected the symptoms of pain at that moment. The Fibromyalgia Impact Questionnaire, a pain subscale, was also used to measure pain intensity. On the FIQ tool, the maximum score is 10, with scores of 10 representing higher pain intensity and lower scores representing lower pain intensity. It is also noteworthy that patients in this study were given a questionnaire on the adverse effects of tDCS so as to evaluate the adverse effects of the tDCS brain stimulation technique.

tDCS stimulation

Patients received 10 daily sessions (3 sessions each week) of either sham stimulation or anodal stimulation of the left primary motor cortex (M1). Direct current (DC) was applied by a saline-soaked pair of surface sponges (25 cm2) and delivered by a specially developed, battery-driven, constant current stimulator with a maximum output of 4 mA (ATTENDA, Iran). For anodal stimulation of M1, the anode electrode was placed over C3 according to the 10–20 system for EEG electrode placement. The cathode electrode was placed over the contralateral supraorbital area. A constant current of 2 mA was applied for 20 min. The electrodes were placed in the same positions for sham stimulation as for anodal M1 stimulation, but the stimulator was turned off after 30 s of stimulation as previously described as being a reliable method of blinding [21].

Statistical Analysis

Statistical analysis was performed using SPSS22.0 software (IBM, Armonk, NY, USA). Changes in VAS score and pain subscale of FIQ Questionnaire were considered as the primary outcome. The t-student test was used to compare outcomes in the two groups by time. Repeated measure (RM) ANOVA was also applied to consider the time trend as well as to assess differences in clinical variables across conditions. Differences were considered significant if *p-value* <0.05.

Results

Twenty-five patients were randomly assigned to the treatment group, and twenty-five were assigned to the sham group. The clinical and demographic characteristics of the enrolled patients are shown in Table 1. The results indicate that there was no statistically significant baseline difference in demographics and clinical characteristics. Comparing visual pain analog results revealed a statistically significant difference (*p value* = 0.001) for VAS immediately after intervention and one month post-intervention between sham and treatment groups (*p value* = 0.002) (Table 2). No patient left the study. All patients tolerated the tDCS treatment well.

Table 1. Comparison of demographic properties between sham and treatment groups

Parameter	Treatment group	Sham group	*p value* (Independent T-Test)
Age (Years)	58.8±40.00	58.7±08.84	0.887
BMI (kg/m^2)	25.3±82.64	26.48±3.54	0.518
Disease Length	7.3±56.36	6.2±24.78	0.139

Table 2. Comparison of visual pain analog between sham and treatment groups at different times of study

Measurement time of VAS	Treatment group	Sham group	*p value* (Independent T-Test)
Before intervention	6.80±1.22	7.28±1.33	0.192
Immediately after intervention	5.04±0.97	6.80±1.41	0.001
One month post-intervention	5.48±1.00	6.92±1.32	0.002

Assessment of pain level

Independent t-test results identified a significant pain reduction immediately after intervention (*p value*= 0.0001) and one month post-intervention (*p value* = 0.0001) in the treatment group compared to the sham group (Table 3).

The RM ANOVA test was used to compare both outcome measurements between the two groups at three different time points. The Machley sphericity assumption was established, the difference between the intervention and control groups was significant, and the trend of SF36 changes before the intervention compared to the next and one month later was significantly different (SF-36-Pain: F = 7.122, *p value*= 0.0001), (VAS: F = 7.301, *p value* = 0.0001).

Table 3. Comparison of SF-36-Pain between sham and treatment groups at different times of study

Measurement time of SF-36-Pain	Treatment group	Sham group	*p value* (independent T-Test)
Before intervention	31.80±18.37	28.3±16.14	0.478
Immediately after intervention	53.50±16.58	35.40±11.58	*p-value*=0.0001
One month post-intervention	45.3±14.88	31.00±12.03	*p-value*=0.0001

Discussion

To the best of our knowledge, the current study is the first to assess the effect of multiple sessions of anodal tDCS stimulation of M1 on pain intensity in elderly women with FM. Results from the present study indicate that 10 sessions of anodal tDCS treatment over the left M1 area induced significant, long-lasting, pain relief in older patients with FM. This study employed the tDCS noninvasive method for several reasons: it is easy to apply, it is a reliable and powerful technique for modulating brain activity, and it has an efficient sham condition [22] that is recommended mainly for FM studies.

A body of evidence confirms the relationship between FM-related pain and brain dysfunction: (i) Non–rapid eye movement sleep is modified in FM patients so that it is directly associated with disease symptom severity [23, 24]; (ii) Depression is associated with FM such that some researchers even assume that depression and FM may have similar pathophysiological backgrounds [25, 26]; (iii) Antidepressants such as tricyclic ones may be efficacious in promoting pain relief in patients with FM and other pain syndromes [26, 27]; (iv) Neuroimaging observations have revealed that regional cerebral flow in the pain-related brain areas of FM patients, such as thalamic nuclei, differ with that of healthy individuals [28, 29].

A great number of studies in the literature also report on the powerful modulatory impacts of the tDCS technique on

brain activity. Animal studies on how tDCS works have shown that polarizing currents applied to the special areas of the brain modulate cortical activity according to the stimulation polarity [30, 31]. This data was recently confirmed by pilot studies on humans in which anodal tDCS stimulation increased motor cortical excitability, while cathodal tDCS stimulation decreased it [32, 33]. Because tDCS alters the excitability of local cortices, it can modulate changes in FM-associated dysfunctional brain activity. Noting the increasing cortical excitability by anodal stimulation, it seems that reducing FM-associated pain results from an up-regulation of motor cortex excitability through indirect impacts of neural networks on thalamic nuclei (a pain-modulating area) [34, 35].

Regarding the above facts, the current study investigated the effects of 10 sessions of M1 tDCS on pain intensity in older FM patients. The findings of this study are in line with the evidence cited above. Other researchers have also confirmed the current results. For example, Lefaucheur et al. assessed the effects of active tDCS of the cortex in relieving pain. They concluded that patients who received active tDCS showed more significant pain improvement than patients who received sham stimulation [36]. Furthermore, Fregni et al. showed that anodal tDCS of the motor cortex in FM patients resulted in a significant improvement of pain in comparison with sham stimulation.

To recognize clinical properties that might be correlated with the tDCS treatment response, the current study conducted correlation tests with some demographic and clinical variables including age, BMI, and disease length. The data showed that there is no significant association between treatment and the studied demographic and clinical variables. This result is inconsistent with those of other studies. Fregni et al. found significant correlations, including a positive relationship between pain improvement and tender point scores and a negative relationship between pain improvement and BMI. They stated that the negative relationship between pain relief and BMI is intriguing and declared that being a surrogate of BMI for the clinical symptoms of FM can be a possible cause for this association. In fact, higher BMIs in FM patients result in higher resistance of the disease to treatment [37]. Thus, patients with more severe and refractory FM may have a poorer clinical outcome or might need more sessions of tDCS treatment to achieve the same level of pain relief.

Limitations

Similar to any other study, this one has some limitations. In addition to the small sample size that may not be representative of the population, there are other drawbacks. First of all, only female patients were recruited, and the conclusions reached in this research are not extensible to males, because of the emotional differences between males and females (i.e. stress, fear, and anxiety). Thus, in this context, gender may be a significant confounding factor. Second, the current study did not include normal subjects (control group) for comparison with differences between patients and controls. Although the present results are important to understand the possible effects of tDCS on pain reduction in elderly women with FM, the data does not provide sufficient or reliable evidence to guide decision making in clinical settings.

Conclusion

Taken together, the current results indicate that anodal tDCS is an effective non-pharmacological treatment for pain reduction in elderly women with FM. The clinical improvements observed in this study may have significant effects on older adults' quality of life. A further larger sample trial needs to be carried out to duplicate our results.

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Conflict of interest

The authors declare they have no conflicts of interest.

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