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Effects of transcranial direct current stimulation on pain, mood and serum endorphin level in the treatment of fibromyalgia: A double blinded, randomized clinical trial

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ABSTRACT

Background: Recent studies have shown that novel neuro-modulating techniques can have pain-relieving effects in the treatment of chronic pain. The aim of this work is to evaluate the effects of transcranial direct current stimulation (tDCS) in relieving fibromyalgia pain and its relation with beta-endorphin changes.

Material and methods: Forty eligible patients with primary fibromyalgia were randomized to receive real anodal tDCS or sham tDCS of the left motor cortex (M1) daily for 10 days. Each patient was evaluated using widespread pain index (WPI), symptom severity of fibromyalgia (SS), visual analogue scale (VAS), and determination of pain threshold as a primary outcome. Hamilton depression and anxiety scales (HAM-D and HAM-A) and estimation of serum beta-endorphin level pre and post-sessions were used as secondary outcome. All rating scales were conducted at the baseline, after the 5th, 10th session, 15 days and 1 month after the end of the sessions.

Results: Eighteen patients from each group completed the follow-up schedule with no significant difference between them regarding the duration of illness or the baseline scales. A significant TIME × GROUP interaction for each rating scale (WPI, SS, VAS, pain threshold, HAM-A, HAM-D) indicated that the effect of treatment differed in the two groups with higher improvement in the experimental scores of the patients in the real tDCS group ($P = 0.001$ for WPI, SS, VAS, pain threshold, and 0.002, 0.03 for HAM-A, HAM-D respectively). Negative correlations between changes in serum beta-endorphin level and the changes in different rating scales were found ($P = 0.003$, 0.003, 0.05, 0.002, 0002 for WPI, SS, VAS, HAM-A, and HAM-D respectively).

Conclusion: Ten sessions of real tDCS over M1 can induce pain relief and mood improvement in patients with fibromyalgia, which were found to be related to changes in serum endorphin levels.

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Introduction

Fibromyalgia syndrome (FMS) is a chronic painful, non-inflammatory condition characterized by a history of widespread

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pain, fatigue and diffuse tenderness on examination. The official definition of FMS, which is most commonly referred to, was published in 2010 by the American College of Rheumatology (ACR) [1]. According to these new criteria, the most important diagnostic variables were the widespread pain index (WPI) and categorical scales for cognitive symptoms, un-refreshed sleep, fatigue, and a number of somatic symptoms. The categorical scales were summed to create symptom severity for fibromyalgia [1]. Approximately 6–20% of the population has FMS with peak prevalence ranging between 25 and 55 years of age being higher in females than males [2].

In the past decade, a number of studies have revealed changes in brain activity associated with fibromyalgia. The pathophysiology of fibromyalgia is still unclear but appears to involve central nervous system dysregulation [3]. Panerai et al. [4] identified lower concentrations of beta-endorphins in mononuclear cells of the peripheral blood in fibromyalgia patients. Harris et al. [5] also found decreased mu-opioid receptor availability in the brains of fibromyalgia patients. However some studies that compared peptide concentrations in fibromyalgia and control groups found no differences in blood plasma [6,7]. Younger et al. [8] also found no evidence found for abnormal endogenous opioid activity in women with fibromyalgia.

Ceko and colleagues [9] explored structural and fMRI changes in young FMS patients, and found a decoupling between the insula and anterior mid-cingulate cortex, two brain regions that are normally strongly connected in healthy adults, as part of a salience network. Proton magnetic resonance spectroscopy (^{1}H-MRS) is a non-invasive MRI technique that can quantify the concentration of multiple metabolites within the human brain. Harris et al. [10] used ^{1}H-MRS to study glutamate and Glx (combined glutamate and glutamine) levels specifically in patients with chronic 'centralized' pain. Subsequently, they compared glutamate and Glx levels within the posterior insula between FM patients and pain-free controls and found significantly elevated levels of these molecules in the FM patients [10]. Findings of elevated Glx within the FM brain have also been reported in the amygdala [11], the posterior cingulate [12], and the ventral lateral prefrontal cortex [13]of individuals with FM. Finally, changes in blood flow in the thalamus, caudate nucleus, and pontine tegmentum detected by single-photon–emission computed tomography (PET) have been observed [14].

These findings have encouraged researchers to evaluate the effect of neuro-modulating techniques in the relief of this type of chronic pain in order to reverse the maladaptive plasticity in central neural circuits. A recent review noted that many studies in other pain syndromes reported increased activation in M1, which had an increased response to nociceptive sensory stimuli [15]. Thus M1 has been a favorite target of neuromodulatory approaches.

Two relatively new forms of neuromodulatory treatment are transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS). Studies using anodal tDCS of M1 have applied stimulation either to the hemisphere contralateral to pain (in case of focal or lateralized pain) or the dominant (left) hemisphere (in case of more diffuse pain) [16]. Anodal tDCS has been shown to increase cortical excitability, which is postulated to mitigate pain symptoms through indirect effects on pain processing regions in the brain [17], M1 tDCS may reduce pain by activating various neural circuits present in the precentral gyrus, which would be afferents or efferents that connect structures involved in sensory or emotional component of pain processing, such as the thalamus or the DLPFC, or by facilitating descending pain inhibitory controls [18]. Patients with central refractory pain have also shown improvements of around 40–80% following M1 stimulation with epidural electrodes or with transcranial magnetic stimulation (TMS) [19–21].

Clinical trials investigating the effects of tDCS over M1 have reported variable amounts of pain reduction in fibromyalgia [17,22,23], and a recent review found no significant difference between sham and real M1 tDCS on short-term pain relief [24]. The lack of consistent effects may be due to significant heterogeneity between the included studies (i.e., stimulation parameters, number of treatment sessions, type of chronic pain). In the present study we have tried to provide additional insight into the effects of anodal tDCS of the left M1 by studying both its effects on relieving pain and its relation to beta-endorphin levels.

Methods

This study was conducted at the Assiut University Hospital during the period from October 2015 to April 2016. All patients with primary fibromyalgia were recruited according to the 2010 American College of Rheumatology Criteria (ACR) [1]. Fibromyalgia is characterized primarily by diffuse musculoskeletal pain, mechanical allodynia, and hyperesthesia [25].

The most important diagnostic variables are WPI and categorical scales for cognitive symptoms, un-refreshed sleep, fatigue, and a number of somatic symptoms. The categorical scales were summed to create SS scale value from 0 to 12, with WPI >7 and a symptom severity scale (SS) > 5 or WPI 3–6 and SS > 9 [1].

All FM patients presented to the hospital fulfilling the below criteria were invited to participate. We included FM patients who reported a mean pain score ≥4 on a 10-point visual analog scale (VAS) during the two weeks preceding the clinical trial. Only patients who consent for participation and from nearby districts were recruited to ensure easiness of the follow-up. We excluded patients with a history of coexisting autoimmune or chronic inflammatory disease (i.e. Rheumatoid arthritis, systemic lupus erythematosus or inflammatory bowel disease), past or present history of substance abuse, neuropsychiatric disorders, (major depression and schizophrenia), pregnant and lactating women.

Sixty patients with primary fibromyalgia were recruited from outpatient clinic in this study. Twenty cases didn't meet inclusion criteria and were therefore excluded: 10 of them had systemic diseases. Another 6 cases had neuropathic pain and 4 cases had psychiatric disorders. Forty cases were allocated into one of the two groups (1:1 ratio) real tDCS group and sham tDCS group. Two cases from each group didn't complete the follow up and the remaining 18 cases in each group completed the study (Fig. 1).

Assiut Medical School Ethical Review Board approved the study. Written informed consent was obtained from all of the subjects after describing the nature of the intervention and the possibility of receiving sham stimulation.

All eligible participants who accepted to participate in the study were submitted to the following rating scales before treatment: WPI and SS for FM [1], and VAS for pain severity. Depression and anxiety were assessed using Hamilton depression and Hamilton anxiety scales (HAM-D and HAM-A) [26,27]. Additionally, the pain threshold for each patient was determined.

Mechanical pain sensitivity threshold

To detect the pain threshold we used Electronic model of Von Frey unit (EVF4) that combines ease-of-use and rapidity for the determination of the mechanical sensitivity threshold. Skin sensory testing with punctate stimuli was performed by the von Frey technique using the von Frey electronic device (BIO-CIS software automatically records the results on a PC through a RS 232 port), with a constant slope of increasing punctate pressure up to the detection of mechanical pain threshold (MPT) [28]. The mean of