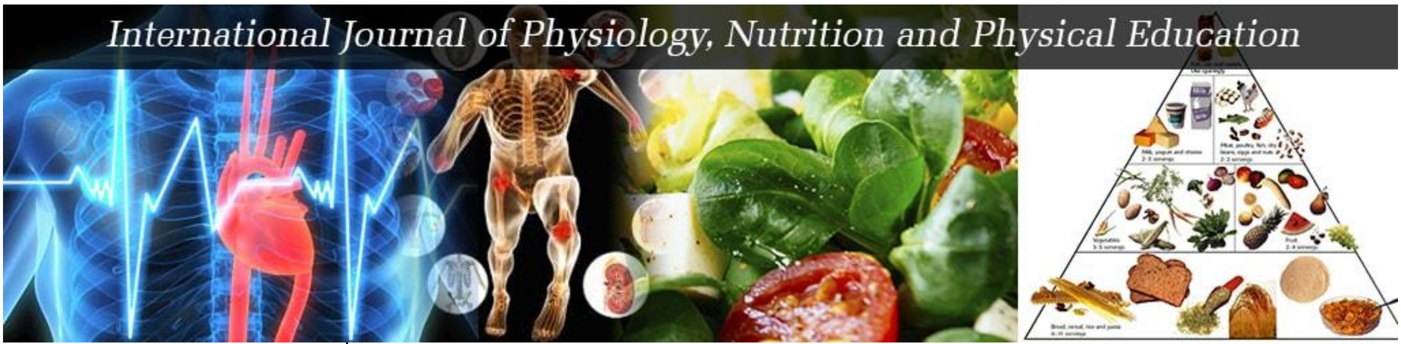
International Journal of Physiology, Nutrition and Physical Education 2018; 3(2): 858-862



ISSN: 2456-0057
IJPNPE 2018; 3(2): 858-862

www.journalofsports.com
Received: 13-05-2018
Accepted: 14-06-2018

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Effect of transcranial direct current stimulation (TDCS) on pain in fibromyalgia-systematic review based on Prisma guidelines

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Abstract
Objective: To evaluate the effectiveness of transcranial direct current stimulation on pain in fibromyalgia patients.
Data source: Pubmed.
Study eligibility criteria: Articles published in English language between 2005 to January 2018.
Participants: Studies should include fibromyalgia patients.
Interventions: Application of tDCS in the treatment group.
Outcome measure: Pain intensity using visual analogue scale and numeric rating scale.
Synthesis: Percentage of difference (% diff) was calculated by pre and post value/pre value x 100.
Results: 14 articles with 437 patients; 320 females and 127 males were included. Pain intensity measured by visual analogue scale and numeric rating scale were used as an outcome measure. Application of anodal tDCS over primary motor cortex (M1), DLPFC and C2 nerve dermatome, resulted in significant decrease in pain, whereas cathodal stimulation resulted in no significant decrease in pain intensity. Application of tDCS over primary motor cortex(M1) resulted in significant reduction in pain scores as compared to stimulation over DLPFC area with a mean difference of 1.05(95% CI 0.82 to 1.28).
Conclusion: The application of anodal tDCS over primary motor cortex (M1) can be the choice of stimulation for reducing pain in fibromyalgia patients. However, effectiveness of tDCS over other areas of stimulation must be explored so that a precise site for better management of pain in fibromyalgia patients can be recommended.
Implications: Anodal tDCS over primary motor cortex can be a preferred site for stimulation for reducing pain in fibromyalgia patients.

Keywords: Transcranial direct current stimulation, pain, fibromyalgia, review

1. Introduction

Fibromyalgia is a musculoskeletal condition with the symptoms of diffuse pain, fatigue, anxiety, depression and it also affects various cognitive functions, and has a prevalence rate in the general population between 0.2 and 6.6 in women [1]. Although, the exact pathophysiology of fibromyalgia is not known, many clinicians term this condition as chronic pain syndrome and malfunction of the central nervous system [2]. Evidences like diminished blood flow in certain cerebral regions [3], improvement in symptoms after administering centrally acting drugs [4], alteration in biochemical composition like GABA, Glx (Glutamate and glutamine) and N acetylaspartate (NAA) levels [5], changes seen in neuroimaging [6] and EEG [7, 8] supports the hypothesis of central nervous system involvement. The possible mechanism for central dysfunction in fibromyalgia is central sensitization. Abnormal information across the afferent pathways of the brain as well as alteration in sensory processing of brain leads to the chronic sensation of pain. This mechanism is governed by the structures that are involved in pain neuromatrix [9]. Central sensitization results in maladaptive changes in the plasticity of primary motor cortex. Therefore, primary motor cortex (M1) is crucial for understanding the pathophysiology of this condition as well as effect of treatment interventions in patients with fibromyalgia. Review by Castillo Saavendra suggested an increased activation of motor cortex (M1) and enhanced response to nociceptive sensory stimuli in pain syndromes and has demonstrated that primary motor cortex (M1) interplays with the areas of brain involved in pain modulation in various types of pain syndromes. Various neuromodulation techniques are used by the researchers for modulating the excitability of the motor cortex in order to alleviate chronic pain [10, 11, 12].

Transcranial direct current stimulation (tDCS), is a non-invasive brain stimulation technique that has potential to modulate the cortical excitability. The effectiveness of transcranial direct current stimulation has been researched extensively in many psychological conditions [13, 14], stroke [15, 16] and neuropathic pain in spinal cord injury [17, 18]. Pain inhibition network primarily, consists of hypothalamus as well as its cortical and subcortical synapses that can be regulated by application of tDCS over M1 montage [20]. Fibromyalgia involves malfunctioning of the central nervous system [2, 19] therefore; application of tDCS theoretically can be useful in relieving the pain and symptoms associated with fibromyalgia. The primary objective of this review was to summarize the information available on the utilization and effectiveness of tDCS in fibromyalgia. The secondary objective was to find out the appropriate site of stimulation for better management of pain in patients with fibromyalgia.

2. Methodology

2.1 Eligibility criteria: Articles comparing the effectiveness of transcranial direct current stimulation with sham tDCS. Articles following the diagnostic criteria for fibromyalgia based on American College of Rheumatology were included (1990 OR 2010 ACR).All published articles in english between 2005 to January 2018 were included in this review.

2.2 Information sources: Pubmed was used as the main source for finding the articles. The search was done in last week of January 2018.

2.3 Search: The term "Transcranial direct current stimulation" or "tDCS" and "Fibromyalgia" (all in title and/or abstract) was used to search for the relevant articles.

2.4 Study selection: Articles in which both real as well as sham tDCS were applied on patients with fibromyalgia were selected. Only those studies which included either visual analogue scale (VAS) or numeric rating scale (NRS) as an outcome measures were selected for this review.

2.5 Data collection process: RC and SK independently searched and selected the articles based on the inclusion criteria. Any disagreement were resolved through discussion with MM, SKS and SJ and the choice of majority was selected. Pre and post values of VAS or NRS for active tDCS and sham tDCS over primary motor cortex (PMC) area, dorsolateral prefrontal cortex (DLPFC) and C2 nerve dermatome (occipital) were separately extracted from the study.

2.6 Data item: Amount of change in pain scores was the outcome of interest which was measured either by visual analogue scale or by numeric rating scale (NRS).Change in pain scores were collected from all the groups (real tDCS as well as sham tDCS).

2.7 Risk Bias in individual studies: Study design (RCT as the gold standard), site of stimulation and the number of tDCS sessions applied were seen as possible bias in the selected articles.

2.8 Summary measures: Mean of mean differences with 95% confidence interval was used to estimate the effect.

2.9 Synthesis of results: Mean for pre and post values as well as the percentage difference was calculated for VAS. Percentage of difference (% diff) was calculated by MD with pre values (i.e) MD/pre-value × 100

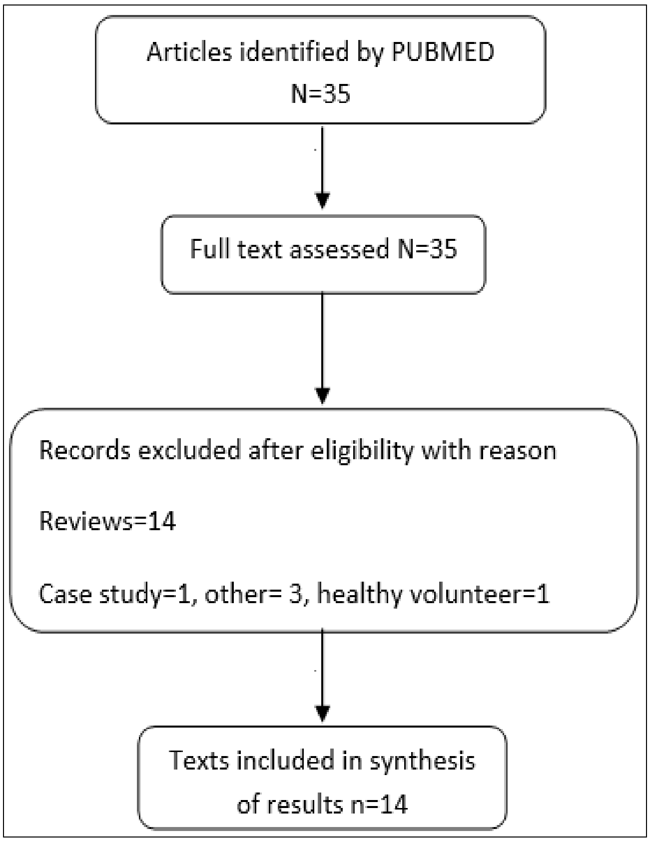
2.10 Synthesis of result: Mean difference (MD) along with 95% CI was calculated for active and sham tDCS on dorsolateral prefrontal cortex, primary motor cortex and on C2 nerve dermatome area from the eligible studies. Mean of mean difference and percentage of difference from maximum possible scores was calculated separately for active and sham tDCS over primary motor cortex (M1), DLPFC, C2 nerve dermatome (Occipital area). Mean of mean difference over stimulation site M1 Vs DLPFC and M1 Vs C2 nerve dermatome was calculated.

2.11 Risk Bias across the studies: Final results were compared with the low risk studies to see the risk biases across the studies.

3. Result

3.1 Study selection: A total of 35 articles were retrieved from Pubmed during the initial literature search, out of which 14 (n=437; 320 females) were included in this review as per inclusion criteria. The basic characteristics of studies included in this review are outlined in table 1.

Table 1: Basic characteristics of studies included in this review



3.2 Study characterstics: Most of the studies included in this review were randomized controlled trial, except two studies, one was a longitudinal trial [30] and other one was a crossover trial [27]. All the studies used active tDCS either at primary motor cortex area or dorsolateral prefrontal cortex or C2 nerve dermatome for stimulation, All the studies used an intensity of 2mA for 20 min duration for stimulation except 2 studies which used 1.5 mA intensity for stimulation [23, 25]. Number of session varied from one to ten over a period of one to four weeks, with follow up period upto 60 days in some studies. Any reduction in pain scores was measured by using Visual analogue scale or Numerical rating scale.

3.3 Risk bias within studies: Most of the studies included in this review were RCT except 2 studies, one study was a crossover trial [27] and another was a longitudinal trial [30]. There was differences in the number of sessions of application of tDCS, 2 studies has used only single session of tDCS application [11, 31]. Few studies had very less number of patients in the treatment group: one study [11] had less than 10 patients in the treatment group and 2 studies had only 12 patients in the treatment group [27, 30]. On the site of stimulation: only 4 studies used DLPFC as stimulation site [18, 21, 23, 32] whereas only 2 studies used C2 nerve dermatome for stimulation in fibromyalgia patients [21, 23] creating a risk bias within the studies.

3.4 Results of individual studies

Anodal tDCS over M1 vs sham tDCS: 11 studies were included in this analysis [11, 18, 22, 26-33] with a total of 414 patients, out of which 207 patients were allotted to anodal group and 207 patients to sham group. The result showed that application of anodal tDCS over M1 significantly decreased pain than sham tDCS. The mean of mean difference was -0.358 (95% CI -0.47 to -0.25).

Anodal tDCS over DLPFC vs sham: 4 studies were included in this analysis [18, 21, 23, 32] with a total of 110 patients, out of which, 52 patients were allotted in DLPFC group and 58 in sham group. The result showed stimulation over DLPFC resulted in significant decrease in pain in fibromyalgia patients. The mean of mean difference was -0.89 (95%CI) -1.07 to - 0.71).

Anodal tDCS over C2 nerve dermatome vs sham: 3 studies were included for this analysis [21, 23, 25] with a total of 100 patients, out of which 52 patients were allotted in the C2 nerve dermatome stimulation group and 48 in sham group. The result showed statistically significant reduction in pain scores. The mean of mean difference was -1.55(95% CI -1.68 to -1.42).

Cathodal tDCS over M1 vs sham: 2 studies were included in this analysis [11, 31] with a total of 48 patients, out of which 28 patients were allotted in cathodal group and 28 in sham group. The application of cathodal tDCS over M1 did not significantly reduced pain as compared to sham tDCS. The mean of mean difference was -0.04(95% CI -0.38 to 0.30).

tDCS over primary motor cortex(M1) vs DLPFC:11 studies were included for this analysis,9 studies on M1 stimulation [18, 22, 26-30, 33-34] and 2 studies on DLPFC [18, 33] with a total of 207 patients, of whom 183 patients were in primary motor cortex group and 24 in DLPFC group. The results showed that the stimulation at primary motor cortex is more likely to decrease the pain. The mean of mean difference was 1.05(95% CI 0.82 to 1.28).

3.5 Synthesis of results: The application of tDCS over all the 3 areas of stimulation (primary motor cortex, DLPFC and C2 nerve dermatome) produced significant reduction of pain in patients with fibromyalgia. However, application of cathodal tDCS over primary motor cortex (M1) showed no significant reduction in pain scores.

3.6 Risk bias across studies: Two studies applied single session of cathodal stimulation over primary motor cortex [11, 31], of which one study had less than 10 number of patients in the treatment arm [11] this might have influenced the significance of its application.

4. Discussion

The result of this review suggests that the application of anodal tDCS over primary motor cortex (M1) has reduced the pain intensity in the patients of fibromyalgia. The result of the study are consistent with the results of previous systematic review [35] which included 192 patients of fibromyalgia suggesting anodal tDCS over M1 relieves pain and symptoms related to fibromyalgia.

Current meta-analysis showed no significant reduction in pain scores on application of cathodal tDCS as compared to sham tDCS. The results were not consistent with the study by Antal and Paulus which reported significant reduction in orofacial pain with cathodal stimulation. However, the results cannot be extrapolated to the general population as this metaanalysis included only 2 studies, with single session of cathodal stimulation.

The meta-analysis of application of anodal tDCS over DLPFC in this review reports significant reduction in pain scores. Meta-analysis by Zhu CB reported that application of anodal tDCS over DLPFC showed no significant reduction in pain. This review included only 2 studies for analysis and with one study establishing while other study contradicting the efficacy of anodal tDCS over DLPFC in pain management. However in the present review, 4 studies were included for meta-analysis, suggesting significant reduction in pain scores. However, more clinical trials are required to confirm the efficacy of cathodal stimulation in management of pain in fibromyalgia patients.

Stimulation over C2 nerve dermatome (occipital area) also showed significant reduction in pain scores in patients with fibromyalgia. However, as only 2 studies were found after extensive literature search, its effectiveness in reducing pain cannot be confirmed.

The application of anodal tDCS over primary motor cortex was more effective in pain management as compared to DLPFC. Thus, primary motor cortex can be a preferred site for stimulation for managing pain in patients with fibromyalgia. The possible mechanism can be the role of primary motor cortex (M1) in regulation of the sensory component of pain, whereas DLPFC regulates the cognitive and emotional aspects of pain [35].

5. Limitations

The main limitation of the study was scarcity of published research studies to establish the efficacy of DLPFC, occipital stimulation over C2 nerve dermatome; as well as investigations on comparing these stimulation sites so that specific stimulation site for better pain management in patients with fibromyalgia can be suggested. Further there were variations in number of sessions of tDCS application for treating patients of fibromyalgia that might have caused biases in the analysis.

6. Conclusion

The application of anodal tDCS over primary motor cortex

(M1) can be the choice of stimulation for reducing pain in fibromyalgia patients; however the effectiveness of tDCS on other areas of brain must be explored further, so that a precise site for better management of pain can be recommended in fibromyalgia patients.

7. Acknowledgement

There is no conflict of interest between the authors of this review.

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