EFFECTS OF TRANSCRANIAL DIRECT CURRENT STIMULATION (tDCS) ON PSYCHOLOGICAL SYMPTOMS OF INDIVIDUALS WITH FIBROMYALGIA

EFEITOS DA ESTIMULAÇÃO TRANSCRANIANA POR CORRENTE CONTÍNUA (ETCC) NOS SÍNTOMAS PSICOLÓGICOS DE INDIVÍDUOS COM FIBROMIALGIA

EFECTOS DE LA ESTIMULACIÓN TRANSCRANEAL DE CORRIENTE DIRECTA (TDCS) SOBRE LOS SÍNTOMAS PSICOLÓGICOS DE INDIVIDUOS CON FIBROMIALGIA

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ABSTRACT
Fibromyalgia (FM) is a syndrome characterized by widespread pain, sleep disturbances, fatigue and cognitive symptoms, often associated with anxiety disorders and depression. The lack of understanding of its etiopathogenesis makes it difficult to develop effective treatments. Transcranial direct current stimulation (tDCS) has been investigated as a complementary approach to FM. A systematic review of nine studies that evaluated the effects of tDCS on symptoms of anxiety and depression in patients with FM was carried out. Most studies used a current intensity of 2 mA and a session duration of 20 minutes, with application on consecutive days. Results have shown a decrease in psychological symptoms in some studies, especially when combined with other therapeutic modalities such as physical exercise. However, some studies have found no significant effects of...

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tDCS on the psychological symptoms of FM. The review suggests that tDCS may play a promising role in treating symptoms of anxiety and depression in FM, highlighting the importance of multimodal approaches in treating the condition and the need for further research to determine the optimal tDCS protocol and understand the neural mechanisms underlying its effects on FM.

Keywords: Fibromyalgia; transcranial direct current stimulation (tDCS); anxiety; depression.

RESUMO

A fibromialgia (FM) é uma síndrome caracterizada por dor generalizada, distúrbios do sono, fadiga e sintomas cognitivos, frequentemente associada a transtornos de ansiedade e depressão. A falta de compreensão de sua etiopatogenia dificulta o desenvolvimento de tratamentos eficazes. A estimulação transcraniana por corrente contínua (tDCS) tem sido investigada como uma abordagem complementar para a FM. Foi realizada uma revisão sistemática de nove estudos que avaliaram os efeitos da tDCS nos sintomas de ansiedade e depressão em pacientes com FM. A maioria dos estudos utilizou uma intensidade de corrente de 2 mA e uma duração de sessão de 20 minutos, com aplicação em dias consecutivos. Os resultados mostraram uma diminuição dos sintomas psicológicos em alguns estudos, especialmente quando combinados com outras modalidades terapêuticas, como o exercício físico. No entanto, alguns estudos não encontraram efeitos significativos da tDCS nos sintomas psicológicos da FM. A revisão sugere que a tDCS pode desempenhar um papel promissor no tratamento dos sintomas de ansiedade e depressão na FM, destacando a importância de abordagens multimodais no tratamento da condição e a necessidade de mais pesquisas para determinar o protocolo ideal de tDCS e entender os mecanismos neurais subjacentes aos seus efeitos na FM.

Palavras-chave: Fibromialgia; estimulação transcraniana por corrente contínua (tDCS); ansiedade; depressão.

RESUMEN

La fibromialgia (FM) es un síndrome caracterizado por dolor generalizado, alteraciones del sueño, fatiga y síntomas cognitivos, a menudo asociados con trastornos de ansiedad y depresión. La falta de conocimiento de su etiopatogenia dificulta el desarrollo de tratamientos eficaces. La estimulación transcraneal de corriente continua (tDCS) se ha investigado como un enfoque complementario a la FM. Se llevó a cabo una revisión sistemática de nueve estudios que evaluaron los efectos de la tDCS sobre los síntomas de ansiedad y depresión en pacientes con FM. La mayoría de los estudios utilizaron una intensidad de corriente de 2 mA y una duración de sesión de 20 minutos, con aplicación en días consecutivos. Los resultados han mostrado una disminución de los síntomas psicológicos en algunos estudios, especialmente cuando se combina con otras modalidades terapéuticas como el ejercicio físico. Sin embargo, algunos estudios no han encontrado efectos significativos de la tDCS sobre los síntomas psicológicos de la FM. La revisión sugiere que la tDCS puede desempeñar un papel promisor en el tratamiento de los síntomas de ansiedad y depresión en la FM, destacando la importancia de los enfoques multimodales en el tratamiento de la afección y la necesidad de realizar más investigaciones para determinar el protocolo tDCS óptimo y comprender los mecanismos neuronales subyacentes. Efectos sobre la FM.

Palabras clave: Fibromialgia; estimulación transcraneal por corriente directa (tDCS); ansiedad; depresión.
1. Introduction

Fibromyalgia (FM) is a syndrome primarily related to dysfunctions of the central nervous system (Goldenberg et al., 2008). FM is a painful syndrome in which the individual reports generalized pain, sleep disorders, fatigue, and cognitive symptoms (Khedr et al., 2017). Although the pathophysiology of the syndrome is not entirely clear, recent studies indicate that FM is correlated with changes of the brain activity (Fregni et al., 2006) in areas related to pain processing and other cognitive processes (Mendonca et al., 2016).

Currently, literature shows that the prevalence of FM in the general population is between 0.2 and 6.6% (Marques, Espírito Santo, Berssaneti, Matsutani, & Yuan, 2016). People with FM are more likely to develop depression and anxiety disorders compared to healthy individuals (İşik-Uluso, 2019). Depression and anxiety are comorbidities that modify lifestyle and decrease quality of life (Lee et al., 2017). Individuals with FM show higher levels of nervousness, tension and anxiety (Pagano et al., 2004).

The lack of knowledge about its etiopathogenesis hinders the development of effective treatments for the FM. In general, it should combine pharmacological and non-pharmacological therapies, such as psychotherapy, health education, and physical activity with physiotherapy (Goldenberg et al., 2008, Heymann et al., 2010, Helfenstein; Goldenfum; Siena, 2012).

The current treatments for FM are not curative and involve the administration of medications such as anti-inflammatories, antidepressants and anticonvulsants (Castelo-Branco et al., 2019). Frequently, these drugs may cause significant adverse effects, demanding their constant replacement (Häuser; Petzke; Sommer, 2010). In this sense, other methods are needed to complement FM treatments and to promote fewer adverse effects.

Transcranial Direct Current Stimulation (tDCS) has been studied as a possible complementary treatment in FM. It consists of a non-invasive technique capable of modulating the brain activity (Monte-Silva et al., 2013). In general, tDCS is considered a safe and easy procedure to apply (Gandiga; Hummel; Cohen, 2006). The application of an electrical stimulation at the intensity of 1 to
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2 mA, during 10 to 20 minutes, causes no harm to the neural tissue (Roizenblatt et al., 2007). The electric current passes through the scalp and reaches the underlying brain tissue, resulting in changes in cortical excitability. Typically, the anodal stimulation in M1 increases the cortical excitability, whereas the cathodal stimulation decreases it (Nitsche; Paulus, 2000; Nitsche et al., 2003). Some studies indicate that the tDCS modulates brain areas related to emotion and pain processing, decreasing the psychological symptoms and pain in FM (Fregni et al., 2006).

Still with inconclusive results, some systematic reviews analyzed the therapeutic potential of the tDCS in reducing pain in FM (Lloyd et al., 2020; Zhu et al., 2017). However, none of them focused on the effects of the tDCS on the psychological symptoms associated with the disorder. Here, we carried out a systematic review of tDCS studies that evaluated the symptoms of anxiety and depression in FM as a primary or a secondary outcome. Furthermore, we also analyzed the safety of the procedure and its efficacy in reducing pain symptoms.

2. Method

We carried out the research in the databases PubMed, BVS, SCIELO, Lilacs, PsycInfo, PEDro and Science Direct, using the following descriptors: "Fibromyalgia AND transcranial direct current stimulation AND depression" and "Fibromyalgia AND transcranial direct current stimulation AND anxiety" in English and Portuguese. We also checked the references of the selected studies in order to identify additional works related to the review.

The inclusion criteria were: studies with adults (more than 18 years old); studies that addressed the effects of tDCS on symptoms of depression and anxiety as primary or secondary outcomes; publications in English, Portuguese or Spanish; cross-sectional or longitudinal studies, pilot studies and clinical trials. These were not included in the review: studies that used the application of tDCS for other clinical conditions than FM; review articles; repeated articles in the databases; case studies and dissertations. We used the criteria of PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (Moher
Initially, searches were carried out independently by two evaluators who filtered works based on the analysis of the title and abstract. Subsequently, a third reviewer analyzed the selected articles and verified their duplicity and, finally, the exclusion criteria was applied. After the selection, the articles were fully examined by a trio of independent evaluators who filled out a standardized summary form with the most relevant information for the review. In this step, we considered categories previously defined: general information about tDCS; neurophysiological mechanisms of tDCS; brain areas modulation by tDCS; tDCS protocols; adverse effects of tDCS; and effects of tDCS on the symptoms of anxiety and depression.

3. Results

By using the descriptors "fibromyalgia AND transcranial direct current stimulation AND depression" and “fibromyalgia AND transcranial direct current stimulation AND anxiety” we found 211 and 142 articles, respectively. No articles were found in Lilacs and PsycInfo databases. After applying the eligibility criteria, 15 articles remained, which were fully read. Five articles were selected, and another four articles were included by checking the references of the selected works. Therefore, nine studies were included in the review.

In most studies, the main outcome was the intensity of the pain, and the psychological symptoms were assessed as a secondary outcome. Quality of life, sleep, and functionality were also analyzed as secondaries outcomes. The total sample of the studies was 322 participants, predominantly female (n = 313). Four studies included only women participants. The age group studied ranged from 18 to 69 years and the average age ranged from 31.3 to 58.3 years. Most studies (n = 6) were published in the last five years, reflecting a growing interest in the subject.

The association of tDCS with other therapeutic modalities was studied, such as with the physical exercise (Riberto et al., 2011; Mendonça et al., 2016) and stimulation of the occipital nerve (Yoo et al., 2018). Only one study observed
the effects of neuromodulation using neuroimaging (Jales Junior et al., 2015), in which the application of the tDCS on the primary motor cortex (M1) normalized the bilateral parietal hypoperfusion.

3.1 tDCS Usage Protocols

Studies differed in regard to the current intensity. Khedr et al. (2017), Mendonca et al. (2016), Brietzke et al. (2019), Fagerlund et al. (2015), Riberto et al. (2011), Valle et al. (2009) and Fregni et al. (2006) used the intensity of 2 mA. Yoo et al. (2018) used the intensity of 2 mA, and the intensity of 1.5 mA to stimulate the occipital nerve. Jales Junior et al. (2015) used the lower intensity (1 mA).

Regarding the duration of the application of the current, all studies used 20 minutes sessions. Only the study of Brietzke et al. (2019) applied the current for 30 minutes. In most studies, the stimulation was applied on consecutive days. The number of weeks varied between one week (Fagerlund et al., 2015, Mendonca et al., 2016), two weeks (Khedr et al., 2018, Valle et al., 2009), three weeks (Fregni et al., 2006) and 12 weeks (Brietzke et al., 2019). Yoo et al. (2018) applied the stimulation for two days a week during four weeks, and Riberto et al. (2011) and Jales Junior et al. (2015) applied it once a week for 10 weeks.

Better clinical results were found with stimulation sessions applied in consecutive days. A recent meta-analysis showed that most studies, which found satisfactory results in reducing pain, used anodic stimulation of 2mA, applied for 20 minutes to M1, in consecutive sessions (typically five consecutive sessions over two weeks) (Lloyd et al., 2020).

As for the treatment duration, we found that the shortest tDCS treatment lasted one week (Mendonca et al., 2016, and Fagerlund et al., 2015) and the longest one lasted 12 weeks (Brietzke et al., 2019). Loo et al. (2010) found that 10 treatment sessions at 1mA for 20 minutes significantly reduced the symptoms of depression. In contrast, no significant effect was found for five sessions (Loo et al., 2010).

With regard to the brain region stimulated, Mendonca et al. (2016),
Fagerlund et al. (2015), Valle et al. (2009), Fregni et al. (2006), Riberto et al. (2011) and Jales Junior et al. (2015) placed the anodic electrode on left M1 and the cathodic electrode on the contralateral supraorbital area.

Using a different protocol, with the placement of the anodic electrode on the left M1 and the reference electrode on the contralateral arm, Khedr et al. (2019) found a diminishing of the reported pain and depression symptoms. This extracephalic location can avoid ambiguous effects of the placement of two electrodes of different polarities on the brain and may stimulate deep brain structures involved in pain processing (DaSilva et al., 2012).

The other studies with satisfactory results placed the anode electrode on the left M1 (Jales Junior et al., 2015; Mendonca et al., 2016; Khedr et al., 2017), a region considered more effective in controlling pain (Hou; Wang; Kang, 2016; Zhu et al., 2016) and modulating its sensory component (Diers et al., 2008).

Another region commonly used for stimulation is anodic electrode placed on the left DLPFC and the cathodic electrode on the contralateral supraorbital region (Yoo et al., 2018; Valle et al., 2009; Fregni et al., 2006). Mergazora et al. (2010) found hemodynamic changes with the anodic stimulation, but not with the cathodic one.

Deldar, Rustamov, Bois, Blanchette and Piché (2018) considered that the anodic tDCS on the DLPFC may produce indirect effects on pain inhibition by means of changes in cognitive processes. Boggio et al. (2008) points out that the analgesic effects observed after the stimulation of the DLPFC may be associated to an indirect inhibitory modulation of the thalamic activity. The left DLPFC is primarily related to cognitive and emotional aspects, such as anxiety and depression (Duquette et al., 2007). Silva et al. (2017) observed a reduction in pain levels in FM when stimulating DLPFC. Differing from other protocols, Brietzke et al. (2019) placed the anodic electrode on the left DLPFC and the cathode on the right DLPFC and found positive results.

Yoo et al. (2018) stimulated the DLPFC and occipital nerve, placing the anode in the right occipital region and the cathode on the left. Yoo et al. (2018) observed that the application of tDCS only on the occipital nerve lead to clinical benefits in the emotional subcomponents of FM, such as depression.
Currently, there is limited knowledge about the ideal parameter of the stimulation (Hou; Wang; Kang, 2016). Protocols vary in regard to the target region stimulated as well as in relation to number and frequency of sessions. However, it appears to be almost a consensus the using of stimulation sessions with the duration of 20 minutes.

4. Discussion

In the present work, we carried out a systematic review of studies that analyzed the effects of the application of tDCS on the symptoms of anxiety and depression in FM. In addition, we analyzed the safe parameters and the effectiveness of the procedure in alleviating pain.

4.1 tDCS Action on Symptoms of Anxiety and Depression in FM

In the most recent study (Brietzke et al., 2019), the application of 60 sessions of tDCS, in association with physical activity, was effective in reducing anxiety and depression in women with FM. Furthermore, authors found a decrease in the reported pain and an improvement in the sleep quality. According to Monte-Silva et al. (2013) and Fritsch et al. (2010), the prolonged application of the tDCS can modify the synaptic plasticity by means of the activation of the NMDA receptors and long-term potentiation. The acetylcholine, by its turn, strengthens the neuroplastic effects (Kuo et al., 2007). However, in the present review, it was possible to find positive results even with a smaller number of sessions, such as five consecutive days, in which a reduction in pain and a slight reduction in anxiety and depression symptoms were observed (Fagerlund et al., 2015).

In some studies, the depression and anxiety levels seem to predict the success of the stimulation in reducing pain. Individuals with a greater degree of depression and anxiety responded better to treatment, especially in a combined intervention of tDCS and aerobic exercise (Mendonca et al., 2016). Possibly, a combined approach may influence other neural circuits, such as those
responsible for the emotional aspects of pain (Brighina et al., 2019).

In the study of Fregni et al. (2006), the depression level was slightly reduced, but at a non-statistically significant value. However, their sample was comprised by participants with mild depressive symptoms. Authors argued that a decrease in the depression symptoms is more likely to occur in individuals with severe depression. In line with this hypothesis, a randomized double-blind study carried out with women with severe depression showed that the anodal stimulation applied on the left dorsolateral prefrontal cortex (DLPFC) for five consecutive days reduced the depression symptoms (Fregni et al., 2006). Similarly, Boggio et al. (2008) treated individuals with more severe symptoms of depression with tDCS and obtained a significant reduction in the scores of depression.

In the study of Jales Junior et al. (2015), the stimulation with tDCS administered once a week was effective in improving emotional aspects compared to sham. Similarly, Riberto et al. (2011) applied the stimulation once a week, and found a decrease in anxiety and depression. However, there was also observed an improvement in the placebo group. Both studies used the same stimulation protocol in relation to the positioning of the electrodes, number of sessions and duration of treatment, but differed in relation to the current intensity: 1 mA (Jales Junior et al., 2015) and 2 mA (Riberto et al., 2011).

Finally, other studies did not find an effect of the tDCS on symptoms of anxiety and depression (Valle et al., 2009; Fagerlund et al., 2015). One factor to be considered is the placebo effect, commonly found in clinical trials. Research involving the endogenous opioid system in placebo analgesia showed that sham stimulation triggered the release of endogenous opioids in the thalamus and the periaqueductal gray matter (DosSantos et al., 2014).

5. Conclusion

In this review, we examined the effects of tDCS on the symptoms of anxiety and depression in FM. In general, we found that the anodic stimulation in M1 for 20 minutes seems to reduce depression symptoms in patients with a more
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severe depressive condition. The neuromodulation seems to be more effective when applied in consecutive days. However, it is important to note that the methodological heterogeneity of the studies indicates the lack of definition about the most appropriate neuromodulation protocol in FM.

Future experimental studies, comparing different neuromodulation protocols, may contribute to identify the best therapeutic response in fibromyalgia. Furthermore, it is necessary to clarify the brain mechanisms involved in the neuromodulation, which will help to determine the most effective targets for applying the neural stimulation.

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