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Prospective Study

Transcranial direct current electrical stimulation in combination with aerobic exercise: a pilot study in post-COVID-19 systemic autoimmune rheumatic patients

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Abstract

BACKGROUND

Systemic autoimmune rheumatic diseases are a group of diseases with multiorgan involvement and a high prevalence of chronic pain and fatigue. Patients with systemic autoimmune rheumatic disease and post-COVID-19 syndrome experience aggravation of symptoms. In this context, it is essential to establish strategies to reduce chronic pain and fatigue and improve quality of life.

AIM

1 Currently, no studies have assessed the efficacy of transcranial direct current stimulation (tDCS) for the treatment of fatigue and pain-associated post-COVID-19 syndrome in patients with systemic autoimmune rheumatic diseases.

METHODS

This study included nine patients with different types of systemic autoimmune rheumatic diseases. All patients had previously confirmed RT-PCR test for COVID-19 as well as significant, persistent fatigue and pain that began to worsen after infection. Anodal tDCS was administered in five daily sessions (2mA, 20 minutes). Concomitantly, patients were involved in aerobic exercise program. All participants were evaluated using specific questionnaires and strength assessment by handgrip and physical function by timed-up-and go test and sit-to-stand test at baseline (within one week before tDCS protocol), and one week after tDCS protocol. During all procedures, the patients' treatments remained unchanged.

RESULTS

The sample comprised eight women and one man with a mean age of 48.7 ± 9.6 . After the tDCS protocol, pain and fatigue significantly improved on the visual analog scale ($P < 0.05$). The physical function also improved 9.5 ± 2.7 vs. 6.8 ± 0.8 ($P = 0.001$) for timed-up-go-test and 10.3 ± 3.7 vs. 15.1 ± 4.0 ($P = 0.037$) for sit-to-stand test. None of the patients experienced any adverse events.

CONCLUSION

The present study showed tDCS⁶ in combination with aerobic exercise was effective in improving physical function, and reducing fatigue/pain in SARDs patients with post-COVID-19 syndrome.

INTRODUCTION

² The World Health Organization (WHO) declared COVID-19, which is caused by the SARS-CoV-2 infection, a pandemic in March 2020 (1). The rapid spread of COVID-19 worldwide has resulted in at least 230 million infections and deaths as of September 2021 (2). In addition, approximately one-third of recovered individuals have persistent symptoms called long-COVID-19 or post-COVID-19 syndrome (3). The syndrome is characterized by signs or symptoms that develop during or after SARS-CoV-2 infection

and persist for more than 12 wk after the COVID-19 recovery period (3,4). Fatigue and musculoskeletal pain have been observed in at least one-third and one-fifth of the patients with post-COVID-19 syndrome, respectively (3,4). As a result, recent studies have pointed to the growing dependence of these patients on health systems because of the slow recovery of quality of life and functionality (3).

Systemic autoimmune rheumatic diseases (SARDs) comprise a broad group of diseases characterized by multiorgan and systemic involvement, including rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome, spondyloarthritis, and systemic autoimmune myopathies. Frequently, patients with SARDs complain of fatigue and chronic pain, which negatively affect their quality of life (5-7). In the context of COVID-19, these individuals may experience aggravated symptoms during and/or after the SARS-CoV-2 infection. Indeed, a recent study showed that patients with chronic pain (e.g., fibromyalgia) experience worsening fatigue and pain after COVID-19 (8). Moreover, these symptoms can persist chronically despite appropriate regular pharmacological treatments and physical exercise (5-7). Therefore, it is essential to establish strategies that can reduce chronic pain and fatigue to minimize functional capacity impairment in these patients (9-11).

⁵ Transcranial direct current electrical stimulation (tDCS) is a noninvasive brain stimulation technique that has been applied to facilitate or inhibit brain areas, with promising results in pain modulation, fatigue reduction, and improvement in functional capacity in patients with regional complex pain (12,13), refractory myofascial syndrome, chronic fatigue (15), and fibromyalgia (12). Recently, Pinto *et al* (14) showed that tDCS of the dorso-lateral pre frontal cortex was largely effective in decreasing fatigue in patients with Sjögren's syndrome.

Nonetheless, moderate aerobic exercise training has been extensively prescribed as a remarkable tool in the management of chronic pain patients (17). Despite this, recent studies also showed that the association between aerobic exercise and tDCS applied to the primary motor cortex leads to a larger effect size than aerobic exercise or tDCS alone in patients with fibromyalgia (18).

To date, there is a lack of information on tDCS in patients with other SARDs, as well as in those with post-COVID-19 syndrome. Based on the multisystemic components of SARDs and post-COVID syndrome, we hypothesized that tDCS of the primary motor cortex can lead to improvements in pain and fatigue related to post-COVID-19 syndrome symptoms in patients with SARDs.

MATERIALS AND METHODS

This was a single-center, prospective, open-label, one-arm study that included adult SARDs patients with fatigue or pain associated with or potentiated by post-COVID-19 syndrome. The clinical trial was conducted from May to July 2021, and individuals who were regularly followed up in our tertiary outpatient rheumatology clinics were consecutively invited to participate in the study. Currently, our center includes approximately 800 patients with rheumatoid arthritis, 1000 with systemic lupus erythematosus, 220 with systemic autoimmune myopathies, 280 with Sjögren's syndrome, and 500 with spondyloarthritis.

The study was conducted in accordance with the Declaration of Helsinki and local regulations. This study was approved by the local ethics committee (CAAE 41916820.3.0000.0068) and registered at ClinicalTrials.gov (NCT04890483). Written informed consent was obtained from all the patients. We implemented the a-tDCS as a protocol as an aerobic exercise program due to evidence of priming effects in studies of patients with fibromyalgia and neurological conditions.

Fatigue or pain associated with or potentiated by COVID-19. Post-COVID-19 syndrome was defined as new or worsened fatigue or pain (local or diffuse) sustained for more than 12 wk after SARS-CoV-2 infection.

Inclusion criteria. SARDs patients who fulfilled the following classification criteria were recruited: rheumatoid arthritis (19), systemic lupus erythematosus (19), systemic autoimmune myopathies (20), Sjögren's syndrome (21), and spondyloarthritis (22); COVID-19 confirmed by real-time RT-PCR or serology for IgG and IgM (16) from

March 2020 to February 2021; persistent fatigue or pain associated with or potentiated by COVID-19 (post-COVID-19 syndrome), defined by new or worsened fatigue, or pain (local or diffuse) sustained for more than 12 wk after the SARS-CoV-2 infection; and relatively stable use of medications in the previous months.

Exclusion criteria. Patients with neoplasms, cardiac pacemaker users, users of cranial metal clips or prostheses, pregnancy, personal history of seizures or epilepsy (related or not to COVID-19), use of drugs that lower seizure threshold, and cutaneous lesions (scalp, in the area of application of the electrodes) (Figure 1).

Two experienced rheumatologists performed the initial patient' screening and a final review of frontline rheumatology with extensive experience with patients with COVID-19 performed the patient eligibility procedure.

Assessments. The following data were collected within one week before the tDCS intervention (pre-tDCS):

- Demographic: age and sex;
- Anthropometric: body mass index;

Physical activity level: The International Physical Activity Questionnaire (IPAQ), which classifies the level of physical activity and the weekly metabolic equivalent (METs), such as: METs as high physical activity score, patients that comply with vigorous physical activity (≥ 5 days/week and ≥ 30 minutes per session or vigorous activities during (≥ 3 days/week and ≥ 20 minutes) and concomitant moderate physical activities (≥ 5 days/week and ≥ 30 minutes per session); moderate activity score - vigorous activities (≥ 3 days/week and ≥ 20 minutes per session) or moderate physical activities (≥ 5 days/week and ≥ 30 minutes per session), or the sum of any activities performed ≥ 5 days/week, and ≥ 150 minutes/ week (24,25);

Comorbidities included systemic arterial hypertension, dyslipidemia, diabetes mellitus, depression, anxiety, and fibromyalgia. Fibromyalgia was defined according to the American College of Rheumatology classification criteria for fibromyalgia (26). Depression and anxiety were based on the criteria defined by the American Psychiatric Association (27);

Pharmacological treatment: current treatment (glucocorticoids and immunosuppressive drugs) and associated medications;

SARDs activity status was assessed using the indices of activity validated for each disease (Clinical Disease Activity Index (CDAI) / Disease Activity Score (DAS)-28 (28), Sjögren's Syndrome Disease Activity Index (ESSDAI) (29), Bath Ankylosing Spondylitis Activity Index (BASDAI) (30), Manual Muscle Testing-8 (MMT-8) (31), Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) (32);

Fatigue status and severity were assessed using the VAS, Fatigue Assessment of Chronic Illness Therapy (FACIT-F) (33), Modified Fatigue Impact Scale (MFIS) (34), and Fatigue Severity Scale (FSS) (35);*

Pain and fatigue diary: performed during the tDCS and training sessions for aerobic exercise, at baseline and session by session by VAS before each tDCS/aerobic exercise protocol;

Physical function: Timed Up and Go (TUG) test (35); Stand-to-Sit test (STS) (36))

-Muscle strength: handgrip test (37);*

Quality of life: EQ-5D (38).*

* These data were also collected within one week (Figure 2). During all protocols, the patient's treatments remained unchanged.

PROCEDURES. tDCS. The anode was sourced from a battery-powered direct current generator (Activadose II, USA) and was exerted by two electrodes measuring 5 x 7 cm (35 cm²) (Ibramed, Brazil) covered by a sponge with saline solution and fixed to the head using Velcro straps. Electrodes were accepted in accordance with the International System 10/20. Targeting the primary motor cortex, positioned in C3 or C4 10/20 EEG positions, with the cathode placed in the supraorbital region (Fp1 and Fp2, respectively). The active current of tDCS was applied with an electrical current intensity of 2 mA and a density of 0.057 mA/cm² for a duration of 20 min, with an up and down ramp of 10 s.

AEROBIC EXERCISE. It was characterized by walking on a treadmill for 30 min with intensity adjusted through measurement of effort (RPE) during and after 20 min of tDCS sessions. In addition, the perception of recovery (PSR) was collected between sessions (39).

ADVERSE EVENTS. They were registered during and after each application through a questionnaire related to sensations such as burning, tingling, itching, burning (head), headache, nausea, fatigue, emotional lability, difficulty in concentrating and nervousness.

ADHERENCE. Adherence to the protocol was assessed by the researchers of this study through registration of controlled gifts.

STATISTICAL ANALYSIS. The data distribution was set at $\alpha = 0.05$. To analyze differences between the clinical characteristics between groups, one-way ANOVA with adjusted factor by group or Friedman test was used, as a posteriori analysis was conducted using a Tukey SD test for multiple comparisons. P value was considered statistically significant when < 0.05 . The individual analysis for the pre-tDCS and post-tDCS values was expressed as percentage change using the formula $((\text{post} - \text{pre}) / \text{pre}) \times 100$. The effect size (ES), a measure of the magnitude of change, was calculated using Cohen's d for the FACIT and MFIS scores and their domains. The software used was SPSS version 25 (Chicago, IL, USA).

RESULTS

Of 2800 SARDs patients followed at our clinics, from April 2020 to February 2021, 92 had COVID-19. Seventeen patients showed new worsening or pain and fatigue for more than 12 wk following SARS-CoV-2 infection. Eight patients refused to participate in the present study (Figure 1). Therefore, nine patients were included in the present study: three with rheumatoid arthritis, two with spondyloarthritis, two with primary Sjögren's syndrome, one with antisynthetase syndrome, and one with systemic lupus

erythematosus. These nine patients, whose general features of the participants are shown in Table 1. Mean VAS scores for pain and fatigue were 5.3 ± 2.7 and 5.4 ± 1.8 , respectively. Concerning the quality-of-life parameters, the patients had a current EQ-5D VAS of 5.3 ± 2.3 (Figure 2).

At their assessment, we classified two patients (#1 and #4) as being in clinical remission, three patients (#5, #8, and #9) with mild disease activity, and three patients (patients #2, #3 and #6) with high underlying disease activity. All patients, regardless of their underlying disease status, reported worsening fatigue or pain after infection with COVID-19.

After tDCS intervention in combination with aerobic exercise training sessions, we observed significant decreases in fatigue and pain VAS scores ($P < 0.05$) (Figure 2). No changes were observed related to fatigue scores and domains assessed by FACIT and MFIS. Nonetheless, we observed a high ES of 1.00 (CI 95% 0.80 - 1.90) in the general FACIT scores. Findings were similar for the physical domains in the same questionnaire: ES of 0.80 (CI 95% -0.16 - 1.70). In contrast, the other FACIT domains the ES for emotional well-being was low: ES of 0.66 (CI 95% -0.28 - 1.50); the ES for functional well-being was very low, ES of 0.38 (CI 95% -0.55 - 1.30), and a very low ES was seen for family well-being, ES: 0.16 (CI 95% -0.77 - 1.12).

Concerning the general MFIS, the ES was large. -0.81 (CI 95% 1.10 - 0.29), as well as the physical domains, ES of -0.81 (CI 95% -1.77 - 0.28). The ES was low for cognitive domains, ES of 0.11 (CI 95% -1.1 - 0.80), and a very low ES was observed for psychosocial domains, ES of -0.19 (CI 95% -0.1 - 0.8).

During all tDCS interventions, the intensity of the aerobic exercise did not change (mean exercise intensity was 5.5 ± 0.8), and the patients' perception of recovery through exercise remained unchanged during the protocol. Furthermore, there were no adverse effects of tDCS. In all protocols, 100% patient adherence.

DISCUSSION

³ To the best of our knowledge, this is the first study to demonstrate the efficacy of tDCS combined with aerobic exercise training in reducing pain and fatigue after COVID-19 in patients with SARDs.

We conducted a prospective analysis with a well-defined study design that included selected SARDs patients. To mitigate the risk of bias, the patients' pharmacological therapy was unchanged and the patients did not engage in other non-pharmacological interventions outside of the aerobic exercise training program. In addition, we followed-up with all patients instant messaging and regularly scheduled face-to-face interviews.

In the analyzed patients who had been classified as having clinical remission, the underlying disease (patients #1 and #4) remained inactive, with no observed recurrence of the disease. Activity rates in two patients had mild disease activity (patients #5 and #8), with no clinical worsening. A patient (patient #2) who was classified as having high disease activity, maintained a high activity rate, with a slight improvement from the initial value. Patients #3 and #6, both classified as having high disease activity in the initial assessment, radically changed their indices, reaching metric values of remission in their final assessment, even though treatment of the underlying diseases did not change during the execution of the study. As the perception of pain is extremely subjective and there were no variations in the laboratory data used, we believe that the worsening of this variable after COVID-19 negatively affected the disease activity indices. These two cases demonstrated that after treatment with tDCS, improvement in pain was reflected in the improvement in disease activity data. Only patient #9 reported worsening of clinical joint symptoms after tDCS, and her ESSDAI changed from mild to moderate activity. Patient #8 did not have her final data evaluated because she was in social isolation due to contact with a family member with a recent diagnosis of COVID-19.

It is important to emphasize that no changes were made to the patients' disease-modifying drug protocols throughout the course of tDCS treatment. Because the application of neurostimulation with tDCS took place for only five days, we chose not

to change the treatments for autoimmune diseases, so that possible positive findings of improvement in relation to pain and/or fatigue would not be affected by other treatment changes. Therefore, we believe that the improvement in the pain and fatigue VAS indices was correlated with the use of neurostimulation.

tDCS has been as a non-pharmacological intervention with notable results in the management of several chronic pain syndromes, such as fibromyalgia (40). Beyond its effects on pain, a significant amount of evidence has demonstrated improvements in physical function, mood and health-related quality of life (40,41). Concerning SARDs, a recent study showed notable improvements in fatigue related to primary Sjögren's syndrome (42), with no adverse effects related to tDCS and the disease status parameters. This result suggests that tDCS is a potentially safe and efficient way to improve fatigue in patients with Sjögren's syndrome (42). However, the authors applied tDCS without concomitant intervention (42). Previous studies have shown that tDCS with a concomitant non-pharmacological strategy (e.g., cognitive, motor task or exercise training) facilitates the identification of tDCS target levels that most effectively produce priming effects. Priming effects are the result of increased functional connectivity due to neurotransmitter release, which leads to increased cortical excitability in the primary cortex and influences pain processing (43-45). Moreover, evidence has shown that aerobic exercise training in conjunction with tDCS affects the motor cortex and can result in a major hypoalgesia response to pain related to fibromyalgia (43). These previous studies support our findings related to improvements in overall pain and fatigue, as measured by the VAS. Interestingly, significant improvements observed in physical function. Similar results have been reported in patients with stroke (46) and Parkinson's disease (47), suggesting that tDCS potentially affects physical function scores (48).

⁴ The limitations of the present study include its limited sample size and the lack of a control group. An observation worthy of attention is that only one patient reported new symptoms of persistent fatigue and pain, whereas all the other patients reported worsening of these symptoms after SARS-CoV-2 infection. Although no studies have

reported that COVID-19 exacerbates pain and fatigue in patients with SARDs, the hypothesis is plausible, given that these individuals are more likely to have chronic pain and related symptoms. SARS-CoV-2 infection may be related to one of the components of a vicious cycle of pain, fatigue, decreased physical function, and decreased quality of life that has been observed in various SARDs patients, leading to worse overall symptoms. However, no study has assessed these relationships. Future multicenter studies and representative sample sizes are needed to investigate the potential relationship between the disease parameters of post-COVID-19 and potential predictive tDCS response in patients with SARDS and post-COVID-19 and the differences between the adds-on therapy tDCS and aerobic exercise *vs* sham-tDCS and aerobic exercise, as well as the inclusion a two-arm double-blind study with vaccinated non-COVID-19 SARDS patients and vaccinated COVID-19 infected patients with SARDS to assess the potential priming effect of tDCS on clinical features in these patients.

CONCLUSION

In conclusion, tDCS may be an effective strategy to reduce fatigue and pain triggered or potentiated by COVID-19 and improve global function and quality of life. Moreover, tDCS combined with aerobic exercise training led to improvements in physical function. Additional studies with larger sample sizes and randomized designs with objective measures of these outcomes are required to confirm our findings.

ARTICLE HIGHLIGHTS

Research background

Patients with systemic autoimmune rheumatic disease with post-COVID-19 syndrome experience aggravated symptoms.

Research motivation

Given this context, it is essential to establish strategies that can reduce chronic pain and fatigue improving their quality of life.

Research objectives

Assess the efficacy of transcranial direct current stimulation to treat fatigue and pain associated post-COVID-19 syndrome in patients with systemic autoimmune rheumatic diseases.

Research methods

This is a quantitative pilot study that included nine patients with different systemic autoimmune rheumatic diseases. All patients had previously confirmed RT-PCR test for COVID-19 as well as significant, persistent fatigue and pain that began to worsen after infection. Anodal tDCS was administered in five daily sessions (2mA, 20 minutes). Concomitantly, patients were involved in aerobic exercise program.

Research results

The sample was composed of eight women and one man with a mean age of 48.7 ± 9.6 . After the tDCS protocol, the pain and fatigue significantly improved by a visual analog scale ($P < 0.05$). The physical function also improved 9.5 ± 2.7 vs. 6.8 ± 0.8 ($P = 0.001$) for timed-up-go-test and 10.3 ± 3.7 vs. 15.1 ± 4.0 ($P = 0.037$) for sit-to-stand test. No subject experienced adverse events.

Research conclusions

tDCS may be an effective strategy to treat fatigue and pain due to COVID-19 infection in patients with systemic autoimmune rheumatic diseases and improve the physical function.

Research perspectives

The present study contributes to new therapy options to treat pain and fatigue in patients with systemic autoimmune rheumatic diseases.

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