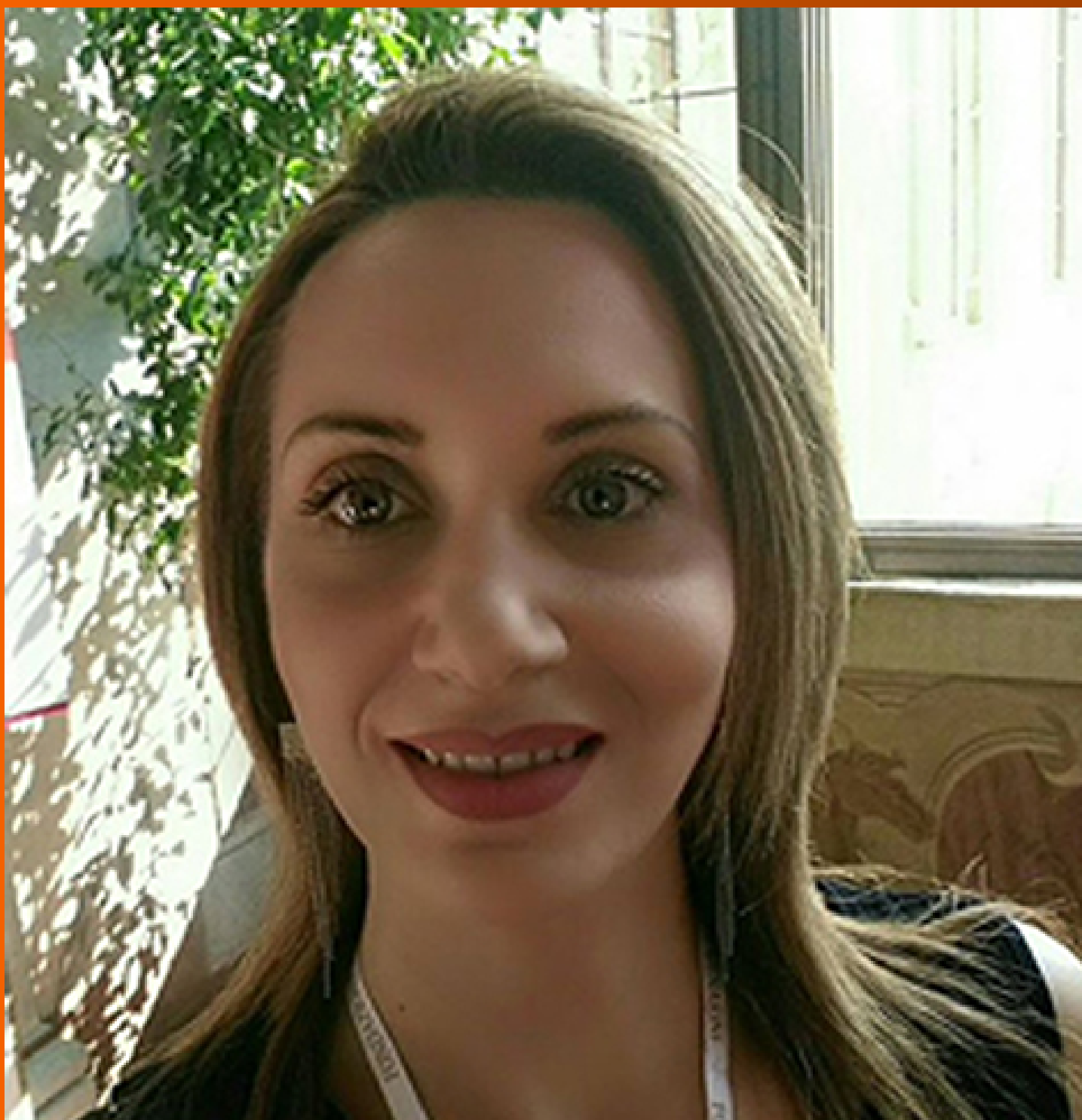


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ORIGINAL ARTICLE**Prospective Study**

- 1 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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Prospective Study

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

Rafael Giovanni Missé, Alexandre Moura dos Santos, Isabela Bruna Pires Borges, Marlise Sítima Mendes Simões, Lorenza Rosa Silvério, Bruna Lindoso Correia, Ana Wook Sook Kim, Aline Marques Caetano, Sandra Gofinet Pasoto, Carla Gonçalves Schahin Saad, Diogo Souza Domiciano, Clarice Tanaka, Julia Maria D'Andrea Greve, Abrahão Fontes Baptista, Samuel Katsuyuki Shinjo

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Abstract

BACKGROUND

Systemic autoimmune rheumatic diseases (SARDs) are a group of diseases with multiorgan involvement and a high prevalence of chronic pain and fatigue. Patients with SARDs and post-coronavirus disease 2019 (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

To assess the efficacy of transcranial direct current stimulation (tDCS) for the treatment of fatigue and pain-associated post-COVID-19 syndrome in patients with SARDs.

METHODS

This study included nine patients with different types of SARDs. All patients had reverse transcription-polymerase chain reaction (RT-PCR) test confirmed 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 min). 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 years. 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 that tDCS in combination with aerobic exercise was effective in improving physical function, and reducing fatigue/pain in SARDs patients with post-COVID-19 syndrome.

Key Words: Autoimmune diseases; COVID-19; Fatigue; Neuromodulation; Physical function; Rheumatic diseases; Pain

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Core Tip: In the present study, we assessed the efficacy of five daily transcranial direct current stimulation (tDCS) sessions for the treatment of fatigue and pain-associated post-coronavirus disease 2019 (COVID-19) syndrome in nine patients with different systemic autoimmune rheumatic diseases (SARDs). After the tDCS protocol, pain and fatigue significantly improved on the visual analog scale. 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. In conclusion, tDCS in combination with aerobic exercise was effective in improving physical function, and reducing fatigue/pain in SARDs patients with post-COVID-19 syndrome.

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INTRODUCTION

The World Health Organization (WHO) declared coronavirus disease 2019 (COVID-19), which is caused by the severe acute respiratory syndrome coronavirus 2 (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 4.6 million 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[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 shown the growing dependence on health systems in these patients 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].

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[14], and fibromyalgia[12]. Recently, Pinto *et al*[15] showed that tDCS of the dorso-lateral pre-frontal cortex was largely effective in reducing 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[16]. Despite this, recent studies also showed that the combined 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[17].

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 hypothesize 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. Our center follows 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.

SARDs patients who fulfilled the following classification criteria were recruited: rheumatoid arthritis [18], systemic lupus erythematosus[19], systemic autoimmune myopathies[20], Sjögren's syndrome[21], and spondyloarthritis[22]; COVID-19 confirmed by real-time reverse transcription-polymerase chain reaction (RT-PCR) or serology for IgG and IgM[23] 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.

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) were excluded.

Two 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.

The following data were collected within one week before the tDCS intervention (pre-tDCS): age and sex; body mass index; the International Physical Activity Questionnaire, 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 d/wk and ≥ 30 min per session or vigorous activities during (≥ 3 d/wk and ≥ 20 min) and concomitant moderate physical activities (≥ 5 d/wk and ≥ 30 min per session); moderate activity score - vigorous activities (≥ 3 d/wk and ≥ 20 min per session) or moderate physical activities (≥ 5 d/wk and ≥ 30 min per session), or the sum of any activities performed ≥ 5 d/wk, and ≥ 150 min/wk[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 includes 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/Disease Activity Score-28[28], Sjögren's Syndrome Disease Activity

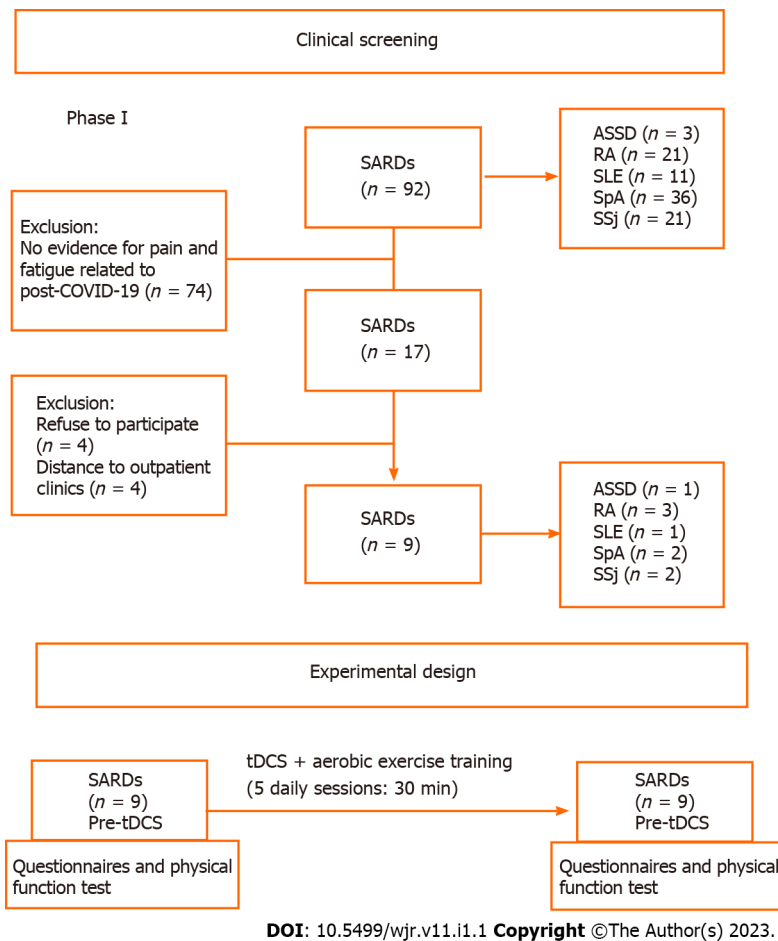


Figure 1 Flow-charts of the study. ASSD: Antisynthetase syndrome; COVID-19: Coronavirus disease 2019; RA: Rheumatoid arthritis; SARDs: Systemic autoimmune rheumatic diseases; SLE: Systemic lupus erythematosus; SpA: Spondyloarthritis; SSj: Sjögren's syndrome.

Index (ESSDAI)[29], Bath Ankylosing Spondylitis Activity Index[30], Manual Muscle Testing-8 (MMT-8)[31], Systemic Lupus Erythematosus Disease Activity Index[32]. Fatigue status and severity were assessed using the visual analog scale (VAS), Fatigue Assessment of Chronic Illness Therapy[33], Modified Fatigue Impact Scale (MFIS)[34], and Fatigue Severity Scale (FSS)[35]. Pain and fatigue diary was recorded 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 was examined with timed-up-and-go test[36] and stand-to-sit test[37]. Muscle strength was examined with Handgrip test [38]; and quality of life was determined by EQ-5D[39].

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

For tDCS, the anode was sourced from a battery-powered direct current generator (Activadose II, United States) and was exerted by two electrodes measuring 5 cm × 7 cm (35 cm²) (Ibramed, Brazil) covered by a sponge with saline solution and fixed to the head using Velcro straps. Electrodes were used 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 20 min, with an up and down ramp of 10 s.

Aerobic exercise was characterized by walking on a treadmill for 30 min with intensity adjusted through measurement of effort during and after 20 min of tDCS sessions. In addition, the perception of recovery was collected between sessions[40].

Adverse events were registered during and after each application through questionnaire related to sensations such as burning, tingling, itching, burning (head), headache, nausea, fatigue, emotional lability (tendency to shift rapidly and dramatically between different emotional states), difficulty in concentrating and nervousness.

Patients' adherence to the protocol was assessed by the researchers in all stages of the study.

Statistical analysis

The data distribution was set at $\alpha = 0.5$. With purpose to analyze differences in the clinical characteristics between groups student t test or U man-Whitney test. *P* value was considered statistically significant

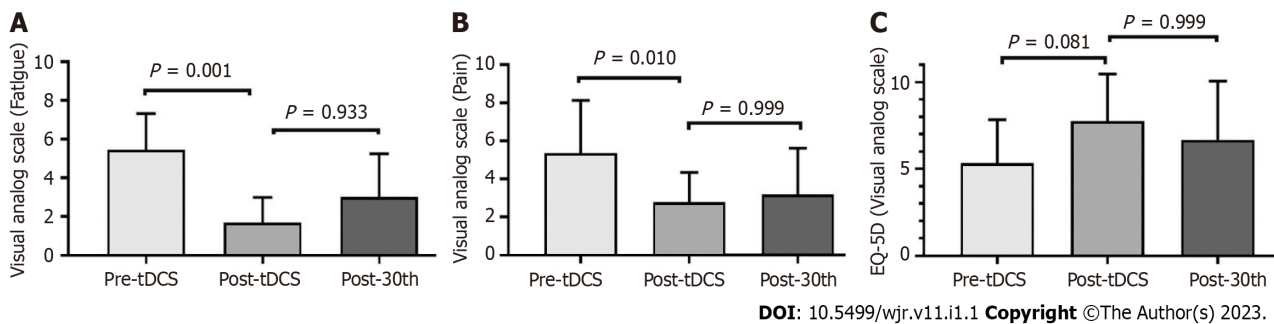


Figure 2 Changes related post transcranial direct current electrical stimulation intervention. Changes related post transcranial direct current electrical stimulation intervention in the A: General fatigue score; B: Pain score; C: Quality of life score. EQ-5D: Health-related quality of life; tDCS: Transcranial direct current electrical stimulation.

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, United States).

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 (Table 1).

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 (Figure 3). Nonetheless, we observed a high ES of 1.00 (95%CI: 0.80-1.90) in the general FACIT scores. Findings were similar for the physical domains in the same questionnaire: ES of 0.80 (95%CI: -0.16 to 1.70). In contrast, the other FACIT domains the ES for emotional well-being was low: ES of 0.66 (95%CI: -0.28 to 1.50); the ES for functional well-being was very low, 0.38 (95%CI: -0.55 to 1.30), and a very low ES was seen for family well-being, 0.16 (95%CI: -0.77 to 1.12). Similar findings were observed by individual data analysis (Table 2).

Concerning the general MFIS, the ES was large -0.81 (95%CI: 1.10 to 0.29), as well as the physical domains, ES of -0.81 (95%CI: -1.77 to 0.28). The ES was low for cognitive domains, 0.11 (95%CI: -1.1 to 0.80), and a very low ES was observed for psychosocial domains, -0.19 (95%CI: -0.10 to 0.80). Concerning the physical function a significant improvement was evidenced on timedupand-go test and sittostand test ($P < 0.05$) (Table 3). 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, patient adherence was 100%.

DISCUSSION

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.

Table 1 General characteristics of the systemic autoimmune rheumatic disease patients

Patient	Sex	Age (yr)	BMI (kg/m ²)	Disease	Disease duration (yr)	Prednisone (mg/d)	IS	Other medications	Comorbidities	Physical activity levels	Initial disease status
#1	F	56	31.7	ASSD	6	0	MTX, LFN	Amitriptyline	SAH	Moderate	MMT-8 = 80; MYOACT = 0
#2	F	39	37.4	RA	15	5	TOF, MTX	Gabapentin, dipyron	DLP, FM	Low	DAS28 = 5.4; CDAI = 28
#3	F	43	34.3	RA	21	5	TOF, MTX	Dipyron	SAH, DLP	Low	DAS28 = 5.7; CDAI = 45
#4	F	55	30.4	RA	4	15	TOF	Dipyron	-	Moderate	DAS28 = 3.2; CDAI = 3
#5	F	29	29.0	SLE	12	5	MMF	Dipyron	-	Low	SLEDAI = 4
#6	M	56	23.7	SpA	22	0	-	Meloxicam	-	Low	BASDAI = 3.5; ASDAS = 2.5
#7	F	46	35.6	SpA	26	5	MTX, CZP	Tramadol	SAH	Low	BASDAI = 5.6; ASDAS = 3.0
#8	F	53	26.8	SSj	6	0	HCQ	Dipyron	SAH	Low	ESSDAI = 2
#9	F	57	26.2	SSj	13	0	HCQ	Sertraline	SAH, FM	Low	ESSDAI = 2

ASSD: Antisynthetase syndrome; AZA: Azathioprine; BMI: Body mass index; CPZ: Certolizumab pegol; DLP: Dyslipidemia; F: Female; FM: Fibromyalgia; HCQ: Hydroxychloroquine; IS: Immunosuppressives; LFN: Leflunomide; M: Male; MMF: Mycophenolate mofetil; MTX: Methotrexate; RA: Rheumatoid arthritis; SAH: Systemic arterial hypertension; SLE: Systemic erythematous lupus; SpA: Spondyloarthritis; SSj: Sjögren's syndrome; tDCS: Transcranial direct current electrical stimulation; TOF: Tofacitinib.

Table 2 Individual data related to the effects of transcranial direct current electrical stimulation on the visual analog scale for pain, fatigue and fatigue severity

Variables		Patients								
		#1	#2	#3	#4	#5	#6	#7	#8	#9
Pre-tDCS	Fatigue, VAS, (0.0-10)	8	5	7	10	3	3	7	2	3
Post-tDCS		3	3	3	6	2	2	2.5	0	3
Δ (%)		-62.5	-40	-57.1	-40	-33.3	-33.3	-64.2	-100	0
Pre-tDCS	Pain, VAS, (0.0-10)	5	5	6	8	2	8	6	4	5
Post-tDCS		0	2	2	4	1	2	1.5	0	3
Δ (%)		-100	-60	-66.6	-50	-50	-75	-75	-100	-40
Pre-tDCS	FSS, (0.0-7.0)	6	5	5	5	5	5	4	3	4
Post-tDCS		3	3	3	3	2	4	0	3	1
Δ (%)		-50	-40	-40	-40	-60	-20	-100	0	-75

Data were expressed as individual value and the percentual change were calculated by the formula: Δ (%) (Post-tDCS-Pre-tDCS)/Pre-tDCS*100. tDCS: Transcranial direct current electrical stimulation.

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. 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

Table 3 Fatigue, physical function and muscle strength before transcranial direct current electrical stimulation, after transcranial direct current electrical stimulation, and after one month of follow-up

	Pre-tDCS	Post-tDCS	P value
MFIS (domains)			
Physical (0-36)	23.2 ± 2.2	19.1 ± 1.8	0.332
Cognitive (0-40)	21.0 ± 5.6	21.6 ± 6.3	0.974
Psychosocial (0-8)	4.3 ± 2.9	3.7 ± 1.3	0.864
FACIT (domains)			
Physical well-being (0-28)	15.4 ± 5.0	20.1 ± 5.0	0.987
Family and social well-being (0-28)	16.4 ± 3.6	17.0 ± 3.7	0.964
Emotional well-being (0-24)	16.3 ± 4.4	19.3 ± 4.4	0.521
Functional well-being (0-28)	15.3 ± 6.1	17.6 ± 3.9	0.683
Physical function			
Timed-Up-Go test (s)	9.5 ± 2.7	6.8 ± 0.8	0.001
Sit-To-Stand test (repetitions)	10.3 ± 3.7	15.1 ± 4.0	0.037
Strength			
Handgrip (kg)	21.1 ± 5.7	24.5 ± 8.3	0.522

pre-tDCS vs post-tDCS. EQ-5D: Health-related quality of life; FACIT: Fatigue Assessment Chronic Illness Therapy MFIS: Modified Fatigue Impact Scale; tDCS: Transcranial direct current electrical stimulation; VAS: Visual Analogue Score.

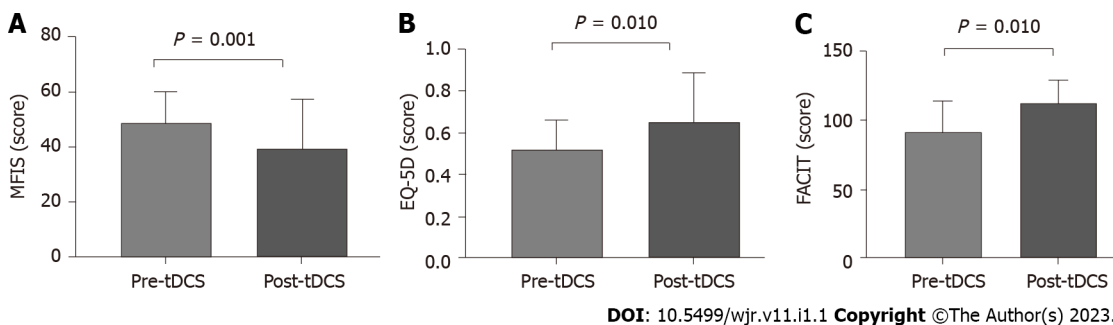


Figure 3 Changes after transcranial direct current electrical stimulation intervention. A: Changes after transcranial direct current electrical stimulation intervention related to the mean Modified Fatigue Impact Scale score; B: Quality of life score; C: Fatigue Assessment of Chronic Illness Therapy mean score. EQ-5D: EuroQual; FACIT: Fatigue Assessment of Chronic Illness Therapy; MFIS: Modified Fatigue Impact Scale; tDCS: Transcranial direct current electrical stimulation.

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 (Table 2).

tDCS has been used as a non-pharmacological intervention with notable results in the management of several chronic pain syndromes, such as fibromyalgia[41,42]. Beyond its effects on pain, a significant amount of evidence has demonstrated improvements in physical function, mood and health-related quality of life[42,43]. Concerning SARDs, a recent study showed notable improvements in fatigue related to primary Sjögren's syndrome[15], 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[15]. However, the authors applied tDCS without concomitant intervention[15]. 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[42-49]. 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[42]. 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].

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 add-on therapy tDCS and aerobic exercise *vs* sham-tDCS and aerobic exercise.

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 (SARDs) with post- coronavirus disease 2019 (COVID-19) syndrome experience aggravated symptoms.

Research motivation

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

Research objectives

To assess the efficacy of transcranial direct current stimulation in treatment of fatigue and pain associated with post-COVID-19 syndrome in patients with SARDs.

Research methods

This is a quantitative pilot study that included nine patients with different SARDs. All patients had reverse transcription-polymerase chain reaction test confirmed COVID-19 as well as significant, persistent fatigue and pain that began to worsen after infection. Anodal transcranial direct current stimulation (tDCS) was administered in five daily sessions (2mA, 20 min). 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 years. After the tDCS protocol, the pain and fatigue significantly improved as shown 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 patient experienced adverse events.

Research conclusions

tDCS may be an effective strategy to treat fatigue and pain due to COVID-19 in patients with SARDs and improve the physical function.

Research perspectives

The present study contributes to new treatment options to treat pain and fatigue in patients with SARDs.

FOOTNOTES

Author contributions: Missé RG, dos Santos AM, Borges IBP contributed to data collection, statistical analysis, manuscript writing; Simões MSM, Silvério LR, Correia BL, Kim AWS, Caetano AM contributed to data collection, manuscript writing; Pasoto SG, Saad CGS, Domiciano DS, Tanaka C, Greve JMA, Baptista AF, Shinjo SK contributed to manuscript writing, study supervision.

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