Transcranial direct current stimulation is safe and effective in autoimmune myopathies: a randomised, double-blind, sham-controlled trial

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Abstract

Objective

We aimed to assess the safety and efficacy of transcranial direct current stimulation (tDCS) in patients with systemic autoimmune myopathies (SAMs).

Methods

This prospective, randomised, sham-controlled, double-blind, study included 20 patients with SAMs allocated to receive sham or active tDCS (2mA, 20 minutes, 3 days). Electrodes were positioned with the anode over the C1 or C2, whereas the cathode was placed over the Fp2 or Fp1, respectively. The groups were evaluated in four periods with specific questionnaires and functional tests: pre-stimulation and after 30 minutes, three weeks, and eight weeks post-tDCS.

Results

Two patients from the sham group withdrew after the three sessions. The demographic data, type of myositis, disease duration, and disease status were comparable between the active and sham tDCS groups. After interventions, in the active tDCS group, the physical aspects of SF-36 in week eight, mean and better timed up-and-go test at each evaluation, peak torque of stimulated inferior limb extension improved significantly ($p<0.05$). The emotional aspect of SF-36 decreased only in the active tDCS group ($p<0.001$). The patients' adherence to the protocol was 100% and no serious adverse event was reported, including disease relapses.

Conclusion

This study evidences the safety of tDCS, as well as its potential efficacy in improving muscle strength and function in SAMs patients. More studies with a larger sample and longer tDCS sessions are necessary to corroborate the results of the present study.

Key words

inflammatory myopathies, myositis, neuromodulation, safety, quality of life

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Introduction

Idiopathic inflammatory myopathies or systemic autoimmune myopathies (SAMs) are a heterogeneous group of autoimmune diseases associated with high morbidity and functional disability (1-3). Considering epidemiological, clinical, laboratory data, and histopathological features, SAMs can be classified in dermatomyositis (DM), clinically amyopathic dermatomyositis, polymyositis (PM), antisynthetase syndrome (ASSD), immune-mediated necrotising myopathies (IMNM), and inclusion body myositis (1-3). SAMs are characterised generally by the presence of symmetrical, progressive, and predominantly proximal muscle weakness. Extra-skeletal manifestations may also be present, aggravating the morbidities and quality of life of patients with SAMs (4, 5).

In the last few years, despite the evolution of pharmacological treatment for SAMs, there has still been little information regarding non-pharmacological treatments, especially regarding rehabilitation, and patients with SAMs are sometimes unable to engage in physical activity with conventional strength training (2, 6, 7). Thus, a proportion of these patients maintain a degree of proximal muscle weakness of the scapular and pelvic girdles, along with mild myalgia and muscle tenderness. In this context, new rehabilitation techniques already approved for other diseases, such as non-invasive brain stimulation, including transcranial direct current stimulation (tDCS), could potentially improve the functionality and quality of life, including reduction of pain, of patients with SAMs.

Besides being a relatively inexpensive and safe method, the potential of tDCS in influencing physical skills such as muscle strength, endurance (8), power (9), flexibility (10), motor learning (11), movement coordination (12) and accuracy (13, 14) has called its attention as a therapeutic option in rheumatological patients. Pain and fatigue in rheumatological diseases are frequently attributed to peripheral factors such as inflammation, and muscle tissue abnormalities, or psychological factors (15, 16). Even when central factors are considered, there is a lack of understanding on their contribution to those phenomena, and treatment is generally directed to peripheral mechanisms (17). Hence, investigating the efficacy of tDCS in SAMs may add to the understanding of central pain mechanisms in rheumatological disease. Non-invasive brain stimulation through tDCS has demonstrated promising results in the control of pain in other rheumatological diseases, such as fibromyalgia, and improving fatigue in Sjögren's syndrome (18, 19), but, to our knowledge, no study has evaluated tDCS in patients with SAMs. Therefore, we assessed the efficacy of tDCS in improving muscle function and strength, safety, and quality of life in patients with SAMs.

Material and methods

Study design

This prospective, randomised, sham-controlled, double-blind, study took place from August 2018 through August 2019. This study was approved by the local research ethics committee (CAAE 95716618.7.0000.0068) and written informed consent was obtained from all participants. The study is registered at ClinicalTrials (no. NCT03749538).

Patients

Patients with DM and PM were defined according to European League Against Rheumatism / American College of Rheumatology (EULAR/ACR) 2017 classification criteria (2), ASSD by criteria used by Cavagna *et al*. (20), and the IMNM by criteria proposed by Allenbech *et al*. (21). The patients attended regular follow-up at the Rheumatology Outpatient Clinic at our tertiary center. Twenty patients participated in the study, respecting the sample calculation performed in the GPower software for clinical and laboratory outcomes.

Inclusion criteria

Patients ≥18 years old and in remission or with minimal disease activity according to International Myositis Assessment & Clinical Studies Group (IMACS) set scores (22).

Exclusion criteria

Patients with a diagnosis of paraneoplasia; suspected or confirmed pregnancy; pacemaker, metal clips or metal prosthesis users; medical histories or personal reports of epilepsy or convulsive crisis; drugs that act on the central nervous system users; moderate or severe disease activity by IMACS set score; or significant impairment of lower limb musculature (>25% of muscle atrophy or fat replacement in thigh muscle assessed in the magnetic resonance).

Protocol

Patients were allocated randomly in two groups: an active anodal stimulation tDCS group (AcG) and a sham anodal tDCS group (ShG), both lasting 20 minutes for three consecutive days. The groups were evaluated at four moments: pre-stimulation, and 30 minutes, three weeks, and eight weeks post-tDCS. The evaluation 30 minutes post-tDCS was performed after the first tDCS session. The randomisation and group allocation were carried out by an external collaborator who was not involved in the study.

Demographic, anthropometric and clinical data

Age, body weight, and height, as well as the ethnicity data of all patients were collected. Body mass index (BMI) was calculated for each patient. Life habits including tobacco and alcohol consumption were obtained. Physical activity data was assessed using the International Physical Activity Questionnaire (23). Comorbidities (systemic arterial hypertension, dyslipidemia, hypothyroidism, and obesity) and associated pharmacological treatment (antihypertensive drugs, levothyroxine, oral anti-diabetics, statins, antidepressants) were assessed. Disease duration, treatment with immunosuppressive, immunomodulatory, or immunobiological drugs (azathioprine, leflunomide, methotrexate, mycophenolate mofetil, tofacitinib, or rituximab) and glucocorticoid use (current and highest dose used) were collected. The presence of specific SAMs antibodies was assessed: anti-Mi-2 as well as Jo-1, PL-7, PL-12, OJ, EJ, SRP, Ku, and PM/Scl antibody assessments were performed using a commercial kit (Euroline, Myositis Profile 3, Euroimmun, Germany) according to the manufacturer's protocol; and anti-HMGCR antibody was assayed by enzyme-linked immunosorbent assay (ELISA), using recombinant HMGCR protein and anti-HMGCR polyclonal antibody (MyBioSource, CA, USA). Disease activity was assessed in the four moments (pre-stimulation, and 30 minutes, three weeks and eight weeks post-tDCS) using the Manual Muscle Testing (MMT)-8, Myositis Disease Activity Assessment Visual Analogue Scales (MYOACT), global assessment of the disease by the physician and the patient using the visual analogue scale (VAS), Health Assessment Quality (HAQ), 36-Item Short-Form Health Survey (SF-36), besides laboratory evaluation (24-28). Moreover, pain was assessed using patient VAS and pain item of SF-36.

Laboratory evaluation

Serum levels of creatine phosphokinase, lactate dehydrogenase, alanine transaminase, and aspartate transaminase were measured at the pre-stimulation, three weeks, and eight weeks post-tDCS moments.

Muscle strength and function

The patients underwent a computerised isokinetic assessment of bilateral flexor and extensor muscles of elbows and knees using a CYBEX 6000 dynamometer, to evaluate the muscle strength with values of peak torque, peak torque/body weight ratio, and total work. The tests were performed in two sessions, and the best absolute value was selected. The exception was the first assessment where there was a learning session before the others.

The muscle functions were evaluated with the Timed Up and Go test (TUG) and the 30-second Time Sit to Stand test (TSST) (29, 30). The tests were performed in two sessions, with average and best absolute values evaluated. The exception was the first assessment where there was a learning session before the others.

Disease remission definition

Low disease activity was assessed according to IMACS set scores with the patients presenting a ≥6-month continuous period with no evidence of disease activity (disease remission) or low disease activity while still or not receiving myositis therapy (31).

Anodal tDCS

Anodal tDCS was applied through a battery-powered DC generator (Activadose II, USA) using two electrodes measuring 5 x 7 cm (35 cm^2) (Ibramed, Brazil) covered with a vegetable sponge, soaked with physiological saline solution, and fixed on the head by Velcro straps. The electrodes were positioned in accordance with the International 10-10 Electroencephalography System for better localisation of M1 (32). The electrode with the positive charge (anode) was positioned at C1 or C2 (contralateral to the dominant limb), and the electrode with a negative charge (cathode) was positioned in the ipsilateral supraorbital region of the dominant limb (Fp2 or Fp1). Active tDCS was applied with an electric current intensity of 2 mA and density of 0.057 mA/cm^2 for 20 minutes. Sham tDCS was applied with the same parameters but only during the first 30 seconds of stimulation, according to parameters classically used in the literature, enough time to identify the presence of the current with no effective brain stimulation (33). During the tDCS application, the patients remained seated. After the tDCS, the patients waited 30 minutes to restart the assessments as demonstrated in previous studies (34, 35).

Safety and adverse effects

The safety was evaluated with careful follow-up of all participants in relation to disease recurrence and clinical complications. The adverse effects were evaluated after each application through spontaneous reports of any unpleasant sensations such as burning, tingling, itching, headache, or nausea.

Statistical analysis

The parameters of extension and flexion were described according to groups, sides of the dominance of the limb, and moments of evaluation, while the other parameters were described according to groups, moments of evaluation using summary measures (mean ± standard

Table I. General baseline data of patients from active and sham groups.

Variable	AcG (n=10)	ShG (n=8)	*p*-value
Demographic data			
Age (years)	42.8 ± 18.4	54.5 ± 12.7	0.131
Female gender	10 (100)	8 (100)	>0.999
White ethnicity	8 (80.0)	6 (75.0)	>0.999
Disease			
Dermatomyositis	5 (50.0)	3 (37.5)	0.664
Polymyositis	0 1 (12.5)	-	
Antisynthetase syndrome	2 (20.0)	1 (12.5)	>0.999
IMNM	3 (30.0)	3 (37.5)	>0.999
Weight (kg)	71.0 (64.5-83.5)	75.5 (72.3-81.3)	0.173
Body mass index (kg/m^2)	26.4 ± 6.5	31.3 ± 3.9	0.065
Alcoholism	0	0	-
Smoking	2 (20.0)	0	-
Physical activity	7 (70.0)	6 (75.0)	>0.999
Disease duration (years)	3.2 (1.3-4.5)	3.6 (3.1-6.4)	0.315
Autoantibodies	4 (40.0)	3 (37.5)	>0.999
Treatment			
Glucocorticoid			
Current use	3 (30.0)	1 (12.5)	0.558
Dose (mg/day)	2.5 ± 4.2	2,5 ± 7.1	>0.999
Methotrexate	5 (50.0)	3 (37.5)	0.664
Azathioprine	3 (30.0)	2 (25.0)	>0.999
Leflunomide	1 (10.0)	0	-
Mycophenolate mofetil	2 (20.0)	0	-
Tofacitinib	0	1 (12.5)	-
Rituximab	2 (20.0)	0	-

Data are expressed as mean ± standard deviation, median (interquartile 25-75%) or number (percentage). AcG: active stimulation group; ShG: sham group; IMNM: immune-mediated necrotising myopathy; SAMs: systemic autoimmune myopathies.

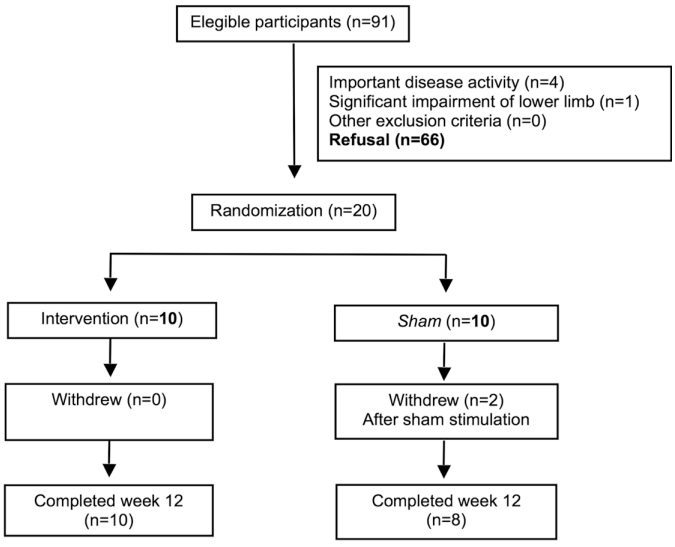

Fig. 1. Flow-chart of the present study.

deviation) and compared between the factors of interest with the use of generalised estimation equations with normal or gamma marginal distribution, only for creatine phosphokinase, according to the data distribution asymmetry and identity link function, assuming a first-order autoregressive correlation matrix between the moments of evaluation and/or sides of dominance. The *p* resulting from the comparisons between groups, without taking into account different moments of the evaluation was represented as Pgroup; the *p* resulting from the comparisons between moments, without taking into account different groups was represented as PMoment; the *p* resulting from the comparison between sides, without taking account groups or moments was represented as PSide; the *p* resulting from the comparison between groups, taking into consideration changes in different evaluation moments was represented as PGroup*Moment; the *p* resulting from the comparison between sides, taking into consideration differences between groups was represented as PSide*Group; the *p* resulting from the comparison between sides, taking into consideration different moments was represented as PSide*Moment; and the *p* resulting from the comparison between sides, taking into account different moments and groups was represented as PGroup*Moment*Side**.** All analyses were followed by Bonferroni's multiple comparisons when significant to identify between which groups, sides or moments the differences occurred. Discomfort and belief in the stimulus were described according to groups using absolute and relative frequencies and verified the existence of association with Fisher's exact test. The statistical analyses were performed with the IBM-SPSS software for Windows 20.0. The tests were performed with a significance level of 5%.

Results

Patients

We enrolled 20 participants from August 2018 through August 2019. Ten patients were randomly assigned to the AcG and 10 patients to the ShG. A total of 18 patients (90%) completed the trial through week 8. The two patients who withdrew from the study were from the ShG. They withdrew after the three sham stimulation sessions due to personal problems, not presenting any complications associated with the sham stimulation. The demographic and anthropometric information, type of SAMs, life habits, and treatment characteristics were similar between the two groups ($p>0.05$) (Table I). In the 8-week follow-up, the patients continued to use the same SAM medications and did not change their lifestyle habits (Fig. 1). The general results of the different outcomes are listed in Table II.

Primary outcomes

Muscle function tests

The AcG presented improvement in relation to the best and average TSST values between each evaluation period

Table II. General features of sham and active groups.

	Sham group				Active group			
Variable	Pre tDCS	Post tDCS	Week 3	Week 8	Pre tDCS	Post tDCS	Week 3	Week 8
IMACS set scores								
MMT-8 (0-80)	79 (76-80)	79 (78-80)	80 (78-80)	80 (79-80)	80 (79-80)	80 (79-80)	80 (79-80)	80 (80-80)
HAQ (0.00-3.00)	0.00 (0.00-0.31)	0.00 (0.00-0.31)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
MYOACT (0-10)	0.03 (0.00-0.07)	0.03 (0.00-0.07)	0.03 (0.00-0.05)	0.00 (0.00-0.00)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)
Patients' VAS (0-10)	2.0 (0.5-4.0)	2.0 (0.5-4.0)	1.5 (0.0-3.8)	0.0 (0.0-2.0)	0.5 (0.0-3.3)	0.5 (0.0-3.3)	0.0 (0.0-1.4)	0.0 (0.0-1.4)
Physician's VAS (0-10)	0.0 (0.0-0.9)	0.0 (0.0-0.9)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.1)	0.0 (0.0-0.1)	0.0 (0.0-0.0)	0.0 (0.0-0.0)
Creatine phosphokinase (U/L)	166 (71-284)	166 (71-284)	115 (70.8-154)	99 (79-166)	208 (120-284)	208 (120-284)	133 (76-239)	128 (128-240)
Lactate dehydrogenase (U/L)	191 (164-214)	191 (164-214)	192 (176-232)	211 (199-250)	191 (179-213)	191 (179-213)	188 (179-233)	189 (189-207)
Aspartate transaminase (U/L)	22 (17-27)	22 (17-27)	19 (16-25)	18 (17-30)	22 (17-29)	22 (17-29)	21 (18-25)	21 (21-24)
Alanine transaminase (U/L)	23 (18-25)	23 (18-25)	22 (18-26)	19 (17-26)	22 (18-29)	22 (18-29)	21 (17-29)	21 (21-28)
Muscle functional parameters								
Sit-and-stand test, best (repetitions)	13.0 (11.8-15.5)	14.0 (12.0-16.5)	14.0 (12.0-19.0)	15.0 (13.0-17.5)	15.0 (10.8-17.8)	16.0 (10.3-18.5)	16.5 (11.8-17.8)	15.0 (11.5-17.8)
Sit-and-stand test, mean (repetitions)	12.8 (11.8-14.9)	13.8 (11.9-16.3)	14.0 (12.0-18.8)	14.0 (12.8-17.5)	14.8 (10.4-17.3)	15.8 (10.1-18.1)	16.0 (11.6-17.4)	14.8 (11.5-16.9)
Timed up-and-go test, best (s)	7.6 (6.3-8.5)	7.3 (6.0-7.8)	6.7 (6.2-7.9)	7.2 (6.0-8.2)	6.9 (6.2-8.7)	6.6 (5.9-8.4)	6.8 (6.3-8.4)	7.2 (6.6-7.9)
Timed up-and-go test, mean (s)	7.7 (6.6-8.6)	7.4 (6.2-8.0)	6.7 (6.3-8.0)	7.2 (6.2-8.3)	7.1 (6.2-8.8)	6.7 (6.1-8.5)	6.9 (6.3-8.4)	7.3 (6.6-7.9)
SF-36 domains								
Functional capacity	82.5 (62.5-95.0)	82.5 (62.5-95.0)	87.5 (85.0-98.8)	92.5 (86.3-100)	92.5 (81.3-100)	92.5 (81.3-100)	92.5 (90.0-100)	100 (95.0-100)
Physical functioning	100 (100-100)	100 (100-100)	100 (100-100)	100 (100-100)	100 (100-100)	100 (100-100)	100 (100-100)	100 (100-100)
Pain	66.5 (61.0-96.0)	66.5 (61.0-96.0)	92.0 (84.0-100)	100 (84.0-100)	100 (91.7-100)	100 (91.7-100)	100 (90.3-100)	100 (72.0-100)
General health	72.0 (59.5-80.8)	72.0 (59.5-80.8)	57.0 (42.0-78.3)	64.5 (62.0-79.5)	84.5 (57.0-100)	84.5 (57.0-100)	62.0 (50.7-92.5)	77.0 (54.5-90.2)
Vitality	62.5 (52.5-78.8)	62.5 (52.5-78.8)	77.5 (67.5-83.8)	82.5 (72.5-90.0)	82.5 (52.5-92.5)	82.5 (52.5-92.5)	77.5 (50.0-100)	87.5 (57.5-96.3)
Social functioning	100 (100-100)	100 (100-100)	100 (100-100)	100 (100-100)	100 (100-100)	100 (100-100)	100 (100-100)	100 (100-100)
Emotional functioning	100 (100-100)	100 (100-100)	100 (100-100)	100 (100-100)	100 (100-100)	100 (100-100)	100 (100-100)	100 (100-100)
Mental health	84.0 (58.0-88.0)	84.0 (58.0-88.0)	82.0 (73.0-92.0)	90.0 (78.0-98.0)	80.0 (63.0-97.0)	80.0 (63.0-97.0)	86.0 (68.0-94.0)	86.0 (86.0-97.0)
Serious adverse events	0	0	0	0	0	0	0	0

Data are expressed as median (interquartile 25-75%).
MMT: manual muscle testing; HAQ: Health Assessment Questionnaire; MYOACT: Myositis Disease Activity Assessment Visual Scales; VAS: visual analogue scale; SF-36: 36-Item Short-Form Health Survey; IMACS: International Myositis Assessment and Clinical Studies Group.

(p<0.05) (Table III, Supplementary Table S1). On the other hand, in the ShG, the best and average TSST values improved between pre-tDCS and other periods, as well as between 30-minute post-tDCS and three and eight weeks (p<0.05), but the group presented decreased best and average TSST values between the third and eight weeks (p<0.001). The average and best TUG values improved between pre-tDCS and post-tDCS and the third week, independently of the group (p<0.05), but did not show statistically significant differences among the eight weeks.

Isokinetic tests (extension tests)

The absolute peak torque and peak torque adjusted by weight of lower limb extension tests presented higher values in the dominant limb compared with the non-dominant one in the AcG (p<0.05), contrary to the ShG, which presented higher values in the non-dominant member in relation to the dominant one (p<0.05) (Table IV, Suppl. Table S2). The values of absolute peak torque, peak torque adjusted by weight, and total work of extension upper limbs showed improvement between post-tDCS and week 3, independently of the group (respectively p=0.049, p=0.041, and p=0.024). The total work of lower limb extension was inferior in the dominant member compared with the non-dominant one only in the ShG (p<0.001).

Isokinetic tests (flexion tests)

The absolute peak torque, peak torque adjusted by weight, and total work of upper member flexion values were superior in the dominant limb compared with the non-dominant one, independently of the group or evaluation period (p<0.001) (Table IV, Suppl. Table S2). Regarding the absolute peak torque of lower limb flexion, the dominant side was again superior compared with the non-dominant one, independently of the group or evaluation period (p=0.042).

Secondary outcomes

Safety

Adverse events. A total of 60% of patients in the AcG and 62.5% patients in ShG presented some discomfort during the active and sham stimulations, respectively, without statistical difference between the groups. The most common adverse effect was pruritus in regions close to the electrodes, mainly at the beginning of the stimulus (50% of both groups). The other adverse effects were sting sensation, burning and fatigue, in the frequency of 20, 10, 10% and 12.5, 12.5, 12.5% in AcG and ShG, respectively (p>0.999). Important to highlight that no patients from both groups presented adverse effects that changed the general condition.

Disease activity. Regarding the domains of SF-36, the physical domain increased by 2.5 points on average at week 8 in relation to the other moments only in the AcG (p<0.001), whereas the emotional domain decreased by 3.3 points on average at all the moments in relation to pre-tDCS (p<0.001) (Table III, Suppl. Table S2). The pain domain improved between pre-tDCS and week 3 independently of the group (p=0.002) and the mental health domain increased between week 8 and the other moments, also, independently of the group (p<0.005).

The patients' VAS decreased on average between week 8 and the pre-tDCS moment independently of the group (p=0.037) and CPK levels decreased on average after the tDCS sessions independently of the group (p<0.05), but within

Table III. Comparison of MMT, muscle function SF-36, disease activity and laboratory data results between groups.

Variable	ShG				AcG				p_{Group}	p_{Moment}	$p_{Group*Moment}$
	Pre tDCs	Post tDCs	Week 3	Week 8	Pre tDCs	Post tDCs	Week 3	Week 8			
MMT (0-80)	78.1 ± 2.3	79 ± 1.2	79.4 ± 0.9	79.8 ± 0.5	79.4 ± 1.4	79.6 ± 0.8	79.6 ± 0.7	80 ± 0	0.181	**0.003**	0.255
TSST best	14.5 ± 3.7	15.4 ± 4.7	16.3 ± 5.2	15.9 ± 5.7	14.2 ± 3.9	15.2 ± 4.7	15.8 ± 5.1	15.9 ± 4.9	0.916	**<0.001**	**<0.001**
TSST mean	14.2 ± 3.6	15.1 ± 4.8	15.9 ± 5.1	15.5 ± 5.3	13.9 ± 3.7	14.9 ± 4.7	15.6 ± 5.1	15.6 ± 4.8	0.922	**<0.001**	**<0.001**
TUG best	7.5 ± 1.8	7.3 ± 1.8	7.3 ± 1.7	7.4 ± 1.5	7.4 ± 1.37	7 ± 1	6.9 ± 1	7.1 ± 1.2	0.660	**0.001**	0.772
TUG mean	7.6 ± 1.9	7.3 ± 1.8	7.4 ± 1.7	7.5 ± 1.5	7.5 ± 1.3	7.1 ± 0.9	7 ± 1	7.2 ± 1.2	0.680	**0.002**	0.778
Physical functioning	78.1 ± 21.5		83.8 ± 22.6	86.9 ± 21.7	89.5 ± 12.8		90.5 ± 13.2	92 ± 20.2	0.358	0.154	0.508
Physical domain	100 ± 0		100 ± 0	100 ± 0	92.5 ± 23.7		92.5 ± 23.7	95 ± 15.8	0.381	**<0.001**	**<0.001**
Pain	73.8 ± 18.9		90.5 ± 10.9	91.3 ± 13.9	83.6 ± 22.5		90.2 ± 21.2	84 ± 27.9	0.930	**0.002**	0.154
General health	68 ± 21.8		58.3 ± 23.9	70.5 ± 14.2	76.9 ± 22.6		68.4 ± 21.5	74.7 ± 19.6	0.349	**0.021**	0.786
Vitality	65.6 ± 15.2		75 ± 10.4	82.5 ± 11.3	74.5 ± 25		73.5 ± 27.4	75 ± 31.1	0.997	0.214	0.236
Social functioning	96.9 ± 8.8		100 ± 0	100 ± 0	93.8 ± 19.8		93.8 ± 19.6	90 ± 31.6	0.439	0.542	0.510
Emotional domain	100 ± 0		100 ± 0	100 ± 0	93.3 ± 21.2		90 ± 31.6	90 ± 31.6	0.381	**<0.001**	**<0.001**
Mental health	74.5 ± 18.9		81.5 ± 10.5	88.5 ± 9.4	76 ± 24.2		76 ± 29.9	79.6 ± 29.7	0.684	**0.003**	0.111
CPK (U/L)	188.6 ± 122.6		128 ± 74.4	126.8 ± 73.3	234.1 ± 170.3		170.4 ± 128.5	163.9 ± 122	0.409	**0.005**	0.979
LDH (U/L)	193.4 ± 31.7		203.5 ± 33.8	222 ± 32	196.6 ± 45.1		198.5 ± 45.7	191.4 ± 40.2	0.516	0.391	0.094
AST (U/L)	21.9 ± 5.2		20 ± 4.7	21.5 ± 6.7	22.3 ± 6.3		21.3 ± 4.6	20.4 ± 5.7	0.925	0.466	0.578
ALT (U/L)	22.6 ± 6.4		21.4 ± 5.9	20 ± 4.9	23.2 ± 10.6		22.6 ± 8.1	21.2 ± 6.5	0.744	0.440	0.973
PaVAS (0-10)	2.3 ± 1.9		1.9 ± 2.1	0.9 ± 1.2	1.4 ± 1.9		0.8 ± 1.4	1 ± 2	0.407	**0.042**	0.086
PhVAS (0-10)	0.3 ± 0.5		0.3 ± 0.7	0.3 ± 0.7	0.2 ± 0.3		0 ± 0	0 ± 0	0.256	0.239	0.784
HAQ (0- 3)	0.2 ± 0.3		0 ± 0.1	0 ± 0.1	0 ± 0		0 ± 0	0 ± 0	0.114	**0.050**	0.131
MYOACT (0-10)	0 ± 0.1		0 ± 0.1	0 ± 0	0 ± 0		0 ± 0	0 ± 0	**0.047**	**0.007**	**0.010**

Data are expressed as mean ± standard deviation.
ShG: sham group; AcG: active stimulation group; tDCS: transcranial direct current stimulation; *p* Group: *p* from the comparison of mean values between groups, without taking into consideration different evaluation moments; *p* Moment: *p* from the comparison of mean values between different evaluation moments, without taking into consideration differences between groups; *p* Group*Moment: *p* from the comparison of mean values between groups, taking into consideration changes in different evaluation moments; MMT: manual muscle testing; TSST: 30-second timed; sit to stand test; TUG: timed up and go test; 36-Item Short-Form Health Survey; CPK: creatine phosphokinase; LDH: lactate dehydrogenase; AST: aspartate transaminase; ALT: alanine transaminase; PaVAS: patients' visual analogue scale; PhVAS: physician's visual analogue scale; HAQ: Health Assessment Quality; MYOACT: Myositis Disease Activity Assessment Visual Analogue Scale.

the normal range in both groups (Table III, Suppl. Table S2). No differences in other muscle enzymes were observed. Regarding the MYOACT scale, there was an improvement between week 8 and the other moments only in ShG ($p<0.05$), although the AcG maintained MYOACT of median 0 throughout all the follow-up. The MMT-8 scale improved between the pre-tDCS and weeks 3 and 8, independently of the group ($p<0.05$) (Tables III, Suppl.Table S1).

No differences in HAQ, physician's VAS, other SF-36 domains (functional capacity, general health, vitality, social functioning), and other laboratory tests (lactate dehydrogenase, alanine transaminase, and aspartate transaminase) were found (Table III, Suppl. Table S2).

Moreover, despite the statistically significant differences detected between the different times inside the groups or in both groups, no difference was detected when the AcG and ShG were compared (Suppl. Tables S1-2).

Blinding. A total of five patients (50%) of the AcG and four patients (50%) of the ShG believed that they had been actively stimulated, demonstrating adequate blinding between the groups ($p>0.999$).

Adherence to the study. Two patients of the sham group withdrew after the three sham stimulation sessions due to personal problems, not presenting any complications associated with the sham stimulation. No patient from the active tDCS group abandoned the study (Fig. 1).

Discussion

This prospective, randomised, sham-controlled, double-blind study is the first to investigate the safety and efficacy of tDCS in patients with SAMs. Despite the small number of participants, this study is one of the largest with such characteristics in this group of diseases due to its rarity. In addition, the patients were selected using rigorous exclusion criteria, and the study had similar baseline groups with a very satisfactory double-blinding.

Regarding patients' quality of life, the tDCS showed to be effective in improving the motor domain of patients with SAMs. tDCS has already been shown to improve SF-36 aspects including physical, emotional, and functional domains in patients with fibromyalgia (36). The trial with fibromyalgia patients also used the anodal stimulation in the left M1 and cathode on the right supraorbital region, reinforcing the potential efficacy to improve quality of life with this electrode position. Moreover, one trial involving patients with Parkinson's disease demonstrated improvement in mental and physical component SF-36 scores after anodal tDCS stimulation in the bilateral prefrontal and motor areas (37). Another study indicating a good relationship between anodal motor tDCS and SF-36 was a trial involving patients with diabetic polyneuropathy (38). In the study with diabetic polyneuropathy patients, they did not show improvement specifically in the SF-36 physical domain, but in other motor outcomes (38). By actively stimulating the motor cortex of our patients, we expected to find an improvement in the physical domain of SF-36, and it is an extremely important finding since it is the most important aspect of the SF36, possibly reflecting the improvement of motor function and strength of patients with SAMs.

The improvement in best and average TSST, besides absolute and adjusted-by-weight peak torque of lower limb extension in the StG, was expected by the stimulation of the M1 with tDCS. Since the start of tDCS research, several studies have demonstrated its role in improving sports performance, when

Table IV. Comparison of extension and flexion isokinetic tests between groups.

Variable	ShG		AcG		p_{Group}	p_{Moment}	p_{Side}	$p_{Group*Moment}$	$p_{Grouo*Side}$	$p_{Moment*Side}$	$p_{Group*Moment*Side}$
	Dominant side	Non-dominant side	Dominant side	Non-dominant side							
PT (n-m) UL extension					0.931	**0.045**	0.767	0.792	0.835	0.130	0.904
Pre tDCs	26.1 ± 8.1	27.3 ± 10.4	26.1 ± 8.8	27 ± 7.5							
Post tDCs	29 ± 10.3	27.3 ± 7.9	27.3 ± 8.4	27.1 ± 8.7							
Week 3	29.4 ± 8.7	30.9 ± 8.5	30.5 ± 8.1	32.2 ± 6.9							
Week 8	30 ± 10.2	29.1 ± 9.5	31.3 ± 8.3	29.9 ± 9.2							
PT (n-m) LL extension					0.589	0.469	0.353	0.484	**<0.001**	0.459	0.278
Pre tDCs	114.4 ± 37.5	121.5 ± 41.6	132.9 ± 50.2	125.4 ± 52.9							
Post tDCs	116.4 ± 33.7	120.5 ± 35.6	128.9 ± 44	126.9 ± 41.4							
Week 3	119 ± 35.5	126.5 ± 37.4	134.2 ± 51.7	124.9 ± 48.1							
Week 8	113.1 ± 37.5	118.1 ± 39.4	137.5 ± 45.4	123.9 ± 41.1							
PT (P/C) % UL extension					0.361	**0.039**	0.911	0.630	0.866	0.152	0.950
Pre tDCs	32.5 ± 10.7	33.4 ± 11	36.3 ± 12.4	36.9 ± 9.2							
Post tDCs	36 ± 13.3	34.3 ± 11.3	37.8 ± 11.5	37.4 ± 11.4							
Week 3	36.4 ± 11.7	38.4 ± 10.6	42.4 ± 12.9	44.9 ± 11.9							
Week 8	37.5 ± 14	36.2 ± 12.9	43.8 ± 13.1	41.7 ± 13.9							
PT (P/C) % LL extension					0.260	0.315	0.337	0.458	**<0.001**	0.362	0.171
Pre tDCs	141.8 ± 41.2	151.2 ± 51.5	183.6 ± 69.9	173.9 ± 75							
Post tDCs	144.9 ± 40.4	150.5 ± 45.4	178.4 ± 62,9	175.8 ± 60.6							
Week 3	148.8 ± 46.5	159.2 ± 54.1	186.3 ± 74	173.5 ± 70.2							
Week 8	140.8 ± 47.6	148 ± 55.1	190.2 ± 65.3	171.4 ± 60.2							
Total Work (J) UL extension					0.809	**0.029**	0.677	0.767	0.237	0.067	0.596
Pre tDCs	158.9 ± 50.6	163.8 ± 69	152.7 ± 60.4	155.8 ± 50.5							
Post tDCs	177.5 ± 65.7	160.8 ± 49.7	155.6 ± 56.6	158.3 ± 58.4							
Week 3	179.1 ± 52.6	185.8 ± 58.9	176.7 ± 56.4	187.3 ± 53.8							
Week 8	187,4 ± 65,6	175.3 ± 59.9	181.2 ± 60.1	173.1 ± 59.8							
Total Work (J) LL extension					0.613	0.463	**0.007**	0.486	**<0.001**	0.586	0.459
Pre tDCs	457.9 ± 164.1	505.6 ± 189.4	530.6 ± 202.7	523.1 ± 195.6							
Post tDCs	469.6 ± 143	505.5 ± 160.6	514.9 ± 166.5	529.8 ± 173.5							
Week 3	484.8 ± 166.7	539.9 ± 175.6	534.5 ± 189.2	524.9 ± 180.5							
Week 8	451.8 ± 173.8	493.4 ± 194.6	553.3 ± 165.9	514.8 ± 166.1							
PT (n-m) UL flexion					0.569	0.340	**<0.001**	0.587	0.202	0.361	0.568
Pre tDCs	33.5 ± 12.8	31.8 ± 15.2	27.9 ± 8.7	27.9 ± 8.4							
Post tDCs	34.2 ± 12.6	30.6 ± 13.4	30.4 ± 10.9	29.6 ± 8.1							
Week 3	32.5 ± 14.4	30.2 ± 13.5	29.9 ± 11.8	26.8 ± 9.4							
Week 8	33.2 ± 13.8	29.6 ± 13.2	31.2 ± 11.3	28.6 ± 10.1							
PT (n-m) LL flexion					0.676	0.518	**0.042**	0.540	0.486	0.734	0.729
Pre tDCs	66 ± 24.7	67 ± 24.4	63.7 ± 21.8	58.6 ± 26.6							
Post tDCs	63.4 ± 21.2	64 ± 24.5	64.4 ± 22.6	63.6 ± 26.9							
Week 3	72.6 ± 27.3	68.6 ± 24.2	67.1 ± 26	64.1 ± 25.8							
Week 8	73.9 ± 21	70.4 ± 26.7	66.3 ± 24.4	62.9 ± 24.4							
PT (P/C) % UL flexion					0.864	0.477	**<0.001**	0.668	0.581	0.647	0.615
Pre tDCs	41 ± 13.1	38.8 ± 16.9	38.8 ± 13.2	38.2 ± 10.8							
Post tDCs	41.7 ± 10.8	37.5 ± 14.7	42 ± 14.9	41 ± 11.8							
Week 3	39.5 ± 14.8	37 ± 14.9	41.5 ± 16.9	36.9 ± 12.8							
Week 8	40.3 ± 12.8	36.4 ± 15.5	42.8 ± 15.4	39.2 ± 13.8							
PT (P/C) % LL flexion					0.810	0.482	0.089	0.443	0.240	0.738	0.633
Pre tDCs	81.1 ± 25.1	84 ± 33.9	89.3 ± 34.6	82.2 ± 40.7							
Post tDCs	78,4 ± 24	79.8 ± 32.7	90 ± 35	89 ± 41.7							
Week 3	90.7 ± 36.2	86.9 ± 36.3	92.8 ± 36.5	89.1 ± 38.8							
Week 8	92.4 ± 27.7	88.9 ± 38.6	92.1 ± 36.8	87.4 ± 37.4							
Total Work (J) UL flexion					0.594	0.174	**<0.001**	0.323	0.250	0.369	0.493
Pre tDCs	199.1 ± 85.1	190.1 ± 93.1	166.9 ± 61.1	157.2 ± 59.4							
Post tDCs	203.2 ± 77.2	178.7 ± 76.6	180 ± 78.1	171.8 ± 59.5							
Week 3	188.5 ± 82.9	177 ± 91	170.6 ± 79.5	155.4 ± 73.7							
Week 8	196.2 ± 90	167.5 ± 78.6	183.6 ± 82.1	167.1 ± 71.8							
Total Work (J) LL flexion					0.625	0.559	0.303	0.683	0.748	0.844	0.505
Pre tDCs	282.5 ± 111.5	297.3 ± 126.3	270.9 ± 93.9	261.4 ± 117.6							
Post tDCs	280.3 ± 90.3	281.7 ± 123.7	282.5 ± 103.1	267.6 ± 114.8							
Week 3	324.2 ± 128.7	302.4 ± 122	282.4 ± 123.4	280.2 ± 117.2							
Week 8	320.4 ± 86.8	310.7 ± 123.3	284.9 ± 113.3	282.5 ± 107.7							

Data are expressed as mean ± standard deviation.
ShG: sham group; AcG: active stimulation group; tDCS: transcranial direct current stimulation; *p*Group: *p* from the comparison of mean values between groups, without taking into consideration different evaluation moments; *p*Moment: *p* from the comparison of mean values between different evaluation moments, without taking into consideration differences between groups; *P*Side: *p* from the comparison between sides, without taking account groups or moments; *p*Group*Moment: *p* from the comparison of mean values between groups, taking into consideration changes in different evaluation moments; *p*Side*Group: *p* from the comparasion between sides, taking into consideration differences between groups; *p*Side*Moment: *p* from the comparison between sides, taking into consideration different moments; *p*Group*Moment*Side: *p* from the comparison between sides, taking into account different moments and PT: peak torque; PT (P/C): peak torque/body weight ratio.

stimulating this region with anodal tDCS (39, 40). In patients with motor deficit, tDCS was studied to recover motor function after stroke demonstrating successful motor recovery, especially in the chronic stage (34, 41). Trials in patients with post-stroke used not only atDCS over ipsilateral M1 like our trial, but also, ctDCS over contralateral M1 and bilateral stimulation. Moreover, some of these studies used a combination of tDCS and additional interventions, such as virtual reality training, occupational therapy, and robot-assisted training (42), proposals that can also be used in future studies in patients with SAMs. Another neurological disease with a motor deficit that showed positive results with anodal tDCS over the M1 representation of the more affected leg is multiple sclerosis (43). Interestingly, our study is the first trial to show the potential efficacy of using tDCS in patients with myopathy, autoimmune or not. Furthermore, by showing that the AcG group improves muscle function and strength by different methods (isokinetic test and TSST), we highlight the potential role of the method in improving muscle function and strength in SAMs patients.

The mechanisms by which tDCS may improve motor function and muscle strength are not fully understood. However, some insights have been recently reveled. Motor function and muscle strength degradation may be attributed to central mechanisms such as decreased connectivity, neuronal hypoexcitability and dopaminergic dysfunction (44, 45). As central dysfunction is present, non-invasive brain stimulation is a feasible alternative, and previous results has shown that the stimulation of the M1, a frequent target of brain stimulation, may increase muscle performance through increasing interhemispheric synchrony (46), and cortico-spinal excitability and intracortical mechanisms (47).

In our study we could not see any effects of tDCS on emotional domains of SF-36. These results must have to do with the site of stimulation, as the target of preference to improve cognitive and emotional aspects are at the prefrontal, and not motor cortex. This has been shown in several studies addressing the treatment of psychiatric disorders, especially depression (35). In these trials, the anode electrode is classically positioned at the left dorsolateral prefrontal cortex, and the cathode electrode at the right dorsolateral prefrontal cortex. The divergence in the electrodes position could explain the lack of improvement in the emotional domain of SF-36, but not its worsening, because this finding has not been demonstrated in other studies involving tDCS for motor rehabilitation.

The safety of tDCS in rheumatic autoimmune diseases has been poorly studied. There is one report in a patient with dermatomyositis of our research group (48), in addition to a trial involving patients with Sjögren's syndrome (19). Regarding the treatment of non-autoimmune diseases, including rheumatic diseases, a larger number of works have demonstrated the safety of this technique (18, 49). Our findings of the safety of tDCS in this population strengthen the results found previously.

This study has some limitations. The most prominent limitation is the small number of participants in each group, despite the rarity of this group of diseases presenting a challenge to recruiting a larger number of participants. Another limitation is the fact that due to the single-center nature of this study, the external validity of the results is limited and will require confirmation in other studies. Furthermore, the relatively small number of tDCS sessions could have limited the impact on improving motor results. Efforts should be made to tackle these limitations in the future, possibly through multicenter collaborative studies.

This trial demonstrated the safety and efficacy of this method in patients with SAMs, innovating by adding a new method that can potentially assist in the rehabilitation of patients with SAMs in clinical practice. New studies with more sessions of tDCS alone or associated with physical activity can improve our findings.

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