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RESEARCH ARTICLE

Transcranial direct current stimulation improves quality of life and physical fitness in diabetic polyneuropathy: a pilot double blind randomized controlled trial

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Abstract

Purpose Diabetes Mellitus (DM) is a chronic disease which presents a big prevalence in the world and several patients with this condition fail to respond to the available treatments. There is a huge unmet clinical need for the development of new therapeutic approaches for this condition. This study aims to evaluate the effects of anodal tDCS on Quality of Life and physical fitness in patients with diabetic polyneuropathy.

Methods A pilot, parallel, sham, randomized, double-blind trial was conducted with twenty patients. Five consecutive sessions of C3/Fp2 tDCS montage were performed. To assess the primary outcome Short Form 36 Health Survey (SF-36) was used. Physical fitness level, according to lower and upper body strength, flexibility, Time Up and Go Test (TUG) and Six-Minute Walking Test (6MWT) were measured as secondary outcomes. The measures were performed at 3 different times (baseline, 1st and 2nd weeks).

Results SF-36 increased throughout the protocol, but no difference between groups were found. However, there was a significant difference between groups at 1st and 2nd weeks, which shows a permanent growth in the active-tDCS group. Physical health and functioning, functional capacity and bodily pain showed significant improvements in active-tDCS group in 1st and 2nd weeks during inter-group analysis. Emotional scores showed significant interaction group-time with interaction effects only for active-group in 1st and 2nd weeks. TUG and 6MWT showed significant improvements only in active-tDCS group.

Conclusions It is suggested that five sessions of anodal M1 tDCS improves QoL and functionality of patients with diabetic polyneuropathy.

Keywords transcranial direct current stimulation · diabetes · diabetic neuropathies · quality of life

Introduction

Diabetes Mellitus (DM) is a chronic metabolic disease which has caused injury in peripheral nerves, muscles and brain [1]. According to the current estimates by the International Diabetes Federation, Brazil, ranking the country as having the fourth largest number of diabetes cases worldwide presenting 11.9 million individuals between 20 and 79 years [2].

DM can also generate neuropathies, which is defined as the presence of symptoms and/or signs of peripheral nerve dysfunction after exclusion of other causes [1]. Peripheral nerve dysfunctions are among the most common long-term complications of diabetes, affecting up to 50% of patients and are characterized by a progressive demyelination, autonomic disorder and sensorial abnormalities [1].

It is important to mention that distal symmetric polyneuropathy occurs in up to 50% of diabetic patients and is the most common form [3]. The presence of distal polyneuropathy is common in diabetes type 1 and type 2 and physical symptoms could increase with the duration of diabetes, chronic hyperglycemia and aging [1]. The severity of nerve fiber abnormalities and chronic pain condition are associated with poor Quality of Life (QoL), functioning and productivity [3, 4].

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Considering the treatments, pharmacological through insulin [5] and non-pharmacological therapies by physical exercises and diet [6] have been proposed to control glycemic levels. Another intervention that has been undertaken to treat many chronic metabolic issues including obesity and eating disorders [7], is Transcranial Direct Current Stimulation (tDCS). This is a safe non-invasive brain stimulation technique that uses a constant electrical current over the scalp to modulate spontaneous neuronal firing in the human brain [8, 9].

DM may affect the central nervous system functioning, including cognitive, [10] motor function, [11] and pain perception [12]. The use of neuromodulation on central nervous system-related to individuals with vascular disorders has led to changes in neurogenesis, angiogenesis, neural protection, and plasticity, [13, 14] to provide functional recovery, enhancements muscle performance and pain improvement [13]. It has been suggested that tDCS can be used in functional rehabilitation programs as an adjuvant therapy [9, 14].

Though tDCS is frequently being used and searched for the treatment of chronic pain, [15, 16] there is only one trial that analyzed data about pain symptomatology from diabetic polyneuropathy [17]. Besides, so far, no evidence of improvements in QoL and physical fitness were demonstrated by using tDCS over patients who were affected by diabetic polyneuropathy. Interventions with rehabilitation programs focused on central nervous system could be a good strategy for the management of symptoms of diabetic polyneuropathy and its influence on QoL. Several patients with this condition fail to respond to the available treatments and there is a huge unmet clinical need for the development of new therapeutic approaches for this condition.

Current researches have shown that tDCS may improve QoL and functionality of individuals with vascular issues [18] and all these evidences suggest that tDCS might be a beneficial therapeutic tool to improve these outcomes from diabetic polyneuropathy patients. Considering these assumptions, this pilot study aims to analyze the effects of anodal tDCS over motor cortex on QoL and physical fitness in patients with diabetic polyneuropathy.

Methods

Study design and participants

It was conducted a pilot, parallel, sham, randomized, double-blind trial following the CONSORT's recommendations [19]. This study was approved by the local institutional ethics committee (Federal University of Rio Grande do Norte) with number: 1.530.846. It is registered on *Registro Brasileiro de Ensaios Clínicos* (ReBEC) (ID U1111-1190-3331). All study participants were notified that they could be randomized into any of the study groups. Besides, it was provided a written informed consent according to resolution No. 466/12 of the National Health Council and The Declaration of Helsinki.

From June 2017 to February 2018 participants were recruited from a specialized outpatient service located in Northeast of Brazil. All of them were regarded as suitable to participate in this study, if they fulfilled the following criteria (1) clinical diagnoses of chronic symmetrical length-dependent sensorimotor polyneuropathy [20, 21]; (2) aged from 18 to 60 years; (3) not lactating; (4) no history of brain surgery, tumor, intracranial metal implantation or epileptic disease; (5) no tDCS experience. Exclusion criteria were (1) pregnancy; (2) signs of severity and/or indications for hospitalization; (3) dizziness; (4) amputation.

Intervention

It was used a continuous electric stimulator with three energy batteries (9 V) connected in parallel controlled by a professional digital multimeter with a standard error of ± 1.5% (DT832, WeiHua Electronic® Co., Ltd, China) [22, 23]. Patients remained at rest in an armchair and sessions took place in a quiet and illuminated room. Electrodes were placed into a 35 cm^2 (5 cm × 7 cm) square sponge soaked in saline solution (150 mMols of NaCl diluted in water Milli-Q) and rubber bandages were used to hold electrodes during stimulation. The 10/20 EEG system was used for electrode montage with the anode electrode placed over C3 for stimulation of the Motor Cortex (M1), and the cathode electrode placed over the contralateral supraorbital area (Fp2). It was performed 20-minute session with 2 mA of intensity for 5 consecutive days. For sham-tDCS, electrodes were placed at the same positions as for active-tDCS, but the current was turned off after 30 s of stimulation, according to methods of clinical studies using tDCS [9, 24]. Previous studies confirm that this method provides the same initial sensory feelings of active-tDCS conditions, including itching and tingling feelings on the scalp for the first few seconds of therapy [9, 24].

Outcomes

The measures of the outcomes were collected one week before the first simulation (baseline), one week after the last stimulation (1st week), and 2 weeks after the last stimulation (2nd week).

Demographic and clinical data, including age, Body Mass Index (BMI), QoL, associated diseases, prevalence/classification of peripheral arterial obstructive disease, gender, elitism, Blood Pressure (BP), tabagism (prevalence) and physical activity levels of all participants were recorded. Primary outcome measure was QoL (Short Form 36 Health Survey (SF-36)) and secondary outcome measure was physical fitness level.

Peripheral arterial disease was determined through Ankle Brachial Index (ABI). A trained clinical staff measured BP and ABI using an 8 MHz CW Vascular Doppler (MEDPEJ® DV-2001) and a sphygmomanometer (Premium®, SP, Brazil). Measurements were taken from patients lying in a supine position after 5 min of rest. ABI was calculated as the ratio of systolic BP obtained from the ankle (posterior tibial artery and dorsalis pedis artery) and brachial arteries. Ankle and brachial systolic BPs were measured separately for the right and left sides, and ABI was assessed separately for the right and left legs, using the highest arm pressure as denominator [25]. In addition, Fontaine classification was used to classify the level of impairment/symptomatology generated by peripheral arterial disease into for stages ranging from 1 to 4 [26].

QoL was assessed by the SF-36, according to eight general health concepts: Physical Functioning (PF), Role Physical (RP), Bodily Pain (BP), General Health (GH), Vitality (VT), Social Functioning (SF), Role Emotional (RE) and Mental Health (MH). Physical Composite Score (PCS), Mental Composite Score (MCS) as well as the total SF-36 score were used to summarize the questionnaire. SF-36 range from 0 to 100, higher scores reflect better QoL and it can be used to assess QoL, pain and mental status of the subjects [27, 28].

The presence of neuropathic pain was classified, if the person reached a score of at least 4 out of 10, while non-neuropathic pain, if the individual presented scores of less than 4 out of 10 according to The Douleur Neuropathique 4 Questionnaire (DN4) [29]. DN4 derived from a list of signs and symptoms associated with neuropathic pain and includes 4 groups of questions consisting of 7 sensory descriptors and 3 signs related to a sensorial exam. In this study it was considered a dependent variable.

Physical activity level was assessed using the self-administered International Physical Activity Questionnaire Short form (IPAQ-S), which includes questions about the amount of time spent engaging in vigorous physical activities, moderate physical activities and walking [30]. The participants were classified in three categories: (a) moderate activity: 05 or more days per week of any combination between walking, and moderate or vigorous-intensity activity, accumulating at least 600 METs*minutes*week^{-1}; (b) high activity: 07 or more days of any combination between these activities, accumulating at least 3000 METs*minutes*week^{-1} and (c) insufficient activity: participants not classified in any of the above categories [30].

The 30-second chair stand test was used to evaluate strength of the lower limbs. It was used a chair with 43 cm high, with backrest, without armrest and a stopwatch. Participants were instructed to keep their arms folded across their chest [31]. When the signal was given, the participant stood up completely and returned to the starting position as fast as possible in 30 s. The score corresponds to the number of times that the person was able to perform the full stands in 30 s [31]. In addition, the 30-second arm curl test was used to measure upper-body muscle function and was assessed by the number of arm curl repetitions performed with a 2-kg dumbbell during 30 s [32].

Sit and reach test was performed to assess the flexibility of the lower limbs (posterior thigh muscles). It was used a chair with 43 cm high and 50 cm of backrest. During the test, the participants were instructed to sit on the edge of the chair with flat feet on the floor, knees and ankles at 90^0 flexion, then the dominant or painful leg was stretched (hip and knee) with the calcaneus supported on the floor and with the ankle flexed at 90^0 [33]. With overlapping hands and middle fingers on the same level, the participants tried to get as close as possible to their toes and hold the position for 2 s in 3 attempts to get the arithmetic mean [33]. A negative score was recorded if the middle fingers did not reach the toes, and a positive score was recorded, if the middle fingers were over the toes [33].

Flexibility of the upper limbs was performed using the back-scratch test. The participants were instructed to pass one hand (dominant) reaching over the shoulder (ipsilateral) to assess flexibility of the shoulder in flexion, abduction and external rotation and try to reach the other hand to assess extension, adduction and internal rotation on the center of the back [32]. The measurements were made using a ruler, and the scores were considered negative, if there was any distance between the middle fingers, and positive if the middle fingers overlapped [32]. Three replicates were made to obtain the arithmetic mean of the results.

Timed Up and Go (TUG) test was used to assess agility, speed, strength and dynamic balance [34]. Subjects were instructed to stand up from the sitting position on the examiner's signal, walk a distance of 3 m, turn around, walk back to the chair and sit down again [34].

A 2-min step test was included in the test battery as an alternative aerobic endurance test. This test involves determining the number of times, during 2 min, which an individual can step in place, raising the knees to a height halfway between the iliac crest (hip bone) and the middle of the patella [35].

Six-Minute Walk Test (6MWT) was used to assess the submaximal level of functional capacity. 6MWT reflects activities of daily life and functional level of daily physical activities. The test measures the maximum distance that the subjects can walk as fast as possible during 6 min according to the standard protocol [36].

Randomization and allocation concealment

Randomization (1:1) was performed with 20 individuals through a numerical sequence generated by an allocated computer using appropriate software (www.randomization.com) to assign each participant to either the active-tDCS group or sham-tDCS group by an independent researcher who was not involved with either stimulation or assessments. Both participants and researchers involved in assessments and

interventions were blind to group allocation throughout the trial. Patients were considered dropouts in case of absence of 1 day of treatment or failed to provide all baseline or post-intervention data.

Data analyses

Analyses were performed using Graph Pad Prism 5 and SPSS version 20 (IBM, Armonk, NY). Quantitative variables were expressed as means and Standard Deviations (SD). To determine the normality of the data, the Shapiro-Wilk test was performed. An unpaired t-test or Mann-Whitney test were used to compare only numerical characteristics between groups. Differences in sociodemographic characteristics between groups were calculated using Chi-square test. Generalized Estimating Equations (GEE) model was used for the analysis in which the dependent variable was the SF-36 scores, and independent fixed variables were days of evaluation (baseline, 1st week, and 2nd week), the stimulation group (Active-tDCS; Sham-tDCS), the pre and post-intervention, and the interaction. GEE analysis uses an unstructured working correlation matrix and a link function for Poisson regression to estimate between and within group correlations. The Wald x^2 test was performed for available independent variable significance in the model and the Bonferroni contrast test was used to compare subgroups in independent variables. Cohen's d (d) effect size was calculated to identify the clinical practice impact on subgroup analyses when there was statistical significance. To determine the difference between groups in physical tests it was performed GEE model and repeated measures ANOVA. When appropriate, post-hoc comparisons were carried out using Bonferroni correction for multiple comparisons. Statistical significance was set at $p \leq 0.05$.

Results

Twenty-eight patients diagnosed with diabetic polyneuropathy were initially screened in this pilot trial. Eight patients were excluded because they did not meet the criteria (n = 06) or rejected participation (n = 02). Twenty patients with diabetic polyneuropathy composed the study sample and all completed the trial (Fig. 1). There were no significant baseline differences in demographics and baseline clinical characteristics between groups (Table 1). All patients tolerated tDCS well and there were minor related adverse events such as itching and tingling. All patients in both groups have a positive diagnoses neuropathic pain according to DN4 Questionnaire.

QoL was assessed using SF-36 at tree intervals (baseline, 1st week and 2nd weeks after tDCS last session). SF-36 total score showed no difference between groups ($x^2 = 1.89$; $p = 0.169$). However, it was observed that the total score increased throughout the protocol ($x^2 = 48.79$; $p < 0.001$), with a significant difference between baseline with 1st week ($p < 0.001$) and 2nd week ($p < 0.001$) (Fig. 2). The interaction group-time showed that sham-tDCS group elevates the total score to each measurement as well as the active-tDCS group. However, it was a significant difference between groups at 1st week ($p = 0.03$; d = 1.7) and 2nd week ($p = 0.03$; d = 3.1), which shows a permanent growth in the active-tDCS group (Fig. 2).

All eight general health concepts of SF36 were evaluated and presented in Fig. 3. Total mental health showed an interaction between group-time ($x^2 = 21.63$; $p = 0.001$). There was no difference between groups at baseline ($p = 0.48$). There was an increase in total mental health in both groups with a significant difference between baseline and 1st week for active-group ($p = 0.01$; d = 1.3) and baseline and 2nd week for sham-group ($p = 0.008$; d = 1.4). No differences were found between groups in 1st week ($p = 0.27$) and 2nd week ($p = 0.41$). Total physical health showed a significant interaction group-time ($x^2 = 59.66$; $p < 0.001$). No differences between groups was found at baseline ($p = 0.28$). Both groups showed increase in total physical health ($p = 0.001$), besides in intergroup analysis active-group presented significant difference in 2nd week ($p = 0.008$; d = 5.4). Emotional scores showed significant interaction group-time ($x^2 = 22.99$; $p < 0.001$) with interaction effects only for active-group in 1st week ($p = 0.004$; d = 2.7) and 2nd week ($p = 0.001$; d = 3.2). Social aspects did not show interaction group-time ($x^2 = 1.50$; $p = 0.91$), or group ($x^2 = 0.46$; $p = 0.49$) and time ($x^2 = 0.42$; $p = 0.80$). Also, vitality did not show interaction group-time $x^2 = 5.67$; $p = 0.34$), or group ($x^2 = 0.17$; $p = 0.67$) and time ($x^2 = 4.61$; $p = 0.10$). General health showed significant interaction group-time ($x^2 = 24.57$; $p < 0.001$) and groups differ from baseline ($p = 0.03$). Sham-group showed significant increase in 1st week ($p < 00{,}001$; d = 1.8). Bodily pain showed significant improvements in 1st week (Sham-group: $p = 0.007$; Active-group: $p < 0.001$), however in 2nd week only Active-group have significant increase ($p = 0.001$; d = 4.1). Post hoc indicated significant difference between groups in 2nd week ($p < 0.05$). Physical functioning and functional capacity showed significant interaction group-time ($x^2 = 27.54$; $p < 0.001$ and $x^2 = 73.77$; $p < 0.001$, respectively). Both groups significantly improved physical function and functional capacity, although in 2nd week, active-group differ when compared to sham-group ($p = 0.03$; d = 4.3 and $p = 0.03$; d = 4, respectively). Mental health did not show interaction group-time ($x^2 = 3.22$, $p = 0.66$) or isolated effect of group ($x^2 = 0.41$, $p = 0.52$) and time ($x^2 = 0.12$, $p = 0.93$).

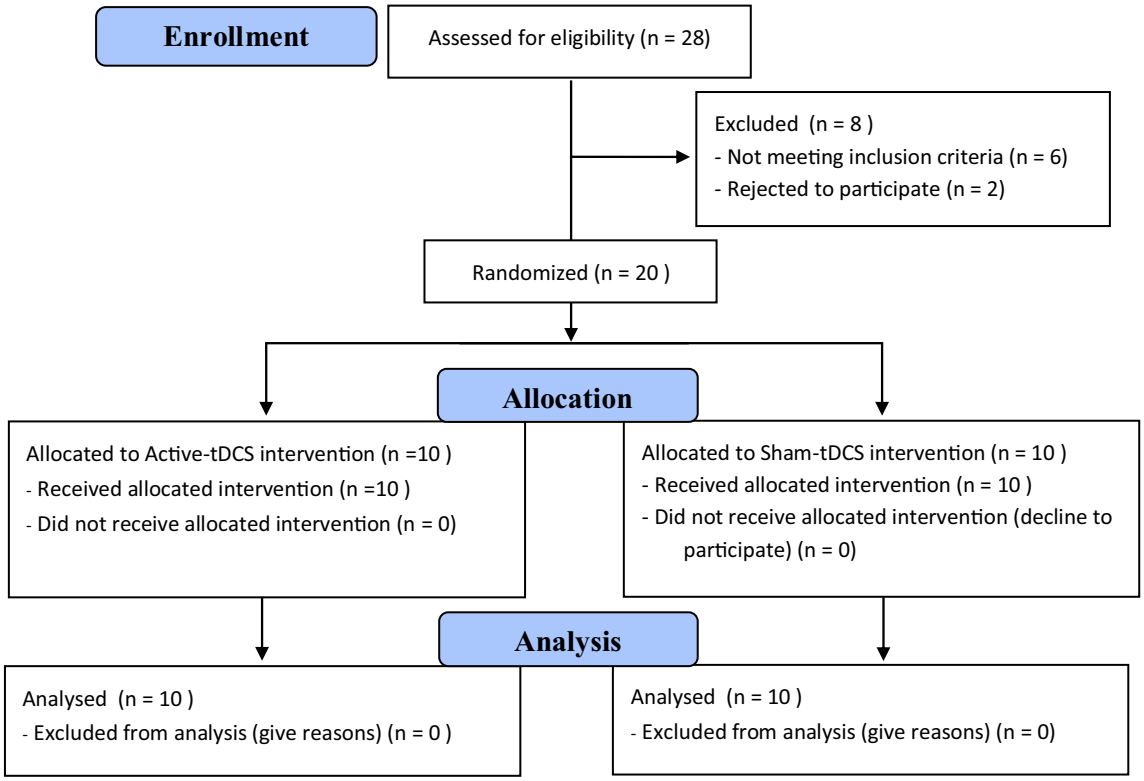


Fig. 1 Flowchart for the study

Table 1 Baseline clinical variables

Sociodemographic factors	Active-tDCS	Sham-tDCS	*p* value
Age	60.9 ± 15.26	60.7 ± 9.21	0.9721
BMI	28.39 ± 3.98	31.38 ± 4.55	0.1350
Pain - SF-36	30.6 ± 27.33	35.2 ± 21.42	0.6803
Physical score - SF-36	41.9 ± 16.34	33.6 ± 20.98	0.3367
Mental score - SF-36	50.5 ± 18.45	44.2 ± 24.13	0.5202
Right Ankle brachial index$^{\beta}$	0.86 ± 0.18	1.01 ± 0.14	0.1301
Left Ankle brachial index	0.97 ± 0.25	0.94 ± 0.23	0.7890
Gender (male) (%)	60%	50%	0.6531
Elitism (%)	20%	30%	0.6056
Hypertension (%)	70%	80%	0.6056
Tabagism (%)	20%	20%	1.000
IPAC-S (%)			0.5866
Insufficient activity	20%	40%	
Moderate activity	60%	40%	
High activity	20%	20%	
Fontaine (%)			0.1709
Stage I	30%	0%	
Stage II	50%	70%	
Stage III	20%	30%	

Clinical variables described with mean and standard deviation. $^{\beta}$ Mann-Whitney test. BMI: Body mass index. SF-36: 36-Item Short Form Health Survey. IPAC-S: International Physical Activity Questionnaire-Short Form

Chair stand, arm curl, sit and reach and back scratch tests did not show significant group-time or group or time interaction. The 2-min step and TUG showed significant group-time interaction ($x^2 = 11.45$; $p = 0.04$ and $x^2 = 20.25$; $p = 0.001$, respectively). TUG and 6MWT have shown significant improvement only in Active-tDCS group ($p = 0.0075$; $p = 0.0001$, respectively) according to repeated measures ANOVA (Table 2).

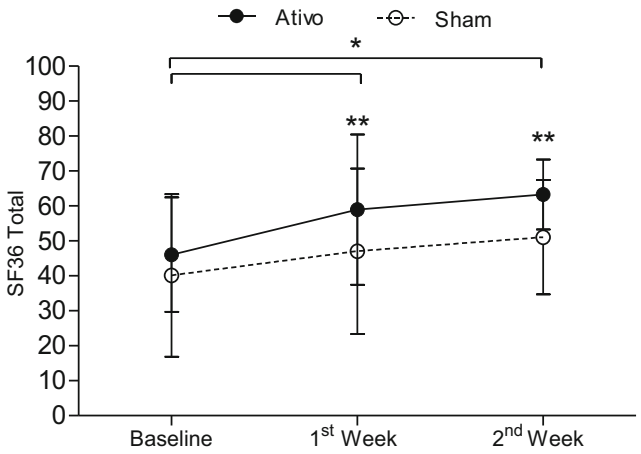
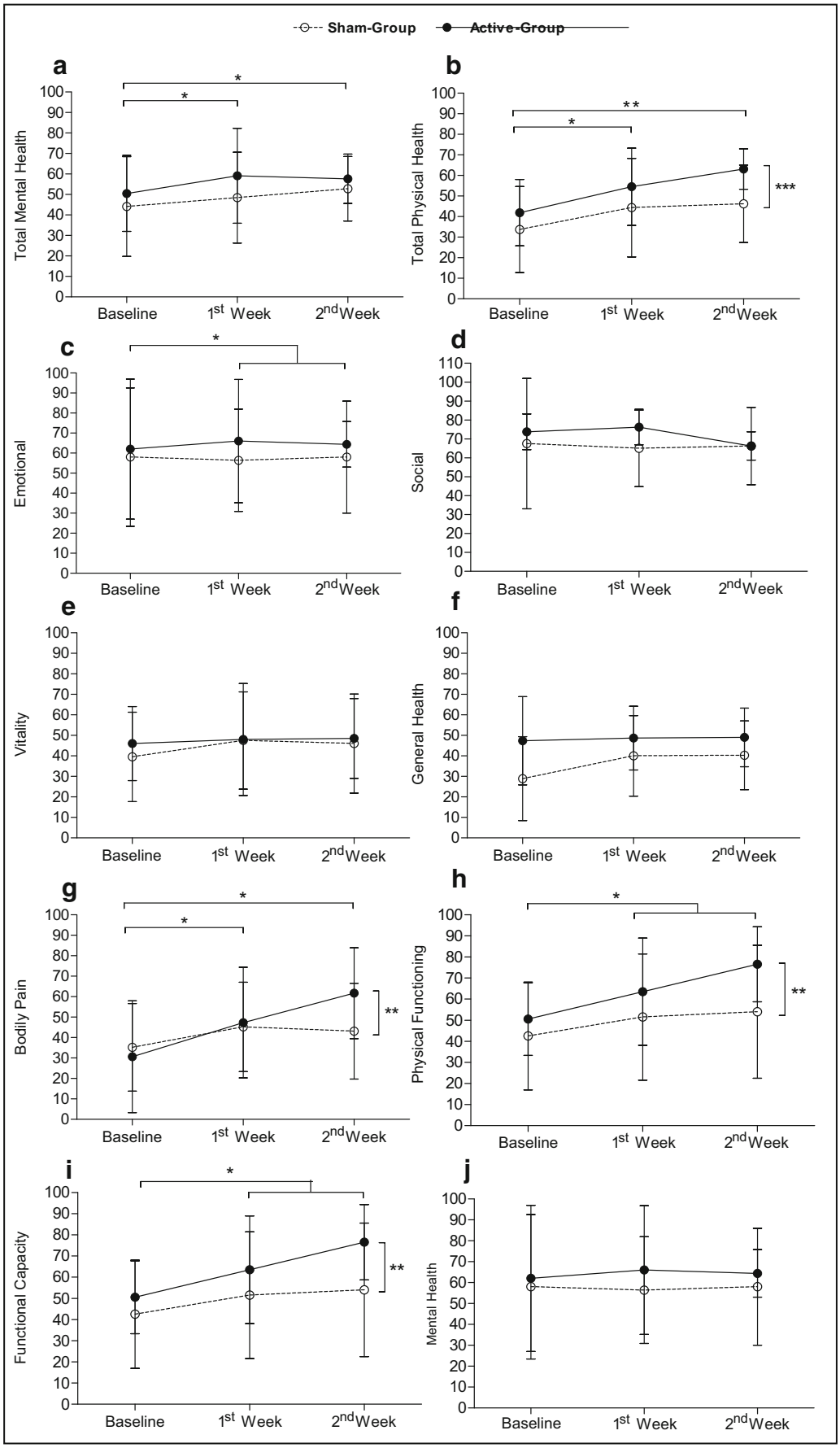


Fig. 2 Short Form 36 Health Survey (SF-36) total score. *Significant difference between baseline with 1st week ($p < 0.001$) and 2nd week ($p < 0.001$) for both groups. Comparing groups, there was a significant difference between groups in 1st week ($p = 0.03$) and 2nd week ($p = 0.03$)


Sham-Group
Active-Group
a
Total Mental Health
b
Total Physical Health
c
Emotional
d
Social
e
Vitality
f
General Health
g
Bodily Pain
h
Physical Functioning
i
Functional Capacity
j
Mental Health
Baseline
1st Week
2nd Week
*
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◀ **Fig. 3** Short Form 36 Health Survey (SF-36) general health concepts. (A) *Significant difference between baseline and 1st week for active-group ($p = 0.01$) and baseline and 2nd week for sham-group ($p = 0.008$). (B): Total Physical Health shown significant difference between baseline with 1st week ($p = 0.001$)* and 2nd week ($p = 0.001$)**. ***Significant difference between groups ($p = 0.008$). (C): *Interaction effects only for active-group in 1st week ($p = 0.004$) and 2nd week ($p = 0.001$). (G): Bodily pain shown significant improvement in 1st week (sham-group: $p = 0.007$; active-group: $p < 0.001$)*, but in 2nd week only active-group have significant increase ($p = 0.001$). Post hoc indicate significant difference between groups in 2nd week ($p = 0.05$)**. (H) Both groups significant increase scores in 1st week and 2nd week ($p < 0.05$)* and active-group showed significant increase in 2nd week when compared to sham-group ($p = 0.03$)**. (I) Both groups significant increase scores in 1st week and 2nd week ($p < 0.05$)* and active-group showed significant increase in 2nd week when compared with sham-group ($p = 0.03$)**

Discussion

Our results showed that 5 daily sessions of 2 mA, 20 min tDCS over left M1 induced significant improvements in QoL and physical fitness in patients with diabetic polyneuropathy. Active-tDCS group improved total score of SF-36, physical health, bodily pain, physical functioning and functional capacity.

The only previous trial with diabetic polyneuropathy subjects and tDCS used five daily sessions over M1 and showed pain relief for 4 weeks after intervention, but no significant differences were observed among the groups in sleep quality, anxiety and depression scores [17]. It is important to mention that the present trial is the first to focus on QoL and physical fitness. The outcomes measured in the present study are important because diabetic polyneuropathy accounts for considerable morbidity and reduced QoL, and the primary focus on management is restoring the maximum of functionality [37].

Although the functionality of patients with diabetic polyneuropathy has been slight explored in clinical trials, the progression of diabetic polyneuropathy decreases somatosensory inputs, reflecting in muscle performance decrease and functional losses [38]. Some authors suggest the use of therapies targeting painful symptomatology in diabetic neuropathy people, considering moderate to large improvements in pain a relief about 30–50%, respectively [39]. Our study showed that mean bodily pain score, using SF-36, improved from 30.6 to 61.7, suggesting a huge clinically significant result. Indeed, chronic pain also contributes to dysfunctional status and low performance in daily activities [38]. Several studies evaluated the use of tDCS in chronic pain syndromes including fibromyalgia, low back pain and chronic post-stroke pain [18]. Many of these studies suggest improvements in QoL, but evaluation using physical tests to measure functionality is uncommon.

Increasing evidence has identified thalamic abnormalities in patients with diabetic neuropathic pain, presenting hyperexcitability and central pain amplification [40]. The sensory and motor impairments generated by this chronic condition lead to lower physical functioning, postural control and balance [41]. Botelho et al. suggest that these changes affect the routine aspects of self-care, promote immobility, risk of falls and decrease QoL [41]. The authors recommend the use of tests with low-cost measurements to evaluate balance, postural control and mobility in ageing adults affected by diabetic polyneuropathy [41].

Regarding the treatment using tDCS, anodal stimulation may reinforce upregulation of M1 activity, inducing motor function improvements [42]. Neuromodulation is intended to increase excitability in the motor cortex and modulate deep brain regions involved in motor performance and pain control [42]. We found that diabetic neuropathic patients did not show difference in force production and flexibility of lower and upper limbs after tDCS, but we suggest that a therapeutic approach focused on preserving or restoring functionality associated to tDCS as a promising strategy. Cogiamanian et al. suggest that anodal M1 tDCS could improve endurance time, decreasing fatigue-related muscle pain, improving synergist muscle coupling and increasing motivation [43]. These benefits may influence daily activities, improve functionality and

Table 2 Secondary outcomes evaluated using Functional Fitness Test

Test	Active-tDCS				Sham-tDCS			
	Baseline	7º Day	14º Day	*p* value	Baseline	7º Day	14º Day	p value
Chair stand	13.1 ± 2.9	14.4 ± 3.1	14.4 ± 3.1	0.4898	12.1 ± 4.2	11.6 ± 4.5	13.3 ± 3.6	0.2939
2-min step	84.5 ± 37.4	109 ± 42.5	84.3 ± 35.7	0.2648	66.8 ± 29.8	70.2 ± 24.7	72 ± 24.7	0.5898
Arm curl	20.2 ± 4.8	21.1 ± 4.5	20.8 ± 10.5	0.9471	20.1 ± 6.3	22.5 ± 5.6	22.4 ± 7.1	0.0639
Sit and reach	7.5 ± 7.7	8.4 ± 8.9	10.9 ± 9.3	0.1171	13.8 ± 10.1	13.8 ± 10.1	13.4 ± 10.8	0.6013
Back scratch	14.1 ± 9.8	12.7 ± 8.7	11.9 ± 10.7	0.2477	15.6 ± 10.5	14.3 ± 9.2	17 ± 11.9	0.5563
TUG	7 ± 2.6	5.3 ± 0.9	4.8 ± 0.3	0.0075*	10.2 ± 7.3	9 ± 6.6	8.2 ± 4.9	0.6013
6MWT	460.9 ± 116.3	499.9 ± 151.3	517.1 ± 143.9	0.0001*	405.9 ± 131.6	431.8 ± 128.5	397.3 ± 178.2	0.6013

Chair Stand: 30-second chair stand test; number of repetitions. 2-min step; number of steps. Arm curl; number of arm curl repetitions. Sit and reach test and Back scratch; measured in centimeters. TUG: timed up and go test; measured in seconds. 6MWT: Six Minute Walk Test –walking distance in meters.
*Statistically significant according to repeated measures ANOVA

QoL. Our study used TUG and 6MWT to evaluate speed, agility, dynamic balance and submaximal level of functional capacity and showed significant improvements only in active-tDCS group. The increase of motor cortical excitability, including premotor areas could influence these results [43].

Emotional score showed significant interaction group-time, suggesting that inclusion of neuromodulation treatment can provide improvements in mood states. A possible explanation for this result is the enhancement in physical function and well-being. We also found no improvements in social, vitality, general and mental health concepts and it may reflect the limited number of session, and/or insufficient period for participants' evaluation to induce changes in normal routine. A different tDCS montage that focused on dorsolateral prefrontal cortex could modulate this region and provide better results in mood and social behavior [44, 45].

Although this trial followed the recommendations of previous studies with diabetic polyneuropathy and chronic pain syndromes, [17, 18] it is important to emphasize that this is a clinical trial phase II, [46, 47] which presents a small sample size and some methodological limitations, such as the precisely design of tDCS protocol, especially in terms of number of sessions, electrode montage, thus demanding careful interpretation of the results. Besides, since simple clinical tools were used for polyneuropathy clinical diagnosis, more complex analysis, such as nerve conduction analysis were not possible. However, the use of clinical tests to diagnose polyneuropathy and detect tDCS influence on QoL and physical fitness, as presented in this study, is relevant due to its large clinical applicability and its application as a predictor of functional decline.

Conclusions

Five sessions of anodal M1 tDCS induced improvements in physical health, bodily pain, physical functioning and functional capacity. Therefore, tDCS has shown to be efficient to ameliorate QoL and physical fitness in patients with diabetic polyneuropathy. It can be suggested that future intervention studies with tDCS and diabetic polyneuropathy should observe not only QoL and physical fitness, but also the social and emotional context of the participants and a protocol with 10 or more sessions of tDCS could be proposed.

Compliance with Ethical Standards

Conflict of Interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical approval This study was approved by the local institutional ethics committee (Federal University of Rio Grande do Norte) with number: 1.530.846. It is registered on *Registro Brasileiro de Ensaios Clínicos* (ReBEC) (ID U1111-1190-3331). All study participants were provided with written informed consent, notified that they could be randomized into any of the study groups, and their participation would be voluntary according to resolution No. 466/12 of the National Health Council and The Declaration of Helsinki.

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