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Transcranial direct current stimulation for chronic chikungunya arthralgia: study protocol for a randomized clinical trial

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Strengths and limitations of this study

Chikungunya is a neglected tropical disease with few studies regarding treatment and rehabilitation programs.

tDCS is a low cost, safe, and mobile intervention that may be implemented for chronic chikungunya arthralgia.

The trial will include participants with chronic pain without any previous treatment for a cost-effectiveness evaluation and quantitative data collection.

The trial will not include laboratorial, image or electrophysiological data regarding brain modulation or maintenance of pain state after tDCS protocol.

Abstract

Introduction: The chikungunya virus infection is still an epidemic in Brazil with an incidence of 59.4 cases per 100,000 in the Northeast region. More than 60% of the patients present relapsing and remitting chronic arthralgia with debilitating pain lasting for years. Persistent pain can lead to incapacitation, requiring long-term pharmacological treatment. Transcranial direct current stimulation (tDCS) appears promising as a novel neuromodulation approach for pain-related networks to alleviate pain in several pain syndromes.

Methods and analysis: We hypothesize that anodal tDCS (C3/Fp2 montage) will improve pain and functionality in patients with chronic chikungunya arthralgia. This protocol is a single-center, parallel-design, double-blind, randomized, sham-controlled trial. Forty participants will be randomized to either an active or sham tDCS. A total of 10 sessions will be administered over 2 weeks (one per weekday) using a monophasic continuous current with an intensity of 2 mA for 20 min. Participants will be evaluated at baseline, after the 10th session, 2 weeks, and 4 weeks after intervention. Primary outcome: pain assessed using numeric rating scale and algometry. Secondary outcomes: muscle strength, functionality, and quality of life. The effects of stimulation will be calculated using a mixed analysis of variance (ANOVA) model.

Ethics and dissemination: The study was approved by the ethics committee of the Faculty of Health Sciences of Trairí, Federal University of Rio Grande do Norte (No. 2.413.851) and registered on the Brazilian Registry of Clinical Trials (identifier RBR-469YD6). Study results will be disseminated through presentations at conferences and publications in peer-reviewed journals.

Keywords: brain stimulation, tDCS, arbovirus infections, arthritis.

Introduction

In the last 8 years, Brazil has been a protagonist in infection caused by chikungunya virus (CHIKV) in America[1]. The spread of the disease in South America is critical and out of control, mainly in Brazil that represents 94% of confirmed chikungunya cases[2,3]. Until 2021, the Brazilian Ministry of Health continues to monitor the occurrence of chikungunya, and from December 2019 to April 2020, 17,636 chikungunya cases were recorded[1]. The re-emergence of chikungunya has become an increasing medical and economic burden in affected areas[4]. The acute phase (<7 days) of the disease is usually characterized by sudden high fever, polyarthritis, tenderness, headache, myalgia, maculopapular rash and vomiting[5,6].

Chikungunya presents as a challenge for health care systems and rehabilitation professionals because most cases are commonly followed by persistent chronic arthralgia lasting for years[7]. Up to 50%–60% of chikungunya cases may progress to the chronic phase that begins when clinical symptoms persist for more than 3 months[8,9]. No specific therapeutic agents can be used to treat and rehabilitate individuals with chronic chikungunya and persistent pain may lead to incapacitation and require long-term pharmacological treatment[10]. Chronic pain is associated with development of adaptive neuroplasticity and functional reorganization that could result in physical and behavioral impairment[11]. Pain has a sensory-discriminative, affective-motivational, motor, and autonomic components, and some areas of the brain were involved in a large distributed neural network called the pain neuromatrix (PNM)[12]. The activation of the primary (S1) and secondary (S2) somatosensory cortices, primary motor cortex (M1), dorsolateral

prefrontal cortex (DLPFC), thalamus, insula, and anterior cingulate cortex are involved in pain processing[12]. The M1 is an important area to understand the pathophysiology and treatment of chronic pain conditions including rheumatic diseases[13].

The efficacy of transcranial direct current stimulation (tDCS) on pain and other clinical outcomes have been published with beneficial results[14–17]. Previous studies have supported the use of anodal tDCS over M1 (M1-SO montage) to reduce pain in osteoarthritis[18], post-stroke pain syndrome[17], back pain[18], fibromyalgia[13], and recently chikungunya[14,15]. In this context, tDCS promotes M1 activation, providing secondary modulatory effects on the PNM circuit that is associated with nociceptive modulation[19]. The first study on CHIKV and neuromodulation suggested pain improvement after five consecutive sessions of tDCS[15]. The second study evaluated six nonconsecutive sessions of anodal tDCS on M1 and showed significant reduction on pain[14]. These studies were the initial investigations of tDCS, but further work to optimize the stimulation parameters is needed to clarify long-term efficacy on pain and functionality in chronic chikungunya arthralgia[14,15].

Furthermore, tDCS could be a non-invasive, low-cost, safe, and accessible treatment option to CHIKV-endemic areas[15]. Herein, we present the methodology of a randomized double-blinded controlled study to evaluate the feasibility of a trial protocol for 10 consecutive sessions of tDCS in chronic chikungunya arthralgia. The primary objective of this protocol is to measure the effect of tDCS on pain. The secondary objective is to assess muscle strength, functionality, and quality of life. The duration and extent of effects of tDCS (long-term effect) will be also investigated. The study hypothesis is that the tDCS protocol will show improvement in pain, muscle strength, functionality, and quality of life when compared with sham tDCS.

Methods and design

Study design

This is a protocol study of a single-center, double-blind, parallel, sham-controlled, randomized clinical trial with two groups and a 1: 1 allocation ratio. A total of 10 sessions of 20 min will be administered over a period of 2 weeks. Outcomes will be measured at baseline (1 week before intervention), immediately after day 10 of intervention, and at 2 and 4 weeks after the end of the treatment as follow-up (Figure 1). The study follows the Template for Intervention Description and Replication checklist[20] and the 2013 Standard Protocol Items: Recommendations for International Trials statement (SPIRIT).

This trial is registered in the Brazilian Registry of Clinical Trials (ReBEC) under the identifier RBR-469YD6. All participants will be informed about the trial's objectives and procedures. Participation is voluntary as determined by Resolution No. 466/12 of the National Health Council. Potentially eligible patients with chronic of chikungunya will receive a detailed explanation of the study from the study research coordinator. Interested participants will be asked to sign the informed consent form before enrollment into the study. The informed consent form was submitted and approved by the ethics committee of the Faculty of Health Sciences of Trairí – Federal University of Rio Grande do Norte (UFRN) (No. 2.413.851).

Participants and Chikungunya diagnosis

Participants with previous serologic confirmation of CHIKV infection based on immunoglobulin (Ig) G and IgM detected by direct enzyme-linked immunosorbent assay/IgM/Euroimmun, according to the Central Laboratory (LACEN, Brazil) or on initial clinical symptoms (in the context of the epidemic) including at least fever and arthralgia who meet the eligibility criteria will be invited to participate in the study[21].

Trial design

All evaluations will start in August 2022. After the initial assessment, participants will be randomly allocated into two evaluator/participant blinded groups: active group and sham group. Randomization will be carried out through a numerical sequence generated by an allocated computer using appropriate software (www.random.org) to assign each participant to either the active or sham group. An external research assistant will generate the allocation sequence and contact participants by telephone. Allocation concealment will be performed using opaque envelopes. Participants and researchers involved in the assessments and interventions will be blinded to group allocation throughout the trial.

Participants of both groups will undergo a 2-week protocol (5 sessions per week) of active or sham tDCS. Sessions will be performed for 20 min by the same trained physical therapist. Two follow-ups will be performed after 2 and 4 weeks at the end of tDCS protocol by the same evaluator blinded for the allocation group. The schedule of enrollment, interventions, and assessments is demonstrated in figure 2.

All assessments and intervention procedures will be performed at the Physical Therapy Outpatient Clinic of Faculty of Healthy Science of Trairí, Federal University of Rio Grande do Norte, Santa Cruz, Brazil.

This study will involve four researchers: one researcher each is responsible for the evaluations, application of the tDCS, randomization of participants, and statistical analysis. Before starting the trial, a series of training steps for evaluations and application of the tDCS will be carried out, aimed at recording activities carried out in the study. Techniques and measures will be improved at this stage of the training to reach a consensus among the researchers.

Recruitment and eligibility criteria

Adults from local communities of the Northeast region of Brazil will be recruited voluntarily through advertisements in electronic media and by health professionals from the communities.

Eligibility criteria for participation in the study are: men and women aged ≥18 years with positive laboratory or clinical diagnosis of chronic chikungunya (at least 3 months from the initial infection); moderate to severe (above 4) pain according to a numeric rating scale (NRS); tolerate physical evaluation; satisfactory cognitive function to understand and sign the informed consent, study explanations and questionnaires. The exclusion criteria adopted are: individuals with electrical implants in the body, history of epilepsy, metallic device implanted in the head, history of drug abuse, pregnancy, signs of severity and/or indication of hospitalization, and history of rheumatic diseases including gout, rheumatoid arthritis, fibromyalgia, lupus, and other chronic pain syndromes diagnosed prior to chikungunya.

Blinding

In this clinical trial, participants and evaluators will be blinded. Moreover, to ensure that the participant is also blinded to the allocation group, electrodes will be

placed in the same position as in the active group, but the stimulator delivered 2 mA of current with the same ramp-up and ramp-down period of 30 s [15,22]. Sham tDCS will consist of delivering an active stimulation for a few seconds to mimic the sensations (itching and tingling) observed during active tDCS[23]. This is considered a valid methodology for clinical protocols with good effectiveness of blinding[14,15,23–25].

Intervention

The treatment will consist of 2 weeks of intervention divided into 10 sessions of 20 min each (one per weekday) using a monophasic continuous current with an intensity of 2 mA. The active and sham groups will be treated by a trained physical therapist at the Physical Therapy Outpatient Clinic of Federal University of Rio Grande do Norte. All patients will be awake and seated in a comfortable chair with back and arm support during tDCS and sham intervention. All tDCS procedures will be conducted in a temperature and noise-controlled room.

tDCS will be delivered using the anode electrode positioned over the left primary motor cortex (C3) and the cathode electrode at the contralateral supraorbital region (Fp2), according to international standards for EEG 10–20 system. The electrodes will be placed into a 35 cm^2 sponge immersed in saline solution (154 mM NaCl, approximately 12 mL per sponge). For stimulation, current ramp-up and ramp-down with 30-s duration will be employed. Electrodes attached to the scalp will be supported by an elastic band. The electrodes (anode and cathode) will be connected to a stimulator MicroEstim Genius (NKL, Santa Catarina, Brazil). Device displays are identical in the active and sham groups.

For ethical reasons, no intervention will be performed in clinical care, and painkillers or other medications will be prescribed as usual. If a participant will begin taking medications during the study period, this will be documented, but the participant will not be excluded from the analysis. To ensure the success of blinding, participants and outcome assessors at the end point will be asked to guess whether the treatment was active or false.

Outcomes

Primary outcomes

Participants will be assessed using a Visual Analog Scale (VAS) for pain, which is a one-dimensional measure of pain intensity in adults, including those with chronic pain due to rheumatic disease[26]. The VAS is a continuous scale comprised of a horizontal line, usually 10 centimeters (100 mm) in length, anchored by 2 verbal descriptors (0 representing “no pain” and 100 representing “pain as bad as you can imagine”)[26]. The VAS is self-completed by the respondent. The respondent is asked to place a line perpendicular to the VAS line at the point that represents their pain intensity[26].

Algometry will be carried out to record pressure pain threshold (PPTh) and pressure pain tolerance (PPTo). Pain PPTh and PPTo will be assessed in eight different anatomical locations: trapezius, at the midpoint of the upper edge; lumbar spine, performed over the erector muscle; lateral epicondyle; knee, over the fatty cushion; and between the index finger and thumb on the dorsal side of the hand. All points will be tested on the left and right sides of the body. Algometry will be performed perpendicular to the skin at 5–10 s intervals by the same qualified examiner. A pressure

algometer will be used (MedDor, Minas Gerais, Brazil) through a 1-cm diameter rubber tip. PPTh and PPTo will be quantified in kg/cm^2. The examiner will position the rubber tip above the area to be examined and gradually increased the pressure by 1 kg/cm^2/s [27]. The PPTh will be measured when the patient says, "I'm starting to feel pain." To measure PPTo, the patient will be asked to bear the maximum amount of pressure from the algometer and use the verbal affirmation "stop."

Secondary outcomes

The Brief Pain Inventory (BPI) is one of the most used instruments to assess chronic pain in clinical trials[28]. The BPI (short form) will be used to assess the severity and effect of pain in daily living activities. It is a questionnaire that presents 15 items, including two multi-item scales to measure pain and its effect on functionality and well-being; the questionnaire is validated for the Brazilian population[28]. In the room allocated for evaluation, participants will be asked by the researcher about each item, and questionnaire will be filled according to the answers of the participants. All questions can be repeated if the participant does not understand. The BPI will be applied in all phases of evaluation and by the same researcher.

In the absence of a specific functional questionnaire for acute and long-term evaluation of rheumatic manifestations of chikungunya, the health assessment questionnaire (HAQ) it will be used. HAQ is commonly used to assess rheumatoid arthritis and to evaluate patients with chikungunya[9,29]. This is a validated tool to measure disability due to persistent arthralgia[30]. Rising, dressing, eating, walking, bathing, reaching, gripping, and performing errands will be assessed on a scale that ranged from 0 to 3. The average of all scores will be considered to classify disability as 0, no difficulty; 0–1, mild disability; 1–1.5, moderate disability; and >1.5, severe disability.

The grip strength will be evaluated by a hydraulic dynamometer Saehan model SH5001 (Saehan Corporation, Yangdeok-Dong, Masan, Korea), and the Bohannon protocol will be used[31]. Participants will remain seated on a chair with the feet and trunk supported, shoulder adducted, elbow flexed at 90°, forearm in neutral position, and wrist in 0° to 30° extension[31]. Participants will be instructed to perform a maximum isometric contraction for 5 s, and the peak force will be recorded. Three evaluations will be performed with an interval of 1 min. For statistical analysis, arithmetic mean of these three measurements will be obtained. If the examiner recognizes some compensatory movement by the participant, a new measurement will be performed and recorded[32].

A short form health survey (SF-36) will be used to assess quality of life[33]. The questionnaire consists of a 36-item divided into 8 domains: functional capacity, limitation by physical aspects, pain, general health, vitality, social and emotional aspects and mental health[33]. These domains have between 2 and 6 response options. For each scale, item scores are coded, summed, and transformed, with final values (expressed as a percentage) ranging from 0 (worst health) to 100 (best health).

Adverse event monitoring and reporting

Serious adverse effect or irreversible injury following the use of conventional tDCS protocols in human trials (20 min, 2 mA, and 10 sessions) has not been reported[24]. Adverse events will be carefully monitored throughout the study. The most commonly reported adverse events included itching and tingling under the electrode sites, which are reported in both active and sham conditions[24,34]. Participants will receive care as

appropriate for any harm that arises following study participation. After the study, results will be presented to the participants in the form of a lecture. If the positive effects of tDCS on the research outcomes are confirmed, tDCS will be offered and guaranteed to all participants in the sham group. The principal investigator will have access to interim results and make the final decision to stop the trial in case of collateral events.

Adherence to treatment will be encouraged with daily messages sent by smartphone, advising on the benefits of the study and scheduling times that do not interfere with the participant's daily activities.

Sample size

The sample size was calculated based on statistical considerations for a parallel trial and on a previous study by Silva-Filho et al[15]. The sample size was estimated using G-Power 3.1.9.2 (RRID:SCR_013726) based on the assumption of significance of 0.05, power of 80%, with 0.3 effect size, and two groups. According to this methodology, the sample should include thirty-two participants. Considering a 20% of possibly loss, the number of participants will be increased by 25%, which corresponds to eight participants. Thus, forty participants will be recruited and allocated in the two groups, with twenty participants each.

Data collection and management

Data will be collected using paper forms and entered electronically on to the trial database. A trained physical therapist will undertake a face-to-face interview to collected quantitative data (questionnaires and physical tests). To maintain confidentiality, each participant will be given a unique trial Participant Identification Number (PIN). PIN will be used for data entered onto the central database stored on the base of UFRN. After completion of the trial, the database will be retained on the servers of UFRN for ongoing analysis of outcomes. The principal investigator will be access to the final trial dataset.

Patients and public involvement

Due to COVID-19 emergency and as this trial is health data-based, patients were not involved in the design of the trial. The results of the study will be communicated to participants through a popular symposium.

Statistical analysis

Statistical analyses will be conducted using the SPSS software version 19.0 (IBM Corp., Armonk, NY, USA). Clinical and sociodemographic characteristics will be described by means, medians, and standard deviations for continuous numeric parameters and by frequency tables with 95% confidence intervals for qualitative parameters. A chi-squared test or Fisher's exact chi-squared test will be used to compare the distributions of qualitative variables. To compare baseline data between groups, an unpaired t-test or a Mann–Whitney test will be used.

Shapiro–Wilk and Levene's test will be applied to assess the normality of the distribution and homogeneity of variance of the data, respectively. Mauchly's test of sphericity will be used to validate the correlation of the repeated measures, and if the

assumption of sphericity is violated, the Greenhouse–Geisser correction will be applied. The effects of stimulation on VAS, PPTh, PPTo, BPI, dynamometry, HAQ, and SF-36 will be calculated using a mixed analysis of variance (ANOVA) model. The dependent variable will be the score of each outcome, and the independent fixed variables will be the time of treatment (baseline, day 10, first follow-up, and second follow-up), stimulation group (active and sham), and time versus group interaction. When appropriate, post-hoc comparisons will be carried out using Bonferroni correction for multiple comparisons.

For non-parametric data, Friedman test will be used. Missing data will be treated by intention-to-treat analysis, evaluating dropout individuals who did not perform the entire treatment protocol. Partial η^2 will be calculated as measures of effect size in the ANOVA results (main effects and interaction effects). Partial η^2 will be used to calculate the effect size, where $\eta^2 = 0.01$ will be considered small, $\eta^2 = 0.06$ moderate, and $\eta 2 = 0.14$ large effect. Level significance will be set at p value less than 0.05.

Discussion

Chikungunya is epidemic in Brazil, with significant incidence in the Northeast (the second-highest incidence with 59.4 cases per 100,000 population)[35]. Most of patients present relapsing and remitting chronic arthralgia with debilitating pain lasting for years, but there are no specific therapeutic agents to treat and rehabilitate persons with chronic disease[32]. Persistent pain can lead to incapacitation, requiring long-term pharmacological treatment[8,29]. Advances in non-pharmacological options are necessary to promote pain relief without side effects and to restore functionality. Herein, we propose a trial protocol with tDCS (M1/Sp2 montage) to reduce pain and restore functionality in patients with chronic chikungunya. We will also determine (1) whether the changes induced by anodal tDCS over M1 correlated with the patient's level of pain according to the clinical evaluation scales and (2) if there is a relationship between pain relief and functionality. Absence of robust results would suggest that anodal tDCS over M1 has no effect on pain in chronic arthralgia caused by CHIKV.

It is urgent assess the clinical benefits and harms of interventions to prevent or treat persisting rheumatic disorders in patients with chikungunya[36]. Martí-Carvajal et al. described that only five small trials with high risk of bias were used in a systematic review of interventions for treating patients with chikungunya-related rheumatic and musculoskeletal disorders[8]. The authors suggested the need for more powered randomized clinical trials with high-quality methodology to assess clinical benefits for this population[8].

tDCS is a novel, safe, effective, and low-cost therapeutic approach to the treatment of chronic pain[16,17,31,37–40]. Previous studies have suggested that M1 anodal stimulation may reduce pain by activating various neural circuits present in the precentral gyrus[17]. This area are involved in the sensory and emotional components of pain processing, such as the thalamus or DLPFC, or in facilitating descending pain inhibitory control[17]. Besides this montage, a protocol with an intensity of 2 mA, an electrode size of 35 cm^2, and more than 10 consecutive sessions is commonly recommended to treat chronic pain[16–19]. Two studies have investigated the effect of tDCS on pain and functionality in chronic chikungunya arthralgia[14,15]. In the first study, Silva-Filho et al.[15] conducted five sessions of anodal M1/Sp2 montage, and in the second study, De Sousa et al.[14] applied six alternate sessions with the same tDCS parameters. These studies have suggested significant pain relief, but no significant difference in functional capacity was observed. Authors suggested that the number of

sessions or brief period of intervention can be employed to improve functionality[14,15]. With promising preliminary results with tDCS and chronic pain in chikungunya, investigating the long-term effect of tDCS and the most adequate dose for this population is necessary.

Clinical measures of this trial include the standard recommended outcomes, including pain intensity scales validated and universally accepted[41]. Secondary outcomes will be used to add information about pain and its effects on activities of daily living, disability, decrease in medication use, and participant satisfaction. Sociodemographic variables that can influence pain or functionality such as gender, age, income, educational level, and ethnicity will be reported[41]. Grip strength will be evaluated by a hydraulic dynamometer. This test was chosen because joint involvement in chronic chikungunya arthralgia is predominant in the wrists (66.3%), hands (72%), shoulders (70.1%), and elbows (40%)[32]. Chronic chikungunya arthralgia can compromise the osteo-myo-articular balance of previously susceptible joints[10]. Furthermore, the overuse of the inflamed areas and loss of muscle strength hasten the degenerative process and related pain and stiffness[10].

This protocol has strengths: (1) a novel treatment option for pain will be used in patients with chronic chikungunya arthralgia and (2) the study will be conducted in an epidemic region with a significant number of patients. However, there are some limitations to the study methodology and execution. First, this study did not receive government funding for financial support. Second, recruitment is limited to patients with chronic chikungunya (>3 months) and no patients with acute or sub-acute stage of the disease will be included. Third, no specific questionnaire is used to measure disability or effect of chikungunya on the quality of life or functionality. Thus, questionnaires for other rheumatic diseases and commonly used for chikungunya will be used[14,15,42]. Finally, this is the third trial with tDCS (the first with 10 sessions) in chronic chikungunya arthralgia, and our results will not support definitive conclusions on the efficacy of this neuromodulatory method.

The results of the present study will provide important long-term treatment information about clinical management of tDCS in persisting rheumatic disorders caused by chikungunya. We believe that these results will interest the broad audience committed to improve the quality of life and functionality of patients and to better understand brain modulation on chikungunya arthralgia.

Trial status

Volunteers were not yet being recruited at the time of manuscript submission.

Author's contributors

ASN and AFLC will perform initial and final evaluation, data entry in the database and informed consent of participants. JDDS and ESF will perform the tDCS protocol. AO will be supported data analysis and writing of the manuscript. LG and RP will perform data management and writing of the manuscript.

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Competing interest

Authors declare no competing interest regarding this trial.

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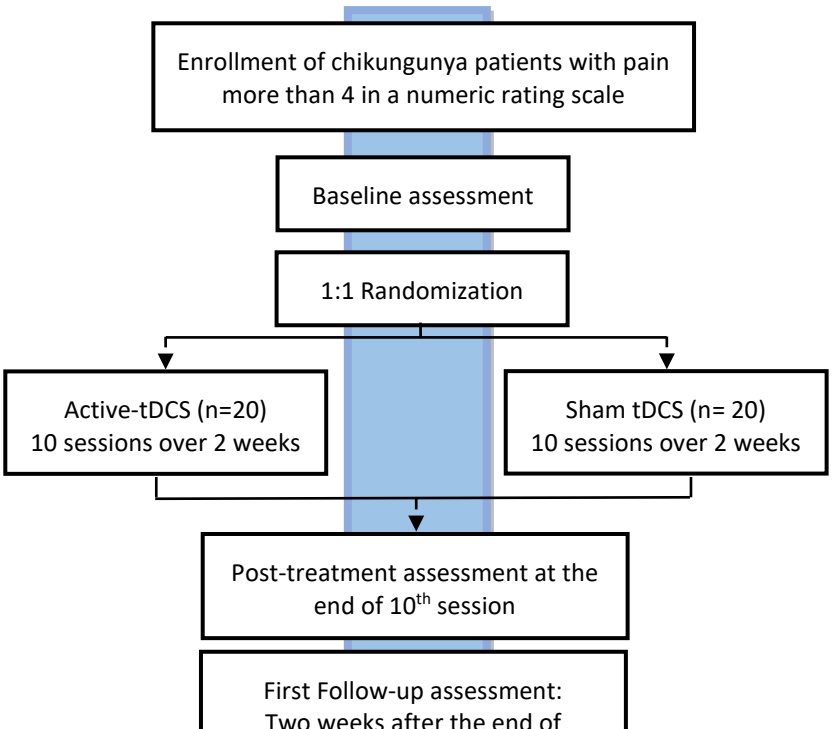
Figure 1. Flowchart summarizing the trial.

Figure 2. Schedule of enrollment, interventions, and assessments. VAS – Visual Analog Scale, BPI - Brief Pain Inventory (Short Form), HAQ - The Health Assessment Questionnaire, SF-36 - Short Form Health Survey.



	Study Period						
	Enrolment	Allocation	Post-allocation			1º Follow-up	2º Follow-up
TIMEPOINT	Week 1	Week 2 Baseline	Intervention			Week 6	Week 8
			Week 3	Week 4	Last day of tDCS protocol		
ENROLMENT	X						
Eligibility screen	X						
Informed consent	X						
Sociodemographic characteristics	X						
Allocation		X					
INTERVENTIONS							
Active tDCS			◆	—	◆		
Sham tDCS			◆	—	◆		
ASSESSMENTS							
VAS		X			X	X	X
Pressure pain threshold		X			X	X	X
Pressure pain tolerance		X			X	X	X
BPI		X			X	X	X
Dynamometry		X			X	X	X
HAQ		X			X	X	X
SF-36							
Medication use		X			X	X	X
Adverse events					X	X	X
Success of blinding							X

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Transcranial direct current stimulation for chronic chikungunya arthralgia: study protocol for a randomized clinical trial
Trial registration	2a	This trial is registered in the Brazilian Registry of Clinical Trials (ReBEC) under the identifier RBR-469yd6 (Date of registration: 25/06/2018).
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	11/05/2022, last approval, version 2.
Funding	4	This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. Abraão Sérvulo do Nascimento was partly financed by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES). Finance Code 001.
Roles and responsibilities	5a	Authors: Abraão Sérvulo do Nascimento, Antônio Felipe Lopes Cavalcante, João Danyell Dantas da Silva, Edson Silva-Filho, Alexandre Okano, Lucien Peroni Gualdi, Rodrigo Pegado.
	5b	Name and contact information for the trial sponsor The study has no sponsor.
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities: *The study has no specific sponsor and fund from any public or private agency. Abraão Sérvulo do Nascimento was partially financed by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES). Finance Code 001, however, the national public agency has no authority over the protocol activities.*
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) The protocol will be performed in a single center coordinated by Professor Rodrigo Pegado. All research previously described will be responsible for the study performance in specific tasks. Abraão Sérvulo do Nascimento and Antônio Felipe Lopes Cavalcante will perform initial and final evaluation, data entry in the database and informed consent of participants. João Danyell Dantas da Silva and Edson Silva-Filho will perform the tDCS protocol. Alexandre Okano will be supported data analysis and writing of the manuscript. Data management and writing of the manuscript will be performed by Lucien Gualdi and Rodrigo Pegado. No other individual or group will be allowed to see data without the study's coordinator permission.

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention: Brazil has been a protagonist in cases of Chikungunya virus (CHIKV) in Americans. Up to 50%–60% of CHIKV infected individuals may evolve into chronic phase that begins when clinical symptoms persist for more than 3 months. There are no specific therapeutic agents to treat and rehabilitee individuals in chronic phase of CHIKV and persistent pain may lead to incapacitation and requirement of long-term pharmacological treatment. Previously studies supported the use of anodal transcranial direct current stimulation (tDCS) over M1 (M1-SO montage) aiming to reduce pain. These studies were the initial investigation of M1 anodal tDCS, but further work to optimize the stimulation parameters is needed to clarify long-term efficacy on pain and functionality in chronic CHIKV arthralgia.
	6b	Explanation for choice of comparators Approximately 50% of patients have chronic arthralgia (chronic phase) for up to 6 years. This phase accounts for a high rate of persistent and incapacitating polyarthralgia, resulting in a reduction of functionality and quality of life. Pain is considered the most important symptom in chronic phase of CHIKV and showed strong association with reduction in daily activities and physical function.
Objectives	7	The primary objective of this protocol is to measure the effect of tDCS on pain. The secondary objective is to assess muscle strength, functionality, and quality of life. The duration and extent of effects of tDCS (long-term effect) will be also investigated. The study hypothesis is that the tDCS protocol will show improvement in pain, muscle strength, functionality, and quality of life when compared with sham tDCS.
Trial design	8	This is a protocol study of a single-center, double-blind, parallel, sham-controlled, randomized clinical trial with two groups and a 1: 1 allocation ratio.

Methods: Participants, interventions, and outcomes

Study setting	9	All procedures will be performed at the Physical Therapy Outpatient Clinic of Faculdade de Ciências da Saúde do Trairi/Universidade Federal do Rio Grande do Norte located in the city of Santa Cruz/ Rio Grande do Norte in Brazil.
Eligibility criteria	10	Adults from local communities of the Northeast region of Brazil will be recruited voluntarily through advertisements in electronic media and by health professionals from the communities. The inclusion criteria were as follows: men and women aged ≥18 years with positive laboratory or clinical diagnosis of chronic chikungunya (at least 3 months from the initial infection); moderate to severe (above 4) pain according to a numeric rating scale (NRS) and can tolerate physical evaluation; and satisfactory cognitive function to understand and sign the informed consent and study explanations and questionnaires. The exclusion were as follows: individuals with electrical implants in the body, history of epilepsy, metallic device implanted in the head, history of drug abuse, pregnancy, signs of severity and/or indication of hospitalization, and history of rheumatic diseases including gout, rheumatoid arthritis, fibromyalgia, lupus, and other chronic pain syndromes diagnosed prior to chikungunya.

Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered: The treatment will consist of 2 weeks intervention divided in 10 sessions of 20 minutes (one per weekday). Both groups AG and SG will be treated by a trained physical therapist at the Physical Therapy Outpatient Clinic of Federal University of Rio Grande do Norte. A monophasic continuous current with an intensity of 2 mA for 20 min will be used. All patients will be awake and sited in a comfortable chair with back and arm support during the tDCS/sham intervention. All tDCS procedures will be conducted in a temperature and noise-controlled room. tDCS will be delivered using the anode electrode positioned over the left primary motor cortex (C3) and the cathode electrode at the contralateral supra orbital region (Fp2), according to international standards for EEG 10–20 system (the "M1-SO" assembly). The electrodes will be placed into a 35 cm^2 square sponge immersed in saline solution (154 mM NaCl, approximately 12 mL per sponge). For stimulation, a current ramp-up and ramp-down with 30s duration will be used. Electrodes attached to the scalp will be supported by an elastic band. The electrodes (anode and cathode) will be connected to a battery (9 v) powered stimulator with current verified by a precision digital multimeter (DT832, WeiHua Electronic Co., Ltd, China) with standard error of ±1.5%. For the SG it will be used a ramp-up of 30 seconds and a ramp-down of 30 seconds. The device displays are identical in active and sham settings. To guarantee the success of blindness, participants and outcome assessors at the end point will be asked to guess whether the treatment was active or false.
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease). Participants who miss two tDCS sessions will be excluded from the study. Allergic skin reactions have been observed in rare cases. If this is suspected tDCS protocol will be stopped. This should be reported as an adverse event. The use of conventional tDCS protocols in human trials (20min, 2mA and 10 sessions) has not produced any reports of a serious adverse effect or irreversible injury. Adverse events will be carefully monitored during all steps of the study. The most reported adverse events included the sensation of itching and tingling under the electrode sites, reported in both active and sham conditions. Participants will receive care as appropriate for any harm that arises as a result of study participation. At the end of the study, the results will be informed to the participants in the form of a lecture, showing the results obtained. If the positive effects of tDCS on the researched outcomes are found, the application of tDCS will be offered and guaranteed to all participants in the sham group.
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests). Adherence to treatment will be encouraged with daily messages sent by smartphone, advising on the benefits of the study and scheduling times that do not interfere with the participant's daily activities.

	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial For ethical reasons, no intervention will be performed in clinical care and previous prescription of painkillers or others medication. If a participant begins medication during the study, it will be documented, but the participant will not be excluded. Participants are encouraged to maintain their normal activity routine.
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended. Primary outcomes: Participants will be assessed using a numeric rating scale (NRS) for pain. The NRS is a segmented numeric version of the visual analogue scale (VAS) in which the participant selects a whole number (0–10 integers) that best reflects the intensity of its pain (0 representing “no pain” and 10 representing the “pain as bad as you can imagine”. Algometry will be carried out to record Pressure Pain Threshold (PPTh) and Pressure Pain Tolerance (PPTo). Pain PPTh and PPTo will be assessed in 8 different anatomical locations: trapezius: at the midpoint of the upper edge; lumbar spine: performed over the erector muscle; lateral epicondyle; knee, over the fatty cushion; and between the index finger and the thumb on the dorsal side of the hand. Pain threshold and tolerance to pressure will be quantified in kg/cm^2. Secondary outcomes: The Brief Pain Inventory (BPI) will be used to assess the severity and impact of pain in daily living activities. It is a questionnaire that presents 15 items, including 2 multi-item scales to measure pain and its impact on functionality and well-being. The DN4 questionnaire will be performed to evaluate neuropathic pain. The presence of neuropathic pain will be considered to be a dependent variable and will need to reach a score of at least 4 out of 10, while non-neuropathic pain will be considered scores of less than 4 out of 10. The health assessment questionnaire (HAQ) will be used to access functionality. Rising, dressing, eating, walking, bathing, reaching, gripping, and performing errands will be assessed on a scale range from 0 to 3. The average of all scores will be considered to classify disability as 0 = no difficulty, 0-1 = mild disability, 1-1.5 = moderate disability, and >1.5 = severe disability. The grip strength will be evaluated by a hydraulic dynamometer in kilogram-force. Three evaluations will be performed with an interval of 1 min between them. For statistical analysis, results will be obtained by arithmetic mean of these three measurements.
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure). Flowchart summarizing the trial was added in the manuscript.
Sample size	14	The sample size was calculated based on statistical considerations for a parallel trial and on a previous study by Silva-Filho et al15. The sample size was estimated using G-Power 3.1.9.2 based on the assumption of significance of 0.05, power of 80%, with 0.3 effect size, and two groups. According to this methodology, the sample should include 32 participants. Considering a 20% loss to follow-up and 5% missing data, the number of participants will be increased by 25%, which corresponds to eight participants. Thus, 40 participants will be recruited and allocated in the two groups, with 20 participants each.
Recruitment	15	Subjects will be recruited at the patients waiting list of the Physical Therapy Outpatient Clinic of Santa Cruz/RN- Brazil. Advertisements about the study will be placed in social media aimed to inform and invite the population.

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Randomization will be carried out through a numerical sequence generated by an allocated computer using appropriate software (www.random.org) to assign each participant to either the active or sham group. An external research assistant will generate the allocation sequence and contact participants by telephone.
Allocation concealment mechanism	16b	Allocation concealment will be performed using opaque envelopes. Participants and researchers involved in the assessments and interventions will be blinded to group allocation throughout the trial.
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions. The allocation sequence will be performed for Abraão Sérvulo do Nascimento and Antônio Felipe Lopes Cavalcante will enroll participants. João Danyell Dantas da Silva and Edson Silva-Filho will assign participants to interventions.
Blinding (masking)	17a	In this clinical trial, both the participants and evaluators will be blinded. Moreover, to ensure that the participant is also blinded to the allocation group, electrodes will be placed in the same position as in the active group, but the stimulator delivered 2 mA of current for only 30 s, with the same ramp-up and ramp-down period of 10 s. Sham tDCS will consist of delivering an active stimulation for a few seconds to mimic the sensations (itching and tingling) observed during active tDCS. This is considered a valid methodology for clinical protocols with good effectiveness of blinding.
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial Unblinding will not be allowed, and the evaluator will have no access to the allocation group until the end of the study.

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol Before starting the trial, a series of training steps for evaluations and application of the tDCS will be carried out, aimed at recording activities carried out in the study. Techniques and measures will be improved at this stage of the training to reach a consensus among the researchers. tDCS will be performed by a physical therapist with previously expertise in clinical trials and background in non-invasive brain stimulation. Assessment will be performed in the morning in a temperature-controlled room without noise or another distractor. NRS, PPTh, PPTo , BPI, DN4 questionnaire , HAQ and grip strength are commonly used in clinical trails aim to assess pain and functionality. All questionnaires are validated and translated for the Brazilian population. The researcher will ask to the participant questions described in the questionnaires, and according to the answers obtained, the researcher will fill in the questionnaire. All questions can be repeated if the question is not understood.

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols The trial will be performed in a small city with easy and free cost transportation to the local of the study. If necessary, the research will develop strategies to transport this individuals to the study setting. The participant will be informed of the benefits of the research and, if necessary, will be referred for physical therapy treatment at the University's Rehabilitation Clinic.
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol Data will be stored at the principal investigator computer and double entry will be performed by two study researchers. Data access will be limited to the study researchers and any other access must be authorized by the coordinator.
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol Statistical analyses will be conducted using the SPSS software version 19.0 (IBM Corp., Armonk, NY, USA). Clinical and sociodemographic characteristics will be described by means, medians, and standard deviations for continuous numeric parameters and by frequency tables with 95% confidence intervals for qualitative parameters. A chi-squared test or Fisher's exact chi-squared test will be used to compare the distributions of qualitative variables. To compare baseline data between groups, an unpaired t-test or a Mann–Whitney test will be used. Shapiro–Wilk and Levene's test will be applied to assess the normality of the distribution and homogeneity of variance of the data, respectively. Mauchly's test of sphericity will be used to validate the correlation of the repeated measures, and if the assumption of sphericity is violated, the Greenhouse–Geisser correction will be applied. The effects of stimulation on NRS, PPTh, PPTo, BPI, DN4, HAQ, and dynamometry will be calculated using a mixed analysis of variance (ANOVA) model. The dependent variable will be the score of each outcome, and the independent fixed variables will be the time of treatment (baseline, day 10, first follow-up, and second follow-up), stimulation group (active and sham), and time versus group interaction. When appropriate, post-hoc comparisons will be carried out using Bonferroni correction for multiple comparisons. For non-parametric data, Friedman test will be used. Missing data will be treated by intention-to-treat analysis, evaluating dropout individuals who did not perform the entire treatment protocol. Partial η2 will be calculated as measures of effect size in the ANOVA results (main effects and interaction effects). Partial η2 will be used to calculate the effect size, where η2 = 0.01 will be considered small, η2 = 0.06 moderate, and η2 = 0.14 large effect. Level significance will be set at p value less than 0.05.
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) The study has no additional analyses planned.
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) Missing data will be treated by intention-to-treat analysis, evaluating dropout individuals who did not perform the entire treatment protocol. Partial η2 will be calculated as measures of effect size in the ANOVA results (main effects and interaction effects). Partial η2 will be used to calculate the effect size, where η2 = 0.01 will be considered small, η2 = 0.06 moderate, and η2 = 0.14 large effect. Level significance will be set at p value less than 0.05.

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed Data will be monitored by the study coordinator and posteriorly accessed by all researchers previously authorized to access data. There will not be an independent database as the study has no sponsor.
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial Trial will follow the guidelines and good practices for managing and reopening non-invasive brain stimulation (NIBS) clinics and laboratories through the immediate and ongoing stages of COVID-19 according to Bikson et al. 2020 (DOI: 10.1016/j.brs.2020.05.010). Final decision will be made by principal investigator.
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct Any adverse effect that occurs during the protocol performance will be reported on the follow-up guide and the information will be referred to the patients' physician.
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor There will be no audit in this study.
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval The study was previously approved by the ethics committee of the Faculty of Health Sciences of Trairí – Federal University of Rio Grande do Norte (No. 2.413.851). Results will be presented in peer-reviewed journals and international conferences.
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators). All protocol modifications will be informed to ethics committee of the Faculty of Health Sciences of Trairí – Federal University of Rio Grande do Norte (No. 2.413.851). After evaluation and approval, the researchers will inform for all participants.
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) Abraão Sérvulo do Nascimento and Antônio Felipe Lopes Cavalcante will obtain informed consent or assent for all participants. Potentially eligible patients with chronic of chikungunya will receive a detailed explanation of the study from the study research coordinator. Interested participants will be asked to sign the informed consent form before enrollment into the study.
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable Not applicable.

Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial The data will be confidential and will be disclosed only in conferences or scientific publications, with no disclosure to third parties and no data that could identify the participants. These data will be kept by the principal researcher in a safe place and for a period of 5 years at the Faculty of Health Sciences of Trairí/UFRN according to Resolution Nº. 466/12 of the National Health Council.
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site Authors declare no competing interests.
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators All data will be available for research time directly upon reasonable request to principal investigator. After the publication of the clinical trial, data will be available to any reader directly upon reasonable request to principal investigator, respecting the privacy and confidentiality of research participants.
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation According to Resolution No. 466/12 of the National Health Council, the investigators are responsible to any compensation to trial participation.
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions After the and of the study, investigators will perform a Symposium to publisher the trial results and all participants and scientific community will be invited. There are no publication restrictions in this trial.
	31b	Authorship eligibility guidelines and any intended use of professional writers There are no intended to use professional writers. All authors are previously described, and the eligibility will follow the ICMJE recommendations to best practice and ethical standards in the conduct and reporting of research.
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code Publication of this protocol in an open-access journal. All data will be available directly upon reasonable request to principal investigator
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates The consent form model followed the Brazilian model for informed consent and was approved by the responsible ethics committee.
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable Not apllicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	3
Protocol version	3	Date and version identifier	3
Funding	4	Sources and types of financial, material, and other support	12
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	12
	5b	Name and contact information for the trial sponsor	-
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	12
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	-

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2
	6b	Explanation for choice of comparators	5,6
Objectives	7	Specific objectives or hypotheses	3
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	3
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	3,4
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	3,4,5
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	6
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	6
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	4
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	5,6
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	3

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	67
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	3
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	3
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	3
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	3
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	3
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	4,5
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	6

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	6
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	7
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	-
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	7
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	-
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	6
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	6
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	-
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	-
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	2

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	3,4
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	-
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	6
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	12
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	6
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	-
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	6
	31b	Authorship eligibility guidelines and any intended use of professional writers	12
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	-
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	-
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	-

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Ten sessions of transcranial direct current stimulation for chronic chikungunya arthralgia: study protocol for a randomized clinical trial

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Ten sessions of transcranial direct current stimulation for chronic chikungunya arthralgia: study protocol for a randomized clinical trial

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Abstract

Introduction: The chikungunya virus infection is still an epidemic in Brazil with an incidence of 59.4 cases per 100,000 in the Northeast region. More than 60% of the patients present relapsing and remitting chronic arthralgia with debilitating pain lasting for years. Transcranial direct current stimulation (tDCS) appears promising as a novel neuromodulation approach for pain-related networks to alleviate pain in several pain syndromes. Our objective is to evaluate the effectiveness of tDCS (C3/Fp2 montage) on pain, muscle strength, functionality, and quality of life in chronic arthralgia.

Methods and analysis: This protocol is a single-center, parallel-design, double-blind, randomized, sham-controlled trial. Forty participants will be randomized to either an active or sham tDCS. A total of 10 sessions will be administered over 2 weeks (one per weekday) using a monophasic continuous current with an intensity of 2 mA for 20 min. Participants will be evaluated at baseline, after the 10th session, 2 weeks, and 4 weeks after intervention. Primary outcome: pain assessed using numeric rating scale and algometry. Secondary outcomes: muscle strength, functionality, and quality of life. The effects of stimulation will be calculated using a mixed analysis of variance (ANOVA) model.

Ethics and dissemination: The study was approved by the ethics committee of the Faculty of Health Sciences of Trairí, Federal University of Rio Grande do Norte (No. 2.413.851) and registered on the Brazilian Registry of Clinical Trials (identifier RBR-469YD6). Study results will be disseminated through presentations at conferences and publications in peer-reviewed journals.

Strengths and limitations of this study

- The trial will be performed in an endemic area with lack of resources for chronic chikungunya arthralgia treatment.
- This is a low cost, safe, and mobile intervention that may be implemented in clinical practice for a neglected tropical disease.
- The trial will include participants with chronic pain without any previous treatment for a cost-effectiveness evaluation and quantitative data collection.
- The trial will not include laboratorial, image or electrophysiological data regarding brain modulation or maintenance of pain state after tDCS protocol.

Introduction

In the last 8 years, Brazil has been a protagonist in infection caused by chikungunya virus (CHIKV) in America[1]. The spread of the disease in South America is critical and out of control, mainly in Brazil that represents 94% of confirmed chikungunya cases[2,3]. Until 2021, the Brazilian Ministry of Health continues to monitor the occurrence of chikungunya, and from December 2019 to April 2020, 17,636 chikungunya cases were recorded[1]. The re-emergence of chikungunya has become an increasing medical and economic burden in affected areas[4]. The acute phase (<7 days) of the disease is usually characterized by sudden high fever, polyarthritis, tenderness, headache, myalgia, maculopapular rash and vomiting[5,6].

Chikungunya presents as a challenge for health care systems and rehabilitation professionals because most cases are commonly followed by persistent chronic arthralgia lasting for years[7]. Up to 50%–60% of chikungunya cases may progress to the chronic phase that begins when clinical symptoms persist for more than 3 months[8,9]. No specific therapeutic agents can be used to treat and rehabilitate individuals with chronic chikungunya and persistent pain may lead to incapacitation and require long-term pharmacological treatment[10]. Chronic pain is associated with development of adaptive neuroplasticity and functional reorganization that could result in physical and behavioral impairment[11]. Pain has a sensory-discriminative, affective-motivational, motor, and autonomic components, and some areas of the brain were involved in a large distributed neural network called the pain neuromatrix (PNM)[12]. The activation of the primary (S1) and secondary (S2) somatosensory cortices, primary motor cortex (M1), dorsolateral prefrontal cortex (DLPFC), thalamus, insula, and anterior cingulate cortex are involved in pain processing[12]. The M1 is an important area to understand the pathophysiology and treatment of chronic pain conditions including rheumatic diseases[13].

The efficacy of transcranial direct current stimulation (tDCS) on pain and other clinical outcomes have been published with beneficial results[14–17]. Previous studies have supported the use of anodal tDCS over M1 (M1-SO montage) to reduce pain in osteoarthritis[18], post-stroke pain syndrome[17], back pain[18], fibromyalgia[13], and recently chikungunya[14,15]. In this context, tDCS promotes M1 activation, providing secondary modulatory effects on the PNM circuit that is associated with nociceptive modulation[19]. The first study on CHIKV and neuromodulation suggested pain improvement after five consecutive sessions of tDCS[15]. The second study evaluated six nonconsecutive sessions of anodal tDCS on M1 and showed significant reduction on pain[14]. These studies were the initial investigations of tDCS, but further work to optimize the stimulation parameters is needed to clarify long-term efficacy on pain and functionality in chronic chikungunya arthralgia[14,15]. It is important to consider that the intensity and session repetition timing have significant influence in some aspects of the non-linear relationship between tDCS settings and the biological effects produced[17]. The number of sessions is associated with the time of duration of neuromodulation and ten sessions could provide a long-term neuromodulation effect and produce a sustained effect on pain and other symptoms[18].

Furthermore, tDCS could be a non-invasive, low-cost, safe, and accessible treatment option to CHIKV-endemic areas[15]. Herein, we present the methodology of a randomized double-blinded controlled study to evaluate the feasibility of a trial protocol for 10 consecutive sessions of tDCS in chronic chikungunya arthralgia. The primary objective of this protocol is to measure the effect of tDCS on pain. The secondary objective is to assess pain threshold and tolerance, muscle strength, functionality, and quality of life. The duration and extent of effects of tDCS (long-term effect) will be also investigated. The study hypothesis is that the tDCS protocol will show improvement in pain, muscle strength, functionality, and quality of life when compared with sham tDCS.

Methods and design

Study design

This is a protocol study of a single-center, double-blind, parallel, sham-controlled, randomized clinical trial with two groups and a 1: 1 allocation ratio. A total of 10 sessions of 20 min will be administered over a period of 2 weeks. Outcomes will be measured at baseline (1 week before intervention), immediately after day 10 of intervention, and at 2 and 4 weeks after the end of the treatment as follow-up (Figure 1). The study follows the

Template for Intervention Description and Replication checklist[20] and the 2013 Standard Protocol Items: Recommendations for International Trials statement (SPIRIT).

This trial is registered in the Brazilian Registry of Clinical Trials (ReBEC) under the identifier RBR-469YD6. All participants will be informed about the trial's objectives and procedures. Participation is voluntary as determined by Resolution No. 466/12 of the National Health Council. Potentially eligible patients with chronic of chikungunya will receive a detailed explanation of the study from the study research coordinator. Interested participants will be asked to sign the Patient Consent Form (Supplementary File) before enrollment into the study. The informed consent form was submitted and approved by the ethics committee of the Faculty of Health Sciences of Trairí – Federal University of Rio Grande do Norte (UFRN) (No. 2.413.851).

Participants and Chikungunya diagnosis

Participants with previous serologic confirmation of CHIKV infection[21] based on immunoglobulin (Ig) G and IgM detected by direct enzyme-linked immunosorbent assay/IgM/Euroimmun, according to the Central Laboratory (LACEN, Brazil) or on initial clinical symptoms (in the context of the epidemic) including at least fever and arthralgia who meet the eligibility criteria will be invited to participate in the study[21].

Trial design

The study will start in August 2022 and is expected to be completed in August 2023. After the initial assessment, participants will be randomly allocated into two evaluator/participant blinded groups: active group and sham group.

Participants of both groups will undergo a 2-week protocol (5 sessions per week) of active or sham tDCS. Sessions will be performed for 20 min by the same trained physical therapist. Two follow-ups will be performed after 2 and 4 weeks at the end of tDCS protocol by the same evaluator blinded for the allocation group. The schedule of enrollment, interventions, and assessments is demonstrated in figure 2.

All assessments and intervention procedures will be performed at the Physical Therapy Outpatient Clinic of Faculty of Healthy Science of Trairí, Federal University of Rio Grande do Norte, Santa Cruz, Brazil.

This study will involve four researchers: one researcher each is responsible for the evaluations, application of the tDCS, randomization of participants, and statistical analysis. Before starting the trial, a series of training steps for evaluations and application of the tDCS will be carried out, aimed at recording activities carried out in the study. Techniques and measures will be improved at this stage of the training to reach a consensus among the researchers.

Recruitment and eligibility criteria

Adults from local communities of the Northeast region of Brazil will be recruited voluntarily through advertisements in electronic media and by health professionals from the communities.

Eligibility criteria for participation in the study are: men and women aged ≥18 years with positive laboratory or clinical diagnosis of chronic chikungunya (at least 3 months from the initial infection); moderate to severe (above 4) pain according to a numeric rating scale (NRS); tolerate physical evaluation; satisfactory cognitive function to understand and sign the informed consent, study explanations and questionnaires. The

exclusion criteria adopted are: individuals with electrical implants in the body, history of epilepsy, metallic device implanted in the head, history of drug abuse, pregnancy, signs of severity and/or indication of hospitalization, previously diagnosis of mental disorder and history of rheumatic diseases including gout, rheumatoid arthritis, fibromyalgia, lupus, and other chronic pain syndromes diagnosed prior to chikungunya.

Randomization

Patients will be enrolled by the investigators and randomly assigned (1:1) to receive active tDCS or sham. Stratified randomization will be performed using the order of entry into the study. To prevent imbalance between treatment groups, patients will be plotted according to gender (male and female) and age (under 20 years, 20–64 years, and 65 years and older). Randomization will be applied to each stratum using appropriate software (www.random.org) to assign each participant to either the active or sham group. An external research assistant will generate the allocation sequence and contact participants by telephone. Allocation concealment will be performed using opaque envelopes. Participants will be blinded to group allocation throughout the trial.

Blinding

In this clinical trial, participants and evaluators will be blinded for allocation group. Moreover, to ensure that the participant is also blinded to the allocation group, electrodes will be placed in the same position as in the active group, but the stimulator delivered 2 mA of current with the same ramp-up and ramp-down period of 30 s [15,22]. Sham tDCS will consist of delivering an active stimulation for a few seconds to mimic the sensations (itching and tingling) observed during active tDCS[23]. This is considered a valid methodology for clinical protocols with good effectiveness of blinding[14,15,23–25]. The tDCS device does not allow a blinded model for the researchers involved in the interventions.

Intervention

The treatment will consist of 2 weeks of intervention divided into 10 sessions of 20 min each (one per weekday) using a monophasic continuous current with an intensity of 2 mA. The active and sham groups will be treated by a trained physical therapist at the Physical Therapy Outpatient Clinic of Federal University of Rio Grande do Norte. All patients will be awake and seated in a comfortable chair with back and arm support during tDCS and sham intervention. All tDCS procedures will be conducted in a temperature and noise-controlled room.

tDCS will be delivered using the anode electrode positioned over the left primary motor cortex (C3) and the cathode electrode at the contralateral supraorbital region (Fp2), according to international standards for EEG 10–20 system. The electrodes will be placed into a 35 cm^2 sponge immersed in saline solution (154 mM NaCl, approximately 12 mL per sponge). For stimulation, current ramp-up and ramp-down with 30-s duration will be employed. Electrodes attached to the scalp will be supported by an elastic band. The electrodes (anode and cathode) will be connected to a stimulator MicroEstim Genius (NKL, Santa Catarina, Brazil). Device displays are identical in the active and sham groups.

For ethical reasons, no intervention will be performed in clinical care, and painkillers or other medications will be prescribed as usual. If a participant will begin taking medications during the study period, this will be documented, but the participant will not be excluded from the analysis. To ensure the success of blinding, participants and outcome assessors at the end point will be asked to guess whether the treatment was active or false.

Outcomes

Primary outcomes

Participants will be assessed using a Visual Analog Scale (VAS) for pain, which is a one-dimensional measure of pain intensity in adults, including those with chronic pain due to rheumatic disease[26]. The VAS is a continuous scale comprised of a horizontal line, usually 10 centimeters (100 mm) in length, anchored by 2 verbal descriptors (0 representing "no pain" and 100 representing "pain as bad as you can imagine")[26]. The VAS is self-completed by the respondent. The respondent is asked to place a line perpendicular to the VAS line at the point that represents their pain intensity[26].

Secondary outcomes

Algometry will be carried out to record pressure pain threshold (PPTh) and pressure pain tolerance (PPTo). Pain PPTh and PPTo will be assessed in eight different anatomical locations: trapezius, at the midpoint of the upper edge; lumbar spine, performed over the erector muscle; lateral epicondyle; knee, over the fatty cushion; and between the index finger and thumb on the dorsal side of the hand. All points will be tested on the left and right sides of the body. Algometry will be performed perpendicular to the skin at 5–10 s intervals by the same qualified examiner. A pressure algometer will be used (MedDor, Minas Gerais, Brazil) through a 1-cm diameter rubber tip. PPTh and PPTo will be quantified in kg/cm^2. The examiner will position the rubber tip above the area to be examined and gradually increased the pressure by 1 $kg/cm^2/s$ [27]. The PPTh will be measured when the patient says, "I'm starting to feel pain." To measure PPTo, the patient will be asked to bear the maximum amount of pressure from the algometer and use the verbal affirmation "stop."

The Brief Pain Inventory (BPI) is one of the most used instruments to assess chronic pain in clinical trials[28]. The BPI (short form) will be used to assess the severity and effect of pain in daily living activities. It is a questionnaire that presents 15 items, including two multi-item scales to measure pain and its effect on functionality and well-being; the questionnaire is validated for the Brazilian population[28]. In the room allocated for evaluation, participants will be asked by the researcher about each item, and questionnaire will be filled according to the answers of the participants. All questions can be repeated if the participant does not understand. The BPI will be applied in all phases of evaluation and by the same researcher.

In the absence of a specific functional questionnaire for acute and long-term evaluation of rheumatic manifestations of chikungunya, the health assessment questionnaire (HAQ) it will be used. HAQ is commonly used to assess rheumatoid arthritis and to evaluate patients with chikungunya[9,29]. This is a validated tool to measure disability due to persistent arthralgia[30]. Rising, dressing, eating, walking, bathing, reaching, gripping, and performing errands will be assessed on a scale that ranged from

0 to 3. The average of all scores will be considered to classify disability as 0, no difficulty; 0–1, mild disability; 1–1.5, moderate disability; and >1.5, severe disability.

The grip strength will be evaluated by a hydraulic dynamometer Saehan model SH5001 (Saehan Corporation, Yangdeok-Dong, Masan, Korea), and the Bohannon protocol will be used[31]. Participants will remain seated on a chair with the feet and trunk supported, shoulder adducted, elbow flexed at 90°, forearm in neutral position, and wrist in 0° to 30° extension[31]. Participants will be instructed to perform a maximum isometric contraction for 5 s, and the peak force will be recorded. Three evaluations will be performed with an interval of 1 min. For statistical analysis, arithmetic mean of these three measurements will be obtained. If the examiner recognizes some compensatory movement by the participant, a new measurement will be performed and recorded[32].

A short form health survey (SF-36) will be used to assess quality of life[33]. The questionnaire consists of a 36-item divided into 8 domains: functional capacity, limitation by physical aspects, pain, general health, vitality, social and emotional aspects and mental health[33]. These domains have between 2 and 6 response options. For each scale, item scores are coded, summed, and transformed, with final values (expressed as a percentage) ranging from 0 (worst health) to 100 (best health).

Adverse event monitoring and reporting

Serious adverse effect or irreversible injury following the use of conventional tDCS protocols in human trials (20 min, 2 mA, and 10 sessions) has not been reported[24]. Adverse events will be carefully monitored throughout the study. The most commonly reported adverse events included itching and tingling under the electrode sites, which are reported in both active and sham conditions[24,34]. Participants will receive care as appropriate for any harm that arises following study participation. After the study, results will be presented to the participants in the form of a lecture. If the positive effects of tDCS on the research outcomes are confirmed, tDCS will be offered and guaranteed to all participants in the sham group. The principal investigator will have access to interim results and make the final decision to stop the trial in case of collateral events.

Adherence to treatment will be encouraged with daily messages sent by smartphone, advising on the benefits of the study and scheduling times that do not interfere with the participant's daily activities.

Sample size

The sample size was calculated based on statistical considerations for a parallel trial and on a previous study by Silva-Filho et al[15]. The sample size was estimated using G-Power 3.1.9.2 (RRID:SCR_013726) based on the assumption of significance of 0.05, power of 80%, with 0.3 effect size, and two groups. According to this methodology, the sample should include thirty-two participants. Considering a 20% of possibly loss, the number of participants will be increased by 25%, which corresponds to eight participants. Thus, forty participants will be recruited and allocated in the two groups, with twenty participants each.

Data collection and management

Sociodemographic and clinical data will be collected and recorded by trained and blinded research assistants in our research centre. A trained physical therapist will undertake a face-to-face interview to collected quantitative data (questionnaires and

physical tests). Consistency checks by another researcher (physical therapist) will be performed to ensure data entry accuracy during data collection. Data will be collected using paper forms and entered electronically on to the trial database. To maintain confidentiality, each participant will be given a unique trial Participant Identification Number (PIN). PIN will be used for data entered onto the central database stored on the base of UFRN. After completion of the trial, the database will be retained on the servers of UFRN for ongoing analysis of outcomes. The principal investigator will be access to the final trial dataset.

The study will be conducted in accordance with Good Clinical Practices to ensure the rights and well-being of the participants. Patients are free to refuse to participate or withdraw from the study at any time without giving any reasons, and their medical care or legal rights will not be affected. In case of any problem during the trial, participants will have the right to free assistance that will be provided by the responsible researcher.

Although no serious adverse[24] events with a causal link with tDCS are expected, adverse events will be reported to the principal investigator. Serious adverse events[24] will be logged and reviewed by the trial researchers and Ethics Committee if necessary. No auditing is planned. If necessary, possible amendments to the research protocol will be reported to the Ethics Review Committee for approval.

Following completion of the trial, datasets used in this study will be available from the corresponding author on reasonable requests.

Patients and public involvement

Due to COVID-19 emergency and as this trial is health data-based, patients were not involved in the design of the trial. The results of the study will be communicated to participants through a popular symposium.

Statistical analysis

Statistical analyses will be conducted using the SPSS software version 19.0 (IBM Corp., Armonk, NY, USA). Clinical and sociodemographic characteristics will be described by means, medians, and standard deviations for continuous numeric parameters and by frequency tables with 95% confidence intervals for qualitative parameters. A chi-squared test or Fisher's exact chi-squared test will be used to compare the distributions of qualitative variables. To compare baseline data between groups, an unpaired t-test or a Mann–Whitney test will be used.

Shapiro–Wilk and Levene's test will be applied to assess the normality of the distribution and homogeneity of variance of the data, respectively. Mauchly's test of sphericity will be used to validate the correlation of the repeated measures, and if the assumption of sphericity is violated, the Greenhouse–Geisser correction will be applied. The effects of stimulation on VAS, PPTh, PPTo, BPI, dynamometry, HAQ, and SF-36 will be calculated using a mixed analysis of variance (ANOVA) model. If necessary, the use of pain killers or other medication will be adjusted on ANOVA model. The dependent variable will be the score of each outcome, and the independent fixed variables will be the time of treatment (baseline, day 10, first follow-up, and second follow-up), stimulation group (active and sham), and time versus group interaction. When appropriate, post-hoc comparisons will be carried out using Bonferroni correction for multiple comparisons.

For non-parametric data, Friedman test will be used. Missing data will be treated by intention-to-treat analysis, evaluating dropout individuals who did not perform the

entire treatment protocol. Partial η^2 will be calculated as measures of effect size in the ANOVA results (main effects and interaction effects). Partial η^2 will be used to calculate the effect size, where $\eta^2 = 0.01$ will be considered small, $\eta^2 = 0.06$ moderate, and $\eta 2 = 0.14$ large effect. Level significance will be set at p value less than 0.05.

Discussion

Chikungunya is epidemic in Brazil, with significant incidence in the Northeast (the second-highest incidence with 59.4 cases per 100,000 population)[35]. Most of patients present relapsing and remitting chronic arthralgia with debilitating pain lasting for years, but there are no specific therapeutic agents to treat and rehabilitate persons with chronic disease[32]. Persistent pain can lead to incapacitation, requiring long-term pharmacological treatment[8,29]. Advances in non-pharmacological options are necessary to promote pain relief without side effects and to restore functionality. Herein, we propose a trial protocol with tDCS (M1/Sp2 montage) to reduce pain and restore functionality in patients with chronic chikungunya. We will also determine (1) whether the changes induced by anodal tDCS over M1 correlated with the patient's level of pain according to the clinical evaluation scales and (2) if there is a relationship between pain relief and functionality. Absence of robust results would suggest that anodal tDCS over M1 has no effect on pain in chronic arthralgia caused by CHIKV.

It is urgent assess the clinical benefits and harms of interventions to prevent or treat persisting rheumatic disorders in patients with chikungunya[36]. Martí-Carvajal et al. described that only five small trials with high risk of bias were used in a systematic review of interventions for treating patients with chikungunya-related rheumatic and musculoskeletal disorders[8]. The authors suggested the need for more powered randomized clinical trials with high-quality methodology to assess clinical benefits for this population[8].

tDCS is a novel, safe, effective, and low-cost therapeutic approach to the treatment of chronic pain[16,17,31,37–40]. Previous studies have suggested that M1 anodal stimulation may reduce pain by activating various neural circuits present in the precentral gyrus[17]. This area are involved in the sensory and emotional components of pain processing, such as the thalamus or DLPFC, or in facilitating descending pain inhibitory control[17]. Besides this montage, a protocol with an intensity of 2 mA, an electrode size of 35 cm^2, and more than 10 consecutive sessions is commonly recommended to treat chronic pain[16–19]. Two studies have investigated the effect of tDCS on pain and functionality in chronic chikungunya arthralgia[14,15]. In the first study, Silva-Filho et al.[15] conducted five sessions of anodal M1/Sp2 montage, and in the second study, De Sousa et al.[14] applied six alternate sessions with the same tDCS parameters. These studies have suggested significant pain relief, but no significant difference in functional capacity was observed. Authors suggested that the number of sessions or brief period of intervention can be employed to improve functionality[14,15]. With promising preliminary results with tDCS and chronic pain in chikungunya, investigating the long-term effect of tDCS and the most adequate dose for this population is necessary.

Clinical measures of this trial include the standard recommended outcomes, including pain intensity scales validated and universally accepted[41]. Secondary outcomes will be used to add information about pain and its effects on activities of daily living, disability, decrease in medication use, and participant satisfaction. Sociodemographic variables that can influence pain or functionality such as gender, age, income, educational level, and ethnicity will be reported[41]. Grip strength will be evaluated by a hydraulic dynamometer. This test was chosen because joint involvement in chronic chikungunya

arthralgia is predominant in the wrists (66.3%), hands (72%), shoulders (70.1%), and elbows (40%)[32]. Chronic chikungunya arthralgia can compromise the osteo-myo-articular balance of previously susceptible joints[10]. Furthermore, the overuse of the inflamed areas and loss of muscle strength hasten the degenerative process and related pain and stiffness[10].

This protocol has strengths: (1) a novel treatment option for pain will be used in patients with chronic chikungunya arthralgia and (2) the study will be conducted in an epidemic region with a significant number of patients. However, there are some limitations to the study methodology and execution. First, this study did not receive government funding for financial support. Second, recruitment is limited to patients with chronic chikungunya (>3 months) and no patients with acute or sub-acute stage of the disease will be included. Third, no specific questionnaire is used to measure disability or effect of chikungunya on the quality of life or functionality. Thus, questionnaires for other rheumatic diseases and commonly used for chikungunya will be used[14,15,42]. Finally, this is the third trial with tDCS (the first with 10 sessions) in chronic chikungunya arthralgia, and our results will not support definitive conclusions on the efficacy of this neuromodulatory method.

The results of the present study will provide important long-term treatment information about clinical management of tDCS in persisting rheumatic disorders caused by chikungunya. We believe that these results will interest the broad audience committed to improve the quality of life and functionality of patients and to better understand brain modulation on chikungunya arthralgia.

Trial status

Volunteers were not yet being recruited at the time of manuscript submission.

Author's contributors

ASN and AFLC will perform initial and final evaluation, data entry in the database and informed consent of participants. TABA, will perform the tDCS protocol and writing of the manuscript. JDDS and ESF will perform the tDCS protocol. AO will be supported data analysis and writing of the manuscript. LG and RP will perform data management and writing of the manuscript.

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Competing interest

Authors declare no competing interest regarding this trial.

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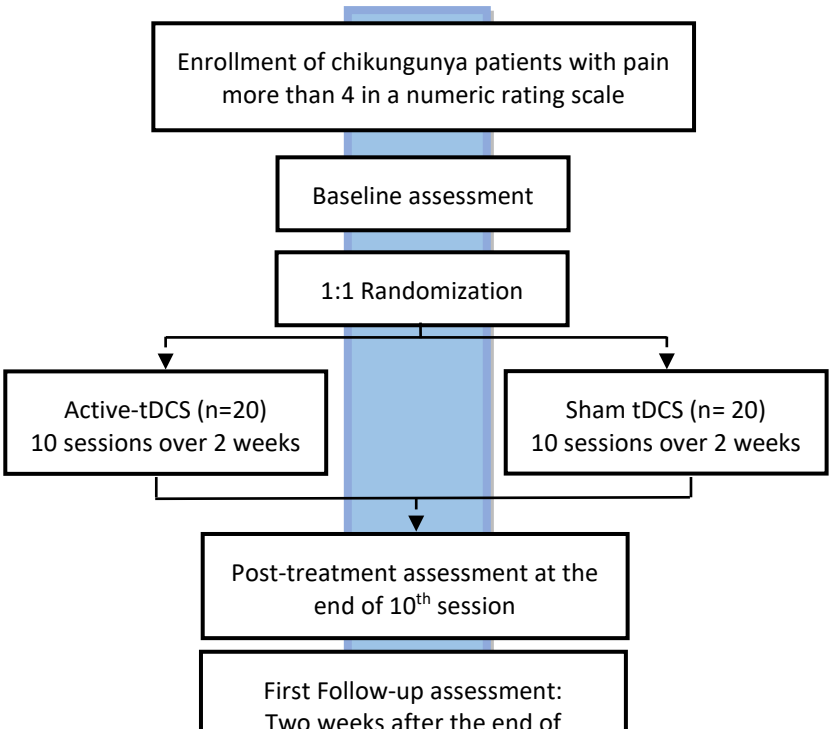
Figure 1. Flowchart summarizing the trial.

Figure 2. Schedule of enrollment, interventions, and assessments. VAS – Visual Analog Scale, BPI - Brief Pain Inventory (Short Form), HAQ - The Health Assessment Questionnaire, SF-36 - Short Form Health Survey.



	Study Period						
	Enrolment	Allocation	Post-allocation			1º Follow-up	2º Follow-up
TIMEPOINT	Week 1	Week 2 Baseline	Intervention			Week 6	Week 8
			Week 3	Week 4	Last day of tDCS protocol		
ENROLMENT	X						
Eligibility screen	X						
Informed consent	X						
Sociodemographic characteristics	X						
Allocation		X					
INTERVENTIONS							
Active tDCS			◆	—	◆		
Sham tDCS			◆	—	◆		
ASSESSMENTS							
VAS		X			X	X	X
Pressure pain threshold		X			X	X	X
Pressure pain tolerance		X			X	X	X
BPI		X			X	X	X
Dynamometry		X			X	X	X
HAQ		X			X	X	X
SF-36							
Medication use		X			X	X	X
Adverse events					X	X	X
Success of blinding							X

UNIVERSIDADE FEDERAL DO RIO GRANDE DO NORTE
FACULDADE DE CIÊNCIAS DA SAÚDE DO TRAIRÍ

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO - TCLE

Esclarecimentos.

Você está sendo convidado a participar de um estudo denominado "**Estimulação transcraniana por corrente contínua (ETCC) e seus efeitos terapêuticos na febre chikungunya: FASE 2**" projeto de pesquisa, a ser realizado na Faculdade de Ciências da Saúde do Trairí Santa Cruz/RN e que tem como pesquisador responsável o professor Rodrigo Pegado de Abreu Freitas (Fisioterapeuta – CREFITO 99038-F).

Essa pesquisa tem como objeto avaliar a aplicação de um pequeno estímulo elétrico na cabeça realizado por um aparelho da fisioterapia para diminuir a dor que você sente por causa da chikungunya e melhorar a sua condição física. Esse estímulo elétrico é tão pequeno que não é percebido pela pessoa ou se sente um pequeno formigamento. A justificativa que nos leva a fazer este estudo é que se tem observado que a aplicação desse aparelho de pequeno estímulo elétrico leva a melhora da dor em muitas doenças, com isso gostaríamos de avaliar se na sua condição também há melhora. É uma terapia sem custo, de fácil aplicação, rápida, onde você não sente nada durante a terapia e os resultados parecem ser bem positivos, melhorando o seu bem-estar.

Sua participação no referido estudo será no sentido de realizar os seguintes procedimentos: uma avaliação inicial através de 3 questionários de avaliação sobre sua dor e sua qualidade de vida. Haverá também testes físicos como andar por 6 minutos e puxar um peso para saber sua força muscular. A avaliação da dor será feita através de um aparelho onde se aperta contra a pele até você começar a sentir dor e falar para parar. Você fará durante 10 dias (2 semanas de segunda a sexta) uma aplicação de um tipo de corrente elétrica muito baixa chamada microcorrente, que será aplicado no couro cabeludo através de borrachas pregadas na cabeça. Cada dia terá 20 minutos de tratamento. O risco que você possuirá ao participar é semelhante àquele sentido num exame físico ou psicológico de rotina. Essa terapia é utilizada mundialmente e bastante segura. Durante a aplicação não há sensação nenhuma, mas algumas pessoas podem relatar uma sensação de coceira, formigamento ou dor de cabeça.

Você foi avisado de que, da pesquisa a se realizar, pode esperar alguns benefícios, tais como: avaliação da fisioterapia e em caso de necessidade será encaminhado para tratamento fisioterapêutico na Clínica Escola da UFRN/FACISA; você será beneficiado pela aplicação de um tratamento seguro, rápido e sem custo, que apresenta bons resultados na melhora da dor crônica e da função física, melhorando a sua qualidade de vida.

Por outro lado, você recebeu os esclarecimentos necessários sobre os possíveis desconfortos e riscos decorrentes do estudo, levando-se em conta que é uma pesquisa, e os resultados positivos ou negativos somente serão obtidos após a sua realização. Assim, o risco envolvido com sua participação poderá ser de algum tipo de constrangimento pessoal durante os exames físicos e resposta aos questionários, que poderá ser interrompido por você a qualquer momento. Há também o risco de desconforto físico como fadiga muscular, câimbras, sensação de peso e cansaço

_____ (Rubrica do Participante) _____ (Rubrica do Pesquisador)

Rua Vila Trairi, S/N, Bloco B, 2º andar Centro, Santa Cruz-RN – 59 200-000. Telefone: (84) 9 9915-0043, funcionamento das 8:00 as 18:00 horas. COMITÊ DE ÉTICA EM PESQUISA – CEP
Rua Vila Trairi, S/N, Bloco B, 1º andar Centro, Santa Cruz-RN – 59 200-000
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durante a aplicação dos testes físicos. Na aplicação da terapia de microcorrente há o risco de você sentir algum tipo de alteração da sensibilidade do local de aplicação, sensação de esquentar (porém sem alteração de temperatura, apenas a sensação), sensação de coceira e desconforto (na maioria das vezes atribuído a fita que segura o eletrodo no couro cabeludo) ou sensação de formigamento durante a aplicação da terapia. No exame para avaliar a dor, há o risco de o local de avaliação ficar dolorido devido a pressão que o aparelho faz na pele, mas nesse teste você diz o momento que quer parar. O riscos apresentados serão minimizados com a sua preparação correta antes de realizar os testes, além disso, tudo será aplicado por fisioterapeuta treinado e em ambiente seguro e próximo a infraestrutura hospitalar. Podemos colocar gelo após os testes físicos em algum local do corpo que você tenha sentido dor. Todos os testes físicos que serão feitos por você é recomendado para se avaliar o paciente com chikungunya de acordo com o Ministério da Saúde e estudos em diversos países.

Em caso de algum problema que você venha ter, relacionado com a pesquisa, você terá o direito a assistência gratuita que será prestada pelo pesquisador responsável.

Durante todo o período da pesquisa você poderá tirar suas dúvidas ligando para o professor coordenador da pesquisa, Rodrigo Pegado pelo telefone 99915-0043.

Você terá a liberdade de se recusar a participar ou retirar seu consentimento, em qualquer fase da pesquisa, sem nenhum prejuízo para você.

Os dados que você irá fornecer serão confidenciais e serão divulgados apenas em congressos ou publicações científicas, não havendo divulgação para terceiros e de nenhum dado que possa lhe identificar. Esses dados serão guardados pelo pesquisador responsável por essa pesquisa em local seguro e por um período de 5 anos na Faculdade de Ciências da Saúde do Trairí/UFRN.

Se você tiver algum gasto pela sua participação nessa pesquisa, como transporte ou alimentação, ele será assumido pelo pesquisador e reembolsado para você. Se você sofrer algum dano decorrente desta pesquisa, você tem direito a solicitar indenização.

A qualquer momento você tem o direito de retirar seus dados e material do local de armazenamento e, caso haja possibilidade de serem usados em futuros projetos de pesquisa, antes, deverá ser feito o contato com você para que possa ser concedida, ou não, uma nova autorização do uso do material. Esta possibilidade só existe se um novo projeto for aprovado pelo comitê de ética em pesquisa (CEP). Todos os resultados advindos dos seus dados serão postos à sua disposição pelo pesquisador, com opção pessoal de tomar ou não conhecimento dessas informações e de suas implicações para sua saúde.

Qualquer dúvida sobre a ética dessa pesquisa você deverá ligar para o Comitê de Ética em Pesquisa da Faculdade de Ciências da Saúde do Trairi (FACISA), telefone 99224-0009 ou mandar e-mail para cepfacisa@gmail.com ou cep@facisa.ufrn.br. O Comitê de Ética em Pesquisa - CEP da FACULDADE DE CIÊNCIAS DA SAÚDE DO TRAIRI - FACISA é um órgão Colegiado interdisciplinar e independente, constituído nos termos da Resolução no 466/2012 do Conselho Nacional de Saúde – CNS, e criado para defender os interesses dos participantes de pesquisas em sua integridade e dignidade.

_____ (Rubrica do Participante) _____ (Rubrica do Pesquisador)

Rua Vila Trairi, S/N, Bloco B, 2º andar Centro, Santa Cruz-RN – 59 200-000. Telefone: (84) 9 9915-0043, funcionamento das 8:00 as 18:00 horas. COMITÊ DE ÉTICA EM PESQUISA – CEP
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Este documento foi impresso em duas vias. Uma ficará com você e a outra com o pesquisador responsável, Rodrigo Pegado de Abreu Freitas, e as duas vias do TCLE devem ser rubricadas em todas as suas páginas.

Consentimento Livre e Esclarecido

Após ter sido esclarecido sobre os objetivos, importância e o modo como os dados serão coletados nessa pesquisa, além de conhecer os riscos, desconfortos e benefícios que ela trará para mim e ter ficado ciente de todos os meus direitos, concordo em participar da pesquisa "**Estimulação transcraniana por corrente contínua (ETCC) e seus efeitos terapêuticos na febre chikungunya: Fase 2**" e autorizo a divulgação das informações por mim fornecidas em congressos e/ou publicações científicas desde que nenhum dado possa me identificar.

_____

Participante

Impressão Dactiloscópica

_____

Pesquisador responsável

Endereço Profissional: Faculdade de Ciências da Saúde do Trairí – Santa Cruz – RN. Rua Trairí s/n Centro. A qualquer momento as participantes podem entrar em contato comigo pelo telefone 99915-0043.

Santa Cruz, ____ de _____ de _____.

Rua Vila Trairi, S/N, Bloco B, 2º andar Centro, Santa Cruz-RN – 59 200-000. Telefone: (84) 9 9915-0043, funcionamento das 8:00 as 18:00 horas. COMITÊ DE ÉTICA EM PESQUISA – CEP
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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	3
Protocol version	3	Date and version identifier	3
Funding	4	Sources and types of financial, material, and other support	12
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	12
	5b	Name and contact information for the trial sponsor	-
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	12
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	-

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2
	6b	Explanation for choice of comparators	5,6
Objectives	7	Specific objectives or hypotheses	3
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	3
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	3,4
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	3,4,5
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	6
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	6
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	4
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	5,6
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	3

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	67
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	3
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	3
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	3
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	3
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	3
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	4,5
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	6

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	6
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	7
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	-
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	7
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	-
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	6
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	6
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	-
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	-
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	2

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	3,4
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	-
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	6
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	12
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	6
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	-
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	6
	31b	Authorship eligibility guidelines and any intended use of professional writers	12
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	-
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	-
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	-

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Transcranial direct current stimulation for chronic chikungunya arthralgia: study protocol for a randomized clinical trial
Trial registration	2a	This trial is registered in the Brazilian Registry of Clinical Trials (ReBEC) under the identifier RBR-469yd6 (Date of registration: 25/06/2018).
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	11/05/2022, last approval, version 2.
Funding	4	This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. Abraão Sérvulo do Nascimento was partly financed by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES). Finance Code 001.
Roles and responsibilities	5a	Authors: Abraão Sérvulo do Nascimento, Antônio Felipe Lopes Cavalcante, João Danyell Dantas da Silva, Edson Silva-Filho, Alexandre Okano, Lucien Peroni Gualdi, Rodrigo Pegado.
	5b	Name and contact information for the trial sponsor The study has no sponsor.
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities: *The study has no specific sponsor and fund from any public or private agency. Abraão Sérvulo do Nascimento was partially financed by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES). Finance Code 001, however, the national public agency has no authority over the protocol activities.*
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) The protocol will be performed in a single center coordinated by Professor Rodrigo Pegado. All research previously described will be responsible for the study performance in specific tasks. Abraão Sérvulo do Nascimento and Antônio Felipe Lopes Cavalcante will perform initial and final evaluation, data entry in the database and informed consent of participants. João Danyell Dantas da Silva and Edson Silva-Filho will perform the tDCS protocol. Alexandre Okano will be supported data analysis and writing of the manuscript. Data management and writing of the manuscript will be performed by Lucien Gualdi and Rodrigo Pegado. No other individual or group will be allowed to see data without the study's coordinator permission.

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention: Brazil has been a protagonist in cases of Chikungunya virus (CHIKV) in Americans. Up to 50%–60% of CHIKV infected individuals may evolve into chronic phase that begins when clinical symptoms persist for more than 3 months. There are no specific therapeutic agents to treat and rehabilitee individuals in chronic phase of CHIKV and persistent pain may lead to incapacitation and requirement of long-term pharmacological treatment. Previously studies supported the use of anodal transcranial direct current stimulation (tDCS) over M1 (M1-SO montage) aiming to reduce pain. These studies were the initial investigation of M1 anodal tDCS, but further work to optimize the stimulation parameters is needed to clarify long-term efficacy on pain and functionality in chronic CHIKV arthralgia.
	6b	Explanation for choice of comparators Approximately 50% of patients have chronic arthralgia (chronic phase) for up to 6 years. This phase accounts for a high rate of persistent and incapacitating polyarthralgia, resulting in a reduction of functionality and quality of life. Pain is considered the most important symptom in chronic phase of CHIKV and showed strong association with reduction in daily activities and physical function.
Objectives	7	The primary objective of this protocol is to measure the effect of tDCS on pain. The secondary objective is to assess muscle strength, functionality, and quality of life. The duration and extent of effects of tDCS (long-term effect) will be also investigated. The study hypothesis is that the tDCS protocol will show improvement in pain, muscle strength, functionality, and quality of life when compared with sham tDCS.
Trial design	8	This is a protocol study of a single-center, double-blind, parallel, sham-controlled, randomized clinical trial with two groups and a 1: 1 allocation ratio.

Methods: Participants, interventions, and outcomes

Study setting	9	All procedures will be performed at the Physical Therapy Outpatient Clinic of Faculdade de Ciências da Saúde do Trairi/Universidade Federal do Rio Grande do Norte located in the city of Santa Cruz/ Rio Grande do Norte in Brazil.
Eligibility criteria	10	Adults from local communities of the Northeast region of Brazil will be recruited voluntarily through advertisements in electronic media and by health professionals from the communities. The inclusion criteria were as follows: men and women aged ≥18 years with positive laboratory or clinical diagnosis of chronic chikungunya (at least 3 months from the initial infection); moderate to severe (above 4) pain according to a numeric rating scale (NRS) and can tolerate physical evaluation; and satisfactory cognitive function to understand and sign the informed consent and study explanations and questionnaires. The exclusion were as follows: individuals with electrical implants in the body, history of epilepsy, metallic device implanted in the head, history of drug abuse, pregnancy, signs of severity and/or indication of hospitalization, and history of rheumatic diseases including gout, rheumatoid arthritis, fibromyalgia, lupus, and other chronic pain syndromes diagnosed prior to chikungunya.

Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered: The treatment will consist of 2 weeks intervention divided in 10 sessions of 20 minutes (one per weekday). Both groups AG and SG will be treated by a trained physical therapist at the Physical Therapy Outpatient Clinic of Federal University of Rio Grande do Norte. A monophasic continuous current with an intensity of 2 mA for 20 min will be used. All patients will be awake and sited in a comfortable chair with back and arm support during the tDCS/sham intervention. All tDCS procedures will be conducted in a temperature and noise-controlled room. tDCS will be delivered using the anode electrode positioned over the left primary motor cortex (C3) and the cathode electrode at the contralateral supra orbital region (Fp2), according to international standards for EEG 10–20 system (the “M1-SO” assembly). The electrodes will be placed into a 35 cm^2 square sponge immersed in saline solution (154 mM NaCl, approximately 12 mL per sponge). For stimulation, a current ramp-up and ramp-down with 30s duration will be used. Electrodes attached to the scalp will be supported by an elastic band. The electrodes (anode and cathode) will be connected to a battery (9 v) powered stimulator with current verified by a precision digital multimeter (DT832, WeiHua Electronic Co., Ltd, China) with standard error of ±1.5%. For the SG it will be used a ramp-up of 30 seconds and a ramp-down of 30 seconds. The device displays are identical in active and sham settings. To guarantee the success of blindness, participants and outcome assessors at the end point will be asked to guess whether the treatment was active or false.
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease). Participants who miss two tDCS sessions will be excluded from the study. Allergic skin reactions have been observed in rare cases. If this is suspected tDCS protocol will be stopped. This should be reported as an adverse event. The use of conventional tDCS protocols in human trials (20min, 2mA and 10 sessions) has not produced any reports of a serious adverse effect or irreversible injury. Adverse events will be carefully monitored during all steps of the study. The most reported adverse events included the sensation of itching and tingling under the electrode sites, reported in both active and sham conditions. Participants will receive care as appropriate for any harm that arises as a result of study participation. At the end of the study, the results will be informed to the participants in the form of a lecture, showing the results obtained. If the positive effects of tDCS on the researched outcomes are found, the application of tDCS will be offered and guaranteed to all participants in the sham group.
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests). Adherence to treatment will be encouraged with daily messages sent by smartphone, advising on the benefits of the study and scheduling times that do not interfere with the participant's daily activities.

	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial For ethical reasons, no intervention will be performed in clinical care and previous prescription of painkillers or others medication. If a participant begins medication during the study, it will be documented, but the participant will not be excluded. Participants are encouraged to maintain their normal activity routine.
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended. Primary outcomes: Participants will be assessed using a numeric rating scale (NRS) for pain. The NRS is a segmented numeric version of the visual analogue scale (VAS) in which the participant selects a whole number (0–10 integers) that best reflects the intensity of its pain (0 representing “no pain” and 10 representing the “pain as bad as you can imagine”. Algometry will be carried out to record Pressure Pain Threshold (PPTh) and Pressure Pain Tolerance (PPTo). Pain PPTh and PPTo will be assessed in 8 different anatomical locations: trapezius: at the midpoint of the upper edge; lumbar spine: performed over the erector muscle; lateral epicondyle; knee, over the fatty cushion; and between the index finger and the thumb on the dorsal side of the hand. Pain threshold and tolerance to pressure will be quantified in kg/cm^2. Secondary outcomes: The Brief Pain Inventory (BPI) will be used to assess the severity and impact of pain in daily living activities. It is a questionnaire that presents 15 items, including 2 multi-item scales to measure pain and its impact on functionality and well-being. The DN4 questionnaire will be performed to evaluate neuropathic pain. The presence of neuropathic pain will be considered to be a dependent variable and will need to reach a score of at least 4 out of 10, while non-neuropathic pain will be considered scores of less than 4 out of 10. The health assessment questionnaire (HAQ) will be used to access functionality. Rising, dressing, eating, walking, bathing, reaching, gripping, and performing errands will be assessed on a scale range from 0 to 3. The average of all scores will be considered to classify disability as 0 = no difficulty, 0-1 = mild disability, 1-1.5 = moderate disability, and >1.5 = severe disability. The grip strength will be evaluated by a hydraulic dynamometer in kilogram-force. Three evaluations will be performed with an interval of 1 min between them. For statistical analysis, results will be obtained by arithmetic mean of these three measurements.
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure). Flowchart summarizing the trial was added in the manuscript.
Sample size	14	The sample size was calculated based on statistical considerations for a parallel trial and on a previous study by Silva-Filho et al15. The sample size was estimated using G-Power 3.1.9.2 based on the assumption of significance of 0.05, power of 80%, with 0.3 effect size, and two groups. According to this methodology, the sample should include 32 participants. Considering a 20% loss to follow-up and 5% missing data, the number of participants will be increased by 25%, which corresponds to eight participants. Thus, 40 participants will be recruited and allocated in the two groups, with 20 participants each.
Recruitment	15	Subjects will be recruited at the patients waiting list of the Physical Therapy Outpatient Clinic of Santa Cruz/RN- Brazil. Advertisements about the study will be placed in social media aimed to inform and invite the population.

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Randomization will be carried out through a numerical sequence generated by an allocated computer using appropriate software (www.random.org) to assign each participant to either the active or sham group. An external research assistant will generate the allocation sequence and contact participants by telephone.
Allocation concealment mechanism	16b	Allocation concealment will be performed using opaque envelopes. Participants and researchers involved in the assessments and interventions will be blinded to group allocation throughout the trial.
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions. The allocation sequence will be performed for Abraão Sérvulo do Nascimento and Antônio Felipe Lopes Cavalcante will enroll participants. João Danyell Dantas da Silva and Edson Silva-Filho will assign participants to interventions.
Blinding (masking)	17a	In this clinical trial, both the participants and evaluators will be blinded. Moreover, to ensure that the participant is also blinded to the allocation group, electrodes will be placed in the same position as in the active group, but the stimulator delivered 2 mA of current for only 30 s, with the same ramp-up and ramp-down period of 10 s. Sham tDCS will consist of delivering an active stimulation for a few seconds to mimic the sensations (itching and tingling) observed during active tDCS. This is considered a valid methodology for clinical protocols with good effectiveness of blinding.
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial Unblinding will not be allowed, and the evaluator will have no access to the allocation group until the end of the study.

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol Before starting the trial, a series of training steps for evaluations and application of the tDCS will be carried out, aimed at recording activities carried out in the study. Techniques and measures will be improved at this stage of the training to reach a consensus among the researchers. tDCS will be performed by a physical therapist with previously expertise in clinical trials and background in non-invasive brain stimulation. Assessment will be performed in the morning in a temperature-controlled room without noise or another distractor. NRS, PPTh, PPTo , BPI, DN4 questionnaire , HAQ and grip strength are commonly used in clinical trails aim to assess pain and functionality. All questionnaires are validated and translated for the Brazilian population. The researcher will ask to the participant questions described in the questionnaires, and according to the answers obtained, the researcher will fill in the questionnaire. All questions can be repeated if the question is not understood.

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols The trial will be performed in a small city with easy and free cost transportation to the local of the study. If necessary, the research will develop strategies to transport this individuals to the study setting. The participant will be informed of the benefits of the research and, if necessary, will be referred for physical therapy treatment at the University's Rehabilitation Clinic.
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol Data will be stored at the principal investigator computer and double entry will be performed by two study researchers. Data access will be limited to the study researchers and any other access must be authorized by the coordinator.
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol Statistical analyses will be conducted using the SPSS software version 19.0 (IBM Corp., Armonk, NY, USA). Clinical and sociodemographic characteristics will be described by means, medians, and standard deviations for continuous numeric parameters and by frequency tables with 95% confidence intervals for qualitative parameters. A chi-squared test or Fisher's exact chi-squared test will be used to compare the distributions of qualitative variables. To compare baseline data between groups, an unpaired t-test or a Mann–Whitney test will be used. Shapiro–Wilk and Levene's test will be applied to assess the normality of the distribution and homogeneity of variance of the data, respectively. Mauchly's test of sphericity will be used to validate the correlation of the repeated measures, and if the assumption of sphericity is violated, the Greenhouse–Geisser correction will be applied. The effects of stimulation on NRS, PPTh, PPTo, BPI, DN4, HAQ, and dynamometry will be calculated using a mixed analysis of variance (ANOVA) model. The dependent variable will be the score of each outcome, and the independent fixed variables will be the time of treatment (baseline, day 10, first follow-up, and second follow-up), stimulation group (active and sham), and time versus group interaction. When appropriate, post-hoc comparisons will be carried out using Bonferroni correction for multiple comparisons. For non-parametric data, Friedman test will be used. Missing data will be treated by intention-to-treat analysis, evaluating dropout individuals who did not perform the entire treatment protocol. Partial η2 will be calculated as measures of effect size in the ANOVA results (main effects and interaction effects). Partial η2 will be used to calculate the effect size, where η2 = 0.01 will be considered small, η2 = 0.06 moderate, and η2 = 0.14 large effect. Level significance will be set at p value less than 0.05.
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) The study has no additional analyses planned.
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) Missing data will be treated by intention-to-treat analysis, evaluating dropout individuals who did not perform the entire treatment protocol. Partial η2 will be calculated as measures of effect size in the ANOVA results (main effects and interaction effects). Partial η2 will be used to calculate the effect size, where η2 = 0.01 will be considered small, η2 = 0.06 moderate, and η2 = 0.14 large effect. Level significance will be set at p value less than 0.05.

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed Data will be monitored by the study coordinator and posteriorly accessed by all researchers previously authorized to access data. There will not be an independent database as the study has no sponsor.
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial Trial will follow the guidelines and good practices for managing and reopening non-invasive brain stimulation (NIBS) clinics and laboratories through the immediate and ongoing stages of COVID-19 according to Bikson et al. 2020 (DOI: 10.1016/j.brs.2020.05.010). Final decision will be made by principal investigator.
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct Any adverse effect that occurs during the protocol performance will be reported on the follow-up guide and the information will be referred to the patients' physician.
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor There will be no audit in this study.
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval The study was previously approved by the ethics committee of the Faculty of Health Sciences of Trairí – Federal University of Rio Grande do Norte (No. 2.413.851). Results will be presented in peer-reviewed journals and international conferences.
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators). All protocol modifications will be informed to ethics committee of the Faculty of Health Sciences of Trairí – Federal University of Rio Grande do Norte (No. 2.413.851). After evaluation and approval, the researchers will inform for all participants.
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) Abraão Sérvulo do Nascimento and Antônio Felipe Lopes Cavalcante will obtain informed consent or assent for all participants. Potentially eligible patients with chronic of chikungunya will receive a detailed explanation of the study from the study research coordinator. Interested participants will be asked to sign the informed consent form before enrollment into the study.
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable Not applicable.

Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial The data will be confidential and will be disclosed only in conferences or scientific publications, with no disclosure to third parties and no data that could identify the participants. These data will be kept by the principal researcher in a safe place and for a period of 5 years at the Faculty of Health Sciences of Trairí/UFRN according to Resolution Nº. 466/12 of the National Health Council.
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site Authors declare no competing interests.
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators All data will be available for research time directly upon reasonable request to principal investigator. After the publication of the clinical trial, data will be available to any reader directly upon reasonable request to principal investigator, respecting the privacy and confidentiality of research participants.
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation According to Resolution No. 466/12 of the National Health Council, the investigators are responsible to any compensation to trial participation.
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions After the and of the study, investigators will perform a Symposium to publisher the trial results and all participants and scientific community will be invited. There are no publication restrictions in this trial.
	31b	Authorship eligibility guidelines and any intended use of professional writers There are no intended to use professional writers. All authors are previously described, and the eligibility will follow the ICMJE recommendations to best practice and ethical standards in the conduct and reporting of research.
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code Publication of this protocol in an open-access journal. All data will be available directly upon reasonable request to principal investigator
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates The consent form model followed the Brazilian model for informed consent and was approved by the responsible ethics committee.
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable Not apllicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Ten sessions of transcranial direct current stimulation for chronic chikungunya arthralgia: study protocol for a randomized clinical trial

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Ten sessions of transcranial direct current stimulation for chronic chikungunya arthralgia: study protocol for a randomized clinical trial

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Abstract

Introduction: The chikungunya virus infection is still an epidemic in Brazil with an incidence of 59.4 cases per 100,000 in the Northeast region. More than 60% of the patients present relapsing and remitting chronic arthralgia with debilitating pain lasting for years. Transcranial direct current stimulation (tDCS) appears promising as a novel neuromodulation approach for pain-related networks to alleviate pain in several pain syndromes. Our objective is to evaluate the effectiveness of tDCS (C3/Fp2 montage) on pain, muscle strength, functionality, and quality of life in chronic arthralgia.
Methods and analysis: This protocol is a single-center, parallel-design, double-blind, randomized, sham-controlled trial. Forty participants will be randomized to either an active or sham tDCS. A total of 10 sessions will be administered over 2 weeks (one per weekday) using a monophasic continuous current with an intensity of 2 mA for 20 min. Participants will be evaluated at baseline, after the 10th session, 2 weeks, and 4 weeks after intervention. Primary outcome: pain assessed using numeric rating scale and algometry. Secondary outcomes: muscle strength, functionality, and quality of life. The effects of stimulation will be calculated using a mixed analysis of variance (ANOVA) model.
Ethics and dissemination: The study was approved by the ethics committee of the Faculty of Health Sciences of Trairí, Federal University of Rio Grande do Norte (No. 2.413.851) and registered on the Brazilian Registry of Clinical Trials (identifier RBR-469YD6). Study results will be disseminated through presentations at conferences and publications in peer-reviewed journals.

Strengths and limitations of this study

- The trial will be performed in an endemic area with lack of resources for chronic chikungunya arthralgia treatment.
- This is a low cost, safe, and mobile intervention that may be implemented in clinical practice for a neglected tropical disease.
- The trial will include participants with chronic pain without any previous treatment for a cost-effectiveness evaluation and quantitative data collection.
- The trial will not include laboratorial, image or electrophysiological data regarding brain modulation or maintenance of pain state after tDCS protocol.

Introduction

In the last 8 years, Brazil has been a protagonist in infection caused by chikungunya virus (CHIKV) in America[1]. The spread of the disease in South America is critical and out of control, mainly in Brazil that represents 94% of confirmed chikungunya cases[2,3]. Until 2021, the Brazilian Ministry of Health continues to monitor the occurrence of chikungunya, and from December 2019 to April 2020, 17,636 chikungunya cases were recorded[1]. The re-emergence of chikungunya has become an increasing medical and economic problem in endemic areas[4]. The acute phase (<7 days) of chikungunya fever is usually characterized by sudden high fever, polyarthritis, tenderness, headache, myalgia, maculopapular rash and vomiting[5,6].

Chikungunya fever presents as a chronic public health problem and could overtake the capacity of health care systems and rehabilitation centers because most cases are commonly followed by persistent chronic arthralgia lasting for years[7]. Up to 50%–60% of chikungunya cases may progress to the chronic phase that begins when clinical symptoms persist for more than 3 months[8,9]. No specific therapeutic agents can be used to treat and rehabilitate individuals with chronic chikungunya and persistent pain may lead to incapacitation and require long-term pharmacological treatment[10]. Chronic pain is associated with development of adaptive neuroplasticity and functional reorganization that could result in physical and behavioral impairment[11]. Pain has a multidimensional phenomenon that involve sensorial, emotional, motor and autonomic mechanisms associated with different brain areas connected in a large network named by Melzak as pain neuromatrix (PNM)[12]. The activation of the primary (S1) and secondary (S2) somatosensory cortices, primary motor cortex (M1), dorsolateral prefrontal cortex (DLPFC), thalamus, insula, and anterior cingulate cortex are involved in pain processing[12]. The M1 has been the primary target for the study of pain modulation and clinical intervention of chronic pain conditions including rheumatic diseases[13].

The use of transcranial direct current stimulation (tDCS) on pain and other clinical outcomes have been published with significant improvement[14–17]. Previous studies have supported the use of anodal tDCS over M1 (M1-SO montage) to reduce pain in osteoarthritis[18], post-stroke pain syndrome[17], back pain[18], fibromyalgia[13], and recently chikungunya[14,15]. In this context, tDCS promotes M1 activation, providing secondary modulatory effects on the PNM circuit that is associated with nociceptive modulation[19]. The first study on CHIKV and neuromodulation suggested pain improvement after five consecutive sessions of tDCS[15]. The second study evaluated six nonconsecutive sessions of anodal tDCS on M1 and showed significant reduction on pain[14]. These studies were the initial investigations of tDCS, but further work to optimize the stimulation parameters is needed to clarify long-term efficacy on pain and functionality in chronic chikungunya arthralgia[14,15]. It is important to consider that the intensity, time of application and number of session have significant influence in neurophysiology and clinical responses including therapeutic efficacy[17]. The number of sessions is associated with the time of duration of neuromodulation and ten sessions could provide a long-term neuromodulation effect and produce a sustained effect on pain and other symptoms[18].

Furthermore, tDCS could be a non-invasive, low-cost, safe, and accessible treatment option to CHIKV-endemic areas[15]. Herein, we present the methodology of a randomized double-blinded controlled study to evaluate the feasibility of a trial protocol for 10 consecutive sessions of tDCS in chronic chikungunya arthralgia. The primary objective of this protocol is to measure the effect of tDCS on pain. The secondary objective is to assess pain threshold and tolerance, muscle strength, functionality, and quality of life. The duration and extent of effects of tDCS (long-term effect) will be also investigated. The study hypothesis is that the tDCS protocol will show improvement in pain, muscle strength, functionality, and quality of life when compared with sham tDCS.

Methods and design

Study design

This is a protocol study of a single-center, double-blind, parallel, sham-controlled, randomized clinical trial with two groups and a 1: 1 allocation ratio. A total of 10 sessions of 20 min will be administered over a period of 2 weeks. Outcomes will be measured at baseline (1 week before intervention), immediately after day 10 of intervention, and at 2

and 4 weeks after the end of the treatment as follow-up (Figure 1). The Standard Protocol Items: Recommendations for International Trials statement (SPIRIT) 2013 and the Template for Intervention Description and Replication checklist[20] was followed to better describe the clinical trial.

This trial is registered on the Brazilian Registry of Clinical Trials (ReBEC) under the identifier RBR-469YD6. Participation is voluntary as determined by Resolution No. 466/12 of the National Health Council. Potentially eligible patients with chronic of chikungunya will receive a detailed explanation of the study from the study research coordinator. Interested participants will be informed about the methods of the study that include aims, allocation to sham or active group, evaluation procedures and timeline of intervention. All participants need to sing the Informed Consent Form (Supplementary File) before starting the study. The Informed Consent Form was submitted and approved by the ethics committee of the Faculty of Health Sciences of Trairí – Federal University of Rio Grande do Norte (UFRN) (No. 2.413.851).

Participants and Chikungunya diagnosis

Participants with previous serologic confirmation of CHIKV infection[21] based on immunoglobulin (Ig) G and IgM detected by direct enzyme-linked immunosorbent assay/IgM/Euroimmun, according to the Central Laboratory (LACEN, Brazil) or on initial clinical symptoms (in the context of the epidemic) including at least fever and arthralgia who meet the eligibility criteria will be invited to participate in the study[21].

Trial design

The study will start in August 2022 and is expected to be completed in August 2023. After the initial assessment, participants will be randomly allocated into two evaluator/participant blinded groups: active group and sham group.

Participants of both groups will undergo a 2-week protocol (5 sessions per week) of active or sham tDCS. Sessions will be performed for 20 min by the same trained physical therapist. Two follow-ups will be performed after 2 and 4 weeks at the end of tDCS protocol by the same evaluator blinded for the allocation group. The schedule of enrollment, interventions, and assessments is demonstrated in figure 2.

All assessments and intervention procedures will be performed at the Physical Therapy Outpatient Clinic of Faculty of Healthy Science of Trairí, Federal University of Rio Grande do Norte, Santa Cruz, Brazil.

Four researchers will be involved in this clinical trial: one researcher for the evaluation procedures, one for the tDCS application, one for the randomization of participants, and one for statistical analysis. Before starting the trial, all researchers will be trained for evaluations and application of the tDCS.

Recruitment and eligibility criteria

Adults from local communities of the Northeast region of Brazil will be recruited voluntarily through advertisements in electronic media and by health professionals from the communities.

Eligibility criteria for participation in the study are: men and women aged ≥18 years with positive laboratory or clinical diagnosis of chronic chikungunya (at least 3 months from the initial infection); moderate to severe (above 4) pain according to a numeric rating scale (NRS); tolerate physical evaluation; satisfactory cognitive function

to understand and sign the informed consent, study explanations and questionnaires. The exclusion criteria adopted are: individuals with electrical implants in the body, history of epilepsy, metallic device implanted in the head, history of drug abuse, pregnancy, signs of severity and/or indication of hospitalization, previously diagnosis of mental disorder and history of rheumatic diseases including gout, rheumatoid arthritis, fibromyalgia, lupus, and other chronic pain syndromes diagnosed prior to chikungunya.

Randomization

Patients will be enrolled by the investigators and randomly allocated (1:1) to receive active tDCS or sham. Stratified randomization will be performed using the order of entry into the study. To prevent imbalance between treatment groups, patients will be plotted according to gender (male and female) and age (under 20 years, 20–64 years, and 65 years and older). Randomization will be applied to each stratum using appropriate software (www.random.org) to assign each participant to either the active or sham group. An external research assistant will generate the allocation sequence and contact participants by telephone call. Allocation concealment will be performed using opaque envelopes. Participants will be blinded to group allocation throughout the trial.

Blinding

In this clinical trial, participants and evaluators will be blinded for allocation group. Moreover, to ensure that the participant is also blinded to the allocation group, electrodes will be placed in the same position as in the active group, but the stimulator delivered 2 mA of current with the same ramp-up and ramp-down period of 30 s [15,22]. Sham tDCS will consist of delivering an active stimulation for a few seconds to mimic the sensations (itching and tingling) observed during active tDCS[23]. This is considered a valid methodology for clinical protocols with good effectiveness of blinding[14,15,23–25]. The tDCS device does not allow a blinded model for the researchers involved in the interventions.

Intervention

The treatment will consist of 2 weeks of intervention divided into 10 sessions of 20 min each (one per weekday) using a monophasic continuous current with an intensity of 2 mA. The active and sham groups will be treated by a trained physical therapist at the Physical Therapy Outpatient Clinic of Federal University of Rio Grande do Norte. All patients will be awake and seated in a comfortable chair with back and arm support during tDCS and sham intervention. All tDCS procedures will be conducted in a temperature and noise-controlled room.

tDCS will be delivered using the anode electrode positioned over the left primary motor cortex (C3) and the cathode electrode at the contralateral supraorbital region (Fp2), according to international standards for EEG 10–20 system. The electrodes will be placed into a 35 cm^2 sponge immersed in saline solution (154 mM NaCl, approximately 12 mL per sponge). For stimulation, current ramp-up and ramp-down with 30-s duration will be employed. Electrodes attached to the scalp will be supported by an elastic band. The electrodes (anode and cathode) will be connected to a stimulator MicroEstim Genius (NKL, Santa Catarina, Brazil). Device displays are identical in the active and sham groups.

For ethical reasons, no intervention will be performed in clinical care, and painkillers or other medications will be prescribed as usual. If a participant will begin taking medications during the study period, this will be documented, but the participant will not be excluded from the analysis. At the end of the study, participants and outcome assessors will be asked about the treatment to ensure the success of blinding.

Outcomes

Primary outcomes

Participants will be assessed using a Visual Analog Scale (VAS) for pain, which is a one-dimensional measure of pain intensity in adults, including those with chronic pain due to rheumatic disease[26]. The VAS is a continuous scale comprised of a horizontal line, usually 10 centimeters (100 mm) in length, anchored by 2 verbal descriptors (0 representing "no pain" and 100 representing "pain as bad as you can imagine")[26]. The VAS is self-completed by the respondent. The respondent is asked to place a line perpendicular to the VAS line at the point that represents their pain intensity[26].

Secondary outcomes

Algometry will be carried out to record pressure pain threshold (PPTh) and pressure pain tolerance (PPTo). Pain PPTh and PPTo will be assessed in eight different anatomical locations: trapezius, at the midpoint of the upper edge; lumbar spine, performed over the erector muscle; lateral epicondyle; knee, over the fatty cushion; and between the index finger and thumb on the dorsal side of the hand. All points will be tested on the left and right sides of the body. Algometry will be performed perpendicular to the skin at 5–10 s intervals by the same qualified examiner. A pressure algometer will be used (MedDor, Minas Gerais, Brazil) through a 1-cm diameter rubber tip. PPTh and PPTo will be quantified in kg/cm^2. The examiner will position the rubber tip above the area to be examined and gradually increased the pressure by 1 $kg/cm^2/s$ [27]. The PPTh will be measured when the patient says, "I'm starting to feel pain." To measure PPTo, the patient will be asked to bear the maximum amount of pressure from the algometer and use the verbal affirmation "stop."

The Brief Pain Inventory (BPI) is one of the most used instruments to assess chronic pain in clinical trials[28]. The BPI (short form) will be used to assess the severity and effect of pain in daily living activities. It is a questionnaire that presents 15 items, including two multi-item scales to measure pain and its effect on functionality and well-being; the questionnaire is validated for the Brazilian population[28]. In the room allocated for evaluation, participants will be asked by the researcher about each item, and questionnaire will be filled according to the answers of the participants. All questions can be repeated if the participant does not understand. The BPI will be applied in all phases of evaluation and by the same researcher.

In the absence of a specific functional questionnaire for acute and long-term evaluation of rheumatic manifestations of chikungunya, the health assessment questionnaire (HAQ) it will be used. HAQ is commonly used to assess rheumatoid arthritis and to evaluate patients with chikungunya[9,29]. This is a validated tool to measure disability due to persistent arthralgia[30]. Rising, dressing, eating, walking, bathing, reaching, gripping, and performing errands will be assessed on a scale that ranged from 0 to 3. The average of all scores will be considered to classify disability as 0, no difficulty; 0–1, mild disability; 1–1.5, moderate disability; and >1.5, severe disability.

The grip strength will be evaluated by a hydraulic dynamometer Saehan model SH5001 (Saehan Corporation, Yangdeok-Dong, Masan, Korea), and the Bohannon protocol will be used[31]. Participants will remain seated on a chair with the feet and trunk supported, shoulder adducted, elbow flexed at 90°, forearm in neutral position, and wrist in 0° to 30° extension[31]. Participants will be instructed to perform a maximum isometric contraction for 5 s, and the peak force will be recorded. Three evaluations will be performed with an interval of 1 min. For statistical analysis, arithmetic mean of these three measurements will be obtained. If the examiner recognizes some compensatory movement by the participant, a new measurement will be performed and recorded[32].

A short form health survey (SF-36) will be used to assess quality of life[33]. The questionnaire consists of a 36-item divided into 8 domains: functional capacity, limitation by physical aspects, pain, general health, vitality, social and emotional aspects and mental health[33]. These domains have between 2 and 6 response options. For each scale, item scores are coded, summed, and transformed, with final values (expressed as a percentage) ranging from 0 (worst health) to 100 (best health).

Adverse event monitoring and reporting

Serious adverse effect or irreversible injury following the use of conventional tDCS protocols in human trials (20 min, 2 mA, and 10 sessions) has not been reported[24]. Adverse events will be carefully monitored throughout the study. The most commonly reported adverse events included itching and tingling under the electrode sites, which are reported in both active and sham conditions[24,34]. Participants will receive care as appropriate for any harm that arises following study participation. After the study, results will be presented to the participants in the form of a lecture. If the positive effects of tDCS on the research outcomes are confirmed, tDCS will be offered and guaranteed to all participants in the sham group. In case of collateral events, or frequent serious adverse effect the principal investigator makes the final decision to stop the trial.

Adherence to treatment will be encouraged with regular messages sent by smartphone, advising on the benefits of the study and scheduling times that do not interfere with the participant's routine.

Sample size

The sample size was calculated based on statistical considerations for a parallel trial and on a previous study by Silva-Filho et al[15]. The sample size was estimated using G-Power 3.1.9.2 (RRID:SCR_013726) based on the assumption of significance of 0.05, power of 80%, with 0.3 effect size, and two groups. According to this methodology, the sample should include thirty-two participants. Considering a 20% of possibly loss, the number of participants will be increased by 25%, which corresponds to eight participants. Thus, forty participants will be recruited and allocated in the two groups, with twenty participants each.

Data collection and management

Sociodemographic and clinical data will be collected and recorded by trained and blinded research assistants in our research centre. A trained physical therapist will undertake a face-to-face interview to collected quantitative data (questionnaires and physical tests). Consistency checks by another researcher (physical therapist) will be performed to ensure data entry accuracy during data collection. Data will be collected

using paper forms and entered electronically on to the trial database. To maintain confidentiality, each participant will be given a unique trial Participant Identification Number (PIN). PIN will be used for data entered onto the central database stored on the base of UFRN. After completion of the trial, the database will be retained on the servers of UFRN for ongoing analysis of outcomes. The principal investigator will be access to the final trial dataset.

All procedures will be conducted in accordance with the international ethical and scientific standard protocols, following the Good Clinical Practices guidelines with human participants. Participants will be free to refuse to participate or withdraw their consent, at any stage of the research, without any penalty and without prejudice to their care. In case of any problem during the trial, participants will have the right to free assistance that will be provided by the responsible researcher.

Although no serious adverse[24] events with a causal link with tDCS are expected, adverse events will be reported to the principal investigator. Serious adverse events[24] will be logged and reviewed by the trial researchers and Ethics Committee if necessary. No auditing is planned. If necessary, possible amendments to the research protocol will be reported to the Ethics Review Committee for approval.

Following completion of the trial, datasets used in this study will be available from the corresponding author on reasonable requests.

Patients and public involvement

Due to COVID-19 emergency and as this trial is health data-based, patients were not involved in the design of the trial. The results of the study will be communicated to participants through a popular symposium.

Statistical analysis

The SPSS software version 19.0 (IBM Corp., Armonk, NY, USA) will be used for statistical analyses. Clinical and sociodemographic characteristics will be described by means, medians, and standard deviations for continuous numeric parameters and by frequency tables with 95% confidence intervals for qualitative parameters. A chi-squared test or Fisher's exact chi-squared test will be used to compare the distributions of qualitative variables. To compare baseline data between groups, an unpaired t-test or a Mann–Whitney test will be used.

Shapiro–Wilk and Levene's test will be applied to assess the normality of the distribution and homogeneity of variance of the data, respectively. Mauchly's test of sphericity will be used to validate the correlation of the repeated measures, and if the assumption of sphericity is violated, the Greenhouse–Geisser correction will be applied. The effects of stimulation on VAS, PPTh, PPTo, BPI, dynamometry, HAQ, and SF-36 will be calculated using a mixed analysis of variance (ANOVA) model. If necessary, the use of pain killers or other medication will be adjusted on ANOVA model. The dependent variable will be the score of each outcome, and the independent fixed variables will be the time of treatment (baseline, day 10, first follow-up, and second follow-up), stimulation group (active and sham), and time versus group interaction. When appropriate, post-hoc comparisons will be carried out using Bonferroni correction for multiple comparisons.

For non-parametric data, Friedman test will be used. Missing data will be treated by intention-to-treat analysis, evaluating dropout individuals who did not perform the entire treatment protocol. Partial η^2 will be calculated as measures of effect size in the

ANOVA results (main effects and interaction effects). Partial η^2 will be used to calculate the effect size, where $\eta^2 = 0.01$ will be considered small, $\eta^2 = 0.06$ moderate, and $\eta 2 = 0.14$ large effect. Level significance will be set at p value less than 0.05.

Discussion

Chikungunya is epidemic in Brazil, with significant incidence in the Northeast (the second-highest incidence with 59.4 cases per 100,000 population)[35]. Most of patients present relapsing and remitting chronic arthralgia with debilitating pain lasting for years, but there are no specific therapeutic agents to treat and rehabilitate persons with chronic disease[32]. Persistent pain can lead to incapacitation, requiring long-term pharmacological treatment[8,29]. Advances in non-pharmacological options are necessary to promote pain relief without side effects and to restore functionality. Herein, we propose a trial protocol with tDCS (M1/Sp2 montage) to reduce pain and restore functionality in patients with chronic chikungunya. We will also clarify (1) whether the changes induced by anodal tDCS over M1 correlated with the patient's level of pain according to the clinical evaluation scales and (2) if there is a relationship between pain relief and functionality. Previously results would suggest that anodal tDCS over M1 may influence pain in chronic arthralgia caused by CHIKV.

It is urgent assess the clinical benefits and harms of interventions to prevent or treat persisting rheumatic disorders in patients with chikungunya[36]. Martí-Carvajal et al. described that only five small trials with high risk of bias were used in a systematic review of interventions for treating patients with chikungunya-related rheumatic and musculoskeletal disorders[8]. The authors suggested the need for more high-quality randomized clinical trials to find significant clinical benefits for this population[8].

tDCS is a safe, effective, and low-cost therapeutic approach to the treatment of chronic pain[16,17,31,37–40]. Previous studies have suggested that M1 anodal stimulation (C3/Fp2 montage) stimulate neural circuits in this area with subsequently modulatory effect in deep brain areas evolved with pain balance. As a result, an important pain relief was found[17]. Precentral gyrus are involved in sensory and emotional aspects of pain and anodal M1 stimulation could improve pain perception in different chronic pain states[17]. Besides this montage, a protocol with an intensity of 2 mA, an electrode size of 35 cm^2, and more than 10 consecutive sessions is commonly recommended to treat chronic pain[16–19]. Two studies have investigated the effect of tDCS on pain and functionality in chronic chikungunya arthralgia[14,15]. In the first study, Silva-Filho et al.[15] conducted five sessions of anodal M1/Sp2 montage, and in the second study, De Sousa et al.[14] applied six alternate sessions with the same tDCS parameters. These studies have suggested significant pain relief, but no significant difference in functional capacity was observed. Authors suggested that the number of sessions or brief period of intervention can be employed to improve functionality[14,15]. With promising preliminary results with tDCS and chronic pain in chikungunya, investigating the long-term effect of tDCS and the most adequate dose for this population is necessary.

Clinical measures of this trial include the standard recommended outcomes, including pain intensity scales validated and universally accepted[41]. Secondary outcomes will be used to add information about pain and its effects on activities of daily living, disability, decrease in medication use, and participant satisfaction. Sociodemographic variables that can influence pain or functionality such as gender, age, income, educational level, and ethnicity will be reported[41]. Grip strength will be evaluated by a hydraulic dynamometer. This test was chosen because joint involvement in chronic chikungunya arthralgia is predominant in the wrists (66.3%), hands (72%), shoulders (70.1%), and elbows (40%)[32]. Chronic chikungunya arthralgia can promote articular imbalance with

inflammation and degeneration of cartilage and bone[10]. This process can last for years, and the continuous use of arthritic joints may improve the degenerative process. Furthermore, the loss of muscle strength and functional mobility could contribute to joint degeneration[10].

This protocol has strengths: (1) a novel treatment option for pain will be used in patients with chronic chikungunya arthralgia and (2) the study will be conducted in an epidemic region with a significant number of patients. However, there are some limitations to the study methodology and execution. First, this study did not receive government funding for financial support. Second, recruitment is limited to patients with chronic chikungunya (>3 months) and no patients with acute or sub-acute stage of the disease will be included. Third, no specific questionnaire is used to measure disability or effect of chikungunya on the quality of life or functionality. Thus, questionnaires for other rheumatic diseases and commonly used for chikungunya will be used[14,15,42]. Finally, this is the third trial with tDCS (the first with 10 sessions) in chronic chikungunya arthralgia, and our results will not support definitive conclusions on the efficacy of this neuromodulatory method.

The results of the present study will provide important long-term treatment information about clinical management of tDCS in persisting rheumatic disorders caused by chikungunya. We believe that these results will interest the broad audience committed to improve the quality of life and functionality of patients and to better understand brain modulation on chikungunya arthralgia.

Trial status

Volunteers were not yet being recruited at the time of manuscript submission.

Author's contributors

ASN and AFLC will perform initial and final evaluation, data entry in the database and informed consent of participants. TABA, will perform the tDCS protocol and writing of the manuscript. JDDS and ESF will perform the tDCS protocol. AO will be supported data analysis and writing of the manuscript. LG and RP will perform data management and writing of the manuscript.

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Competing interest

Authors declare no competing interest regarding this trial.

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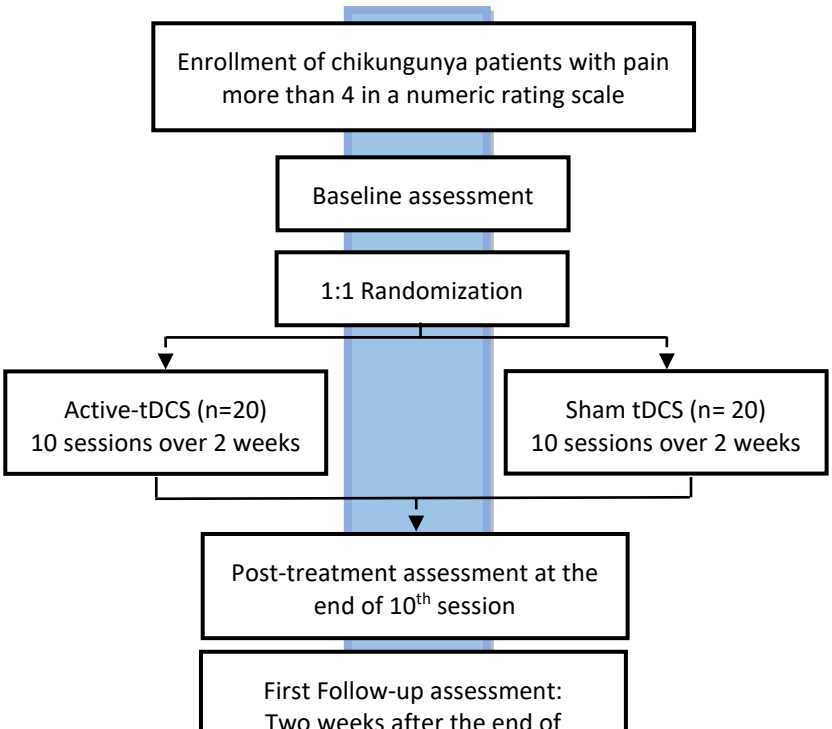
Figure 1. Flowchart summarizing the trial.

Figure 2. Schedule of enrollment, interventions, and assessments. VAS – Visual Analog Scale, BPI - Brief Pain Inventory (Short Form), HAQ - The Health Assessment Questionnaire, SF-36 - Short Form Health Survey.



	Study Period						
	Enrolment	Allocation	Post-allocation			1º Follow-up	2º Follow-up
TIMEPOINT	Week 1	Week 2 Baseline	Intervention			Week 6	Week 8
			Week 3	Week 4	Last day of tDCS protocol		
ENROLMENT	X						
Eligibility screen	X						
Informed consent	X						
Sociodemographic characteristics	X						
Allocation		X					
INTERVENTIONS							
Active tDCS			◆	—	◆		
Sham tDCS			◆	—	◆		
ASSESSMENTS							
VAS		X			X	X	X
Pressure pain threshold		X			X	X	X
Pressure pain tolerance		X			X	X	X
BPI		X			X	X	X
Dynamometry		X			X	X	X
HAQ		X			X	X	X
SF-36							
Medication use		X			X	X	X
Adverse events					X	X	X
Success of blinding							X

UNIVERSIDADE FEDERAL DO RIO GRANDE DO NORTE
FACULDADE DE CIÊNCIAS DA SAÚDE DO TRAIRÍ

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO - TCLE

Esclarecimentos.

Você está sendo convidado a participar de um estudo denominado "**Estimulação transcraniana por corrente contínua (ETCC) e seus efeitos terapêuticos na febre chikungunya: FASE 2**" projeto de pesquisa, a ser realizado na Faculdade de Ciências da Saúde do Trairí Santa Cruz/RN e que tem como pesquisador responsável o professor Rodrigo Pegado de Abreu Freitas (Fisioterapeuta – CREFITO 99038-F).

Essa pesquisa tem como objeto avaliar a aplicação de um pequeno estímulo elétrico na cabeça realizado por um aparelho da fisioterapia para diminuir a dor que você sente por causa da chikungunya e melhorar a sua condição física. Esse estímulo elétrico é tão pequeno que não é percebido pela pessoa ou se sente um pequeno formigamento. A justificativa que nos leva a fazer este estudo é que se tem observado que a aplicação desse aparelho de pequeno estímulo elétrico leva a melhora da dor em muitas doenças, com isso gostaríamos de avaliar se na sua condição também há melhora. É uma terapia sem custo, de fácil aplicação, rápida, onde você não sente nada durante a terapia e os resultados parecem ser bem positivos, melhorando o seu bem-estar.

Sua participação no referido estudo será no sentido de realizar os seguintes procedimentos: uma avaliação inicial através de 3 questionários de avaliação sobre sua dor e sua qualidade de vida. Haverá também testes físicos como andar por 6 minutos e puxar um peso para saber sua força muscular. A avaliação da dor será feita através de um aparelho onde se aperta contra a pele até você começar a sentir dor e falar para parar. Você fará durante 10 dias (2 semanas de segunda a sexta) uma aplicação de um tipo de corrente elétrica muito baixa chamada microcorrente, que será aplicado no couro cabeludo através de borrachas pregadas na cabeça. Cada dia terá 20 minutos de tratamento. O risco que você possuirá ao participar é semelhante àquele sentido num exame físico ou psicológico de rotina. Essa terapia é utilizada mundialmente e bastante segura. Durante a aplicação não há sensação nenhuma, mas algumas pessoas podem relatar uma sensação de coceira, formigamento ou dor de cabeça.

Você foi avisado de que, da pesquisa a se realizar, pode esperar alguns benefícios, tais como: avaliação da fisioterapia e em caso de necessidade será encaminhado para tratamento fisioterapêutico na Clínica Escola da UFRN/FACISA; você será beneficiado pela aplicação de um tratamento seguro, rápido e sem custo, que apresenta bons resultados na melhora da dor crônica e da função física, melhorando a sua qualidade de vida.

Por outro lado, você recebeu os esclarecimentos necessários sobre os possíveis desconfortos e riscos decorrentes do estudo, levando-se em conta que é uma pesquisa, e os resultados positivos ou negativos somente serão obtidos após a sua realização. Assim, o risco envolvido com sua participação poderá ser de algum tipo de constrangimento pessoal durante os exames físicos e resposta aos questionários, que poderá ser interrompido por você a qualquer momento. Há também o risco de desconforto físico como fadiga muscular, câimbras, sensação de peso e cansaço

_____ (Rubrica do Participante) _____ (Rubrica do Pesquisador)

Rua Vila Trairi, S/N, Bloco B, 2º andar Centro, Santa Cruz-RN – 59 200-000. Telefone: (84) 9 9915-0043, funcionamento das 8:00 as 18:00 horas. COMITÊ DE ÉTICA EM PESQUISA – CEP
Rua Vila Trairi, S/N, Bloco B, 1º andar Centro, Santa Cruz-RN – 59 200-000
Telefone: (84) 9 9224-0009 cep@facisa.ufrn.br cepfacisa@gmail.com

durante a aplicação dos testes físicos. Na aplicação da terapia de microcorrente há o risco de você sentir algum tipo de alteração da sensibilidade do local de aplicação, sensação de esquentar (porém sem alteração de temperatura, apenas a sensação), sensação de coceira e desconforto (na maioria das vezes atribuído a fita que segura o eletrodo no couro cabeludo) ou sensação de formigamento durante a aplicação da terapia. No exame para avaliar a dor, há o risco de o local de avaliação ficar dolorido devido a pressão que o aparelho faz na pele, mas nesse teste você diz o momento que quer parar. O riscos apresentados serão minimizados com a sua preparação correta antes de realizar os testes, além disso, tudo será aplicado por fisioterapeuta treinado e em ambiente seguro e próximo a infraestrutura hospitalar. Podemos colocar gelo após os testes físicos em algum local do corpo que você tenha sentido dor. Todos os testes físicos que serão feitos por você é recomendado para se avaliar o paciente com chikungunya de acordo com o Ministério da Saúde e estudos em diversos países.

Em caso de algum problema que você venha ter, relacionado com a pesquisa, você terá o direito a assistência gratuita que será prestada pelo pesquisador responsável.

Durante todo o período da pesquisa você poderá tirar suas dúvidas ligando para o professor coordenador da pesquisa, Rodrigo Pegado pelo telefone 99915-0043.

Você terá a liberdade de se recusar a participar ou retirar seu consentimento, em qualquer fase da pesquisa, sem nenhum prejuízo para você.

Os dados que você irá fornecer serão confidenciais e serão divulgados apenas em congressos ou publicações científicas, não havendo divulgação para terceiros e de nenhum dado que possa lhe identificar. Esses dados serão guardados pelo pesquisador responsável por essa pesquisa em local seguro e por um período de 5 anos na Faculdade de Ciências da Saúde do Trairí/UFRN.

Se você tiver algum gasto pela sua participação nessa pesquisa, como transporte ou alimentação, ele será assumido pelo pesquisador e reembolsado para você. Se você sofrer algum dano decorrente desta pesquisa, você tem direito a solicitar indenização.

A qualquer momento você tem o direito de retirar seus dados e material do local de armazenamento e, caso haja possibilidade de serem usados em futuros projetos de pesquisa, antes, deverá ser feito o contato com você para que possa ser concedida, ou não, uma nova autorização do uso do material. Esta possibilidade só existe se um novo projeto for aprovado pelo comitê de ética em pesquisa (CEP). Todos os resultados advindos dos seus dados serão postos à sua disposição pelo pesquisador, com opção pessoal de tomar ou não conhecimento dessas informações e de suas implicações para sua saúde.

Qualquer dúvida sobre a ética dessa pesquisa você deverá ligar para o Comitê de Ética em Pesquisa da Faculdade de Ciências da Saúde do Trairi (FACISA), telefone 99224-0009 ou mandar e-mail para cepfacisa@gmail.com ou cep@facisa.ufrn.br. O Comitê de Ética em Pesquisa - CEP da FACULDADE DE CIÊNCIAS DA SAÚDE DO TRAIRI - FACISA é um órgão Colegiado interdisciplinar e independente, constituído nos termos da Resolução no 466/2012 do Conselho Nacional de Saúde – CNS, e criado para defender os interesses dos participantes de pesquisas em sua integridade e dignidade.

_____ (Rubrica do Participante) _____ (Rubrica do Pesquisador)

Rua Vila Trairi, S/N, Bloco B, 2º andar Centro, Santa Cruz-RN – 59 200-000. Telefone: (84) 9 9915-0043, funcionamento das 8:00 as 18:00 horas. COMITÊ DE ÉTICA EM PESQUISA – CEP
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Este documento foi impresso em duas vias. Uma ficará com você e a outra com o pesquisador responsável, Rodrigo Pegado de Abreu Freitas, e as duas vias do TCLE devem ser rubricadas em todas as suas páginas.

Consentimento Livre e Esclarecido

Após ter sido esclarecido sobre os objetivos, importância e o modo como os dados serão coletados nessa pesquisa, além de conhecer os riscos, desconfortos e benefícios que ela trará para mim e ter ficado ciente de todos os meus direitos, concordo em participar da pesquisa "**Estimulação transcraniana por corrente contínua (ETCC) e seus efeitos terapêuticos na febre chikungunya: Fase 2**" e autorizo a divulgação das informações por mim fornecidas em congressos e/ou publicações científicas desde que nenhum dado possa me identificar.

_____

Participante

Impressão Dactiloscópica

_____

Pesquisador responsável

Endereço Profissional: Faculdade de Ciências da Saúde do Trairí – Santa Cruz – RN. Rua Trairí s/n Centro. A qualquer momento as participantes podem entrar em contato comigo pelo telefone 99915-0043.

Santa Cruz, ____ de _____ de _____.

Rua Vila Trairi, S/N, Bloco B, 2º andar Centro, Santa Cruz-RN – 59 200-000. Telefone: (84) 9 9915-0043, funcionamento das 8:00 as 18:00 horas. COMITÊ DE ÉTICA EM PESQUISA – CEP
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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	3
Protocol version	3	Date and version identifier	3
Funding	4	Sources and types of financial, material, and other support	12
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	12
	5b	Name and contact information for the trial sponsor	-
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	12
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	-

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2
	6b	Explanation for choice of comparators	5,6
Objectives	7	Specific objectives or hypotheses	3
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	3
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	3,4
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	3,4,5
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	6
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	6
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	4
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	5,6
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	3

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	67
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	3
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	3
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	3
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	3
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	3
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	4,5
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	6

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	6
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	7
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	-
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	7
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	-
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	6
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	6
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	-
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	-
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	2

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	3,4
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	-
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	6
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	12
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	6
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	-
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	6
	31b	Authorship eligibility guidelines and any intended use of professional writers	12
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	-
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	-
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	-

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Transcranial direct current stimulation for chronic chikungunya arthralgia: study protocol for a randomized clinical trial
Trial registration	2a	This trial is registered in the Brazilian Registry of Clinical Trials (ReBEC) under the identifier RBR-469yd6 (Date of registration: 25/06/2018).
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	11/05/2022, last approval, version 2.
Funding	4	This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. Abraão Sérvulo do Nascimento was partly financed by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES). Finance Code 001.
Roles and responsibilities	5a	Authors: Abraão Sérvulo do Nascimento, Antônio Felipe Lopes Cavalcante, João Danyell Dantas da Silva, Edson Silva-Filho, Alexandre Okano, Lucien Peroni Gualdi, Rodrigo Pegado.
	5b	Name and contact information for the trial sponsor The study has no sponsor.
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities: *The study has no specific sponsor and fund from any public or private agency. Abraão Sérvulo do Nascimento was partially financed by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES). Finance Code 001, however, the national public agency has no authority over the protocol activities.*
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) The protocol will be performed in a single center coordinated by Professor Rodrigo Pegado. All research previously described will be responsible for the study performance in specific tasks. Abraão Sérvulo do Nascimento and Antônio Felipe Lopes Cavalcante will perform initial and final evaluation, data entry in the database and informed consent of participants. João Danyell Dantas da Silva and Edson Silva-Filho will perform the tDCS protocol. Alexandre Okano will be supported data analysis and writing of the manuscript. Data management and writing of the manuscript will be performed by Lucien Gualdi and Rodrigo Pegado. No other individual or group will be allowed to see data without the study's coordinator permission.

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention: Brazil has been a protagonist in cases of Chikungunya virus (CHIKV) in Americans. Up to 50%–60% of CHIKV infected individuals may evolve into chronic phase that begins when clinical symptoms persist for more than 3 months. There are no specific therapeutic agents to treat and rehabilitee individuals in chronic phase of CHIKV and persistent pain may lead to incapacitation and requirement of long-term pharmacological treatment. Previously studies supported the use of anodal transcranial direct current stimulation (tDCS) over M1 (M1-SO montage) aiming to reduce pain. These studies were the initial investigation of M1 anodal tDCS, but further work to optimize the stimulation parameters is needed to clarify long-term efficacy on pain and functionality in chronic CHIKV arthralgia.
	6b	Explanation for choice of comparators Approximately 50% of patients have chronic arthralgia (chronic phase) for up to 6 years. This phase accounts for a high rate of persistent and incapacitating polyarthralgia, resulting in a reduction of functionality and quality of life. Pain is considered the most important symptom in chronic phase of CHIKV and showed strong association with reduction in daily activities and physical function.
Objectives	7	The primary objective of this protocol is to measure the effect of tDCS on pain. The secondary objective is to assess muscle strength, functionality, and quality of life. The duration and extent of effects of tDCS (long-term effect) will be also investigated. The study hypothesis is that the tDCS protocol will show improvement in pain, muscle strength, functionality, and quality of life when compared with sham tDCS.
Trial design	8	This is a protocol study of a single-center, double-blind, parallel, sham-controlled, randomized clinical trial with two groups and a 1: 1 allocation ratio.

Methods: Participants, interventions, and outcomes

Study setting	9	All procedures will be performed at the Physical Therapy Outpatient Clinic of Faculdade de Ciências da Saúde do Trairi/Universidade Federal do Rio Grande do Norte located in the city of Santa Cruz/ Rio Grande do Norte in Brazil.
Eligibility criteria	10	Adults from local communities of the Northeast region of Brazil will be recruited voluntarily through advertisements in electronic media and by health professionals from the communities. The inclusion criteria were as follows: men and women aged ≥18 years with positive laboratory or clinical diagnosis of chronic chikungunya (at least 3 months from the initial infection); moderate to severe (above 4) pain according to a numeric rating scale (NRS) and can tolerate physical evaluation; and satisfactory cognitive function to understand and sign the informed consent and study explanations and questionnaires. The exclusion were as follows: individuals with electrical implants in the body, history of epilepsy, metallic device implanted in the head, history of drug abuse, pregnancy, signs of severity and/or indication of hospitalization, and history of rheumatic diseases including gout, rheumatoid arthritis, fibromyalgia, lupus, and other chronic pain syndromes diagnosed prior to chikungunya.

Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered: The treatment will consist of 2 weeks intervention divided in 10 sessions of 20 minutes (one per weekday). Both groups AG and SG will be treated by a trained physical therapist at the Physical Therapy Outpatient Clinic of Federal University of Rio Grande do Norte. A monophasic continuous current with an intensity of 2 mA for 20 min will be used. All patients will be awake and sited in a comfortable chair with back and arm support during the tDCS/sham intervention. All tDCS procedures will be conducted in a temperature and noise-controlled room. tDCS will be delivered using the anode electrode positioned over the left primary motor cortex (C3) and the cathode electrode at the contralateral supra orbital region (Fp2), according to international standards for EEG 10–20 system (the “M1-SO” assembly). The electrodes will be placed into a 35 cm^2 square sponge immersed in saline solution (154 mM NaCl, approximately 12 mL per sponge). For stimulation, a current ramp-up and ramp-down with 30s duration will be used. Electrodes attached to the scalp will be supported by an elastic band. The electrodes (anode and cathode) will be connected to a battery (9 v) powered stimulator with current verified by a precision digital multimeter (DT832, WeiHua Electronic Co., Ltd, China) with standard error of ±1.5%. For the SG it will be used a ramp-up of 30 seconds and a ramp-down of 30 seconds. The device displays are identical in active and sham settings. To guarantee the success of blindness, participants and outcome assessors at the end point will be asked to guess whether the treatment was active or false.
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease). Participants who miss two tDCS sessions will be excluded from the study. Allergic skin reactions have been observed in rare cases. If this is suspected tDCS protocol will be stopped. This should be reported as an adverse event. The use of conventional tDCS protocols in human trials (20min, 2mA and 10 sessions) has not produced any reports of a serious adverse effect or irreversible injury. Adverse events will be carefully monitored during all steps of the study. The most reported adverse events included the sensation of itching and tingling under the electrode sites, reported in both active and sham conditions. Participants will receive care as appropriate for any harm that arises as a result of study participation. At the end of the study, the results will be informed to the participants in the form of a lecture, showing the results obtained. If the positive effects of tDCS on the researched outcomes are found, the application of tDCS will be offered and guaranteed to all participants in the sham group.
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests). Adherence to treatment will be encouraged with daily messages sent by smartphone, advising on the benefits of the study and scheduling times that do not interfere with the participant's daily activities.

	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial For ethical reasons, no intervention will be performed in clinical care and previous prescription of painkillers or others medication. If a participant begins medication during the study, it will be documented, but the participant will not be excluded. Participants are encouraged to maintain their normal activity routine.
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended. Primary outcomes: Participants will be assessed using a numeric rating scale (NRS) for pain. The NRS is a segmented numeric version of the visual analogue scale (VAS) in which the participant selects a whole number (0–10 integers) that best reflects the intensity of its pain (0 representing "no pain" and 10 representing the "pain as bad as you can imagine". Algometry will be carried out to record Pressure Pain Threshold (PPTh) and Pressure Pain Tolerance (PPTo). Pain PPTh and PPTo will be assessed in 8 different anatomical locations: trapezius: at the midpoint of the upper edge; lumbar spine: performed over the erector muscle; lateral epicondyle; knee, over the fatty cushion; and between the index finger and the thumb on the dorsal side of the hand. Pain threshold and tolerance to pressure will be quantified in kg/cm^2. Secondary outcomes: The Brief Pain Inventory (BPI) will be used to assess the severity and impact of pain in daily living activities. It is a questionnaire that presents 15 items, including 2 multi-item scales to measure pain and its impact on functionality and well-being. The DN4 questionnaire will be performed to evaluate neuropathic pain. The presence of neuropathic pain will be considered to be a dependent variable and will need to reach a score of at least 4 out of 10, while non-neuropathic pain will be considered scores of less than 4 out of 10. The health assessment questionnaire (HAQ) will be used to access functionality. Rising, dressing, eating, walking, bathing, reaching, gripping, and performing errands will be assessed on a scale range from 0 to 3. The average of all scores will be considered to classify disability as 0 = no difficulty, 0-1 = mild disability, 1-1.5 = moderate disability, and >1.5 = severe disability. The grip strength will be evaluated by a hydraulic dynamometer in kilogram-force. Three evaluations will be performed with an interval of 1 min between them. For statistical analysis, results will be obtained by arithmetic mean of these three measurements.
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure). Flowchart summarizing the trial was added in the manuscript.
Sample size	14	The sample size was calculated based on statistical considerations for a parallel trial and on a previous study by Silva-Filho et al15. The sample size was estimated using G-Power 3.1.9.2 based on the assumption of significance of 0.05, power of 80%, with 0.3 effect size, and two groups. According to this methodology, the sample should include 32 participants. Considering a 20% loss to follow-up and 5% missing data, the number of participants will be increased by 25%, which corresponds to eight participants. Thus, 40 participants will be recruited and allocated in the two groups, with 20 participants each.
Recruitment	15	Subjects will be recruited at the patients waiting list of the Physical Therapy Outpatient Clinic of Santa Cruz/RN- Brazil. Advertisements about the study will be placed in social media aimed to inform and invite the population.

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Randomization will be carried out through a numerical sequence generated by an allocated computer using appropriate software (www.random.org) to assign each participant to either the active or sham group. An external research assistant will generate the allocation sequence and contact participants by telephone.
Allocation concealment mechanism	16b	Allocation concealment will be performed using opaque envelopes. Participants and researchers involved in the assessments and interventions will be blinded to group allocation throughout the trial.
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions. The allocation sequence will be performed for Abraão Sérvulo do Nascimento and Antônio Felipe Lopes Cavalcante will enroll participants. João Danyell Dantas da Silva and Edson Silva-Filho will assign participants to interventions.
Blinding (masking)	17a	In this clinical trial, both the participants and evaluators will be blinded. Moreover, to ensure that the participant is also blinded to the allocation group, electrodes will be placed in the same position as in the active group, but the stimulator delivered 2 mA of current for only 30 s, with the same ramp-up and ramp-down period of 10 s. Sham tDCS will consist of delivering an active stimulation for a few seconds to mimic the sensations (itching and tingling) observed during active tDCS. This is considered a valid methodology for clinical protocols with good effectiveness of blinding.
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial Unblinding will not be allowed, and the evaluator will have no access to the allocation group until the end of the study.

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol Before starting the trial, a series of training steps for evaluations and application of the tDCS will be carried out, aimed at recording activities carried out in the study. Techniques and measures will be improved at this stage of the training to reach a consensus among the researchers. tDCS will be performed by a physical therapist with previously expertise in clinical trials and background in non-invasive brain stimulation. Assessment will be performed in the morning in a temperature-controlled room without noise or another distractor. NRS, PPTh, PPTo , BPI, DN4 questionnaire , HAQ and grip strength are commonly used in clinical trails aim to assess pain and functionality. All questionnaires are validated and translated for the Brazilian population. The researcher will ask to the participant questions described in the questionnaires, and according to the answers obtained, the researcher will fill in the questionnaire. All questions can be repeated if the question is not understood.

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols The trial will be performed in a small city with easy and free cost transportation to the local of the study. If necessary, the research will develop strategies to transport this individuals to the study setting. The participant will be informed of the benefits of the research and, if necessary, will be referred for physical therapy treatment at the University's Rehabilitation Clinic.
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol Data will be stored at the principal investigator computer and double entry will be performed by two study researchers. Data access will be limited to the study researchers and any other access must be authorized by the coordinator.
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol Statistical analyses will be conducted using the SPSS software version 19.0 (IBM Corp., Armonk, NY, USA). Clinical and sociodemographic characteristics will be described by means, medians, and standard deviations for continuous numeric parameters and by frequency tables with 95% confidence intervals for qualitative parameters. A chi-squared test or Fisher's exact chi-squared test will be used to compare the distributions of qualitative variables. To compare baseline data between groups, an unpaired t-test or a Mann–Whitney test will be used. Shapiro–Wilk and Levene's test will be applied to assess the normality of the distribution and homogeneity of variance of the data, respectively. Mauchly's test of sphericity will be used to validate the correlation of the repeated measures, and if the assumption of sphericity is violated, the Greenhouse–Geisser correction will be applied. The effects of stimulation on NRS, PPTh, PPTo, BPI, DN4, HAQ, and dynamometry will be calculated using a mixed analysis of variance (ANOVA) model. The dependent variable will be the score of each outcome, and the independent fixed variables will be the time of treatment (baseline, day 10, first follow-up, and second follow-up), stimulation group (active and sham), and time versus group interaction. When appropriate, post-hoc comparisons will be carried out using Bonferroni correction for multiple comparisons. For non-parametric data, Friedman test will be used. Missing data will be treated by intention-to-treat analysis, evaluating dropout individuals who did not perform the entire treatment protocol. Partial η2 will be calculated as measures of effect size in the ANOVA results (main effects and interaction effects). Partial η2 will be used to calculate the effect size, where η2 = 0.01 will be considered small, η2 = 0.06 moderate, and η2 = 0.14 large effect. Level significance will be set at p value less than 0.05.
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) The study has no additional analyses planned.
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) Missing data will be treated by intention-to-treat analysis, evaluating dropout individuals who did not perform the entire treatment protocol. Partial η2 will be calculated as measures of effect size in the ANOVA results (main effects and interaction effects). Partial η2 will be used to calculate the effect size, where η2 = 0.01 will be considered small, η2 = 0.06 moderate, and η2 = 0.14 large effect. Level significance will be set at p value less than 0.05.

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed Data will be monitored by the study coordinator and posteriorly accessed by all researchers previously authorized to access data. There will not be an independent database as the study has no sponsor.
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial Trial will follow the guidelines and good practices for managing and reopening non-invasive brain stimulation (NIBS) clinics and laboratories through the immediate and ongoing stages of COVID-19 according to Bikson et al. 2020 (DOI: 10.1016/j.brs.2020.05.010). Final decision will be made by principal investigator.
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct Any adverse effect that occurs during the protocol performance will be reported on the follow-up guide and the information will be referred to the patients' physician.
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor There will be no audit in this study.
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval The study was previously approved by the ethics committee of the Faculty of Health Sciences of Trairí – Federal University of Rio Grande do Norte (No. 2.413.851). Results will be presented in peer-reviewed journals and international conferences.
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators). All protocol modifications will be informed to ethics committee of the Faculty of Health Sciences of Trairí – Federal University of Rio Grande do Norte (No. 2.413.851). After evaluation and approval, the researchers will inform for all participants.
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) Abraão Sérvulo do Nascimento and Antônio Felipe Lopes Cavalcante will obtain informed consent or assent for all participants. Potentially eligible patients with chronic of chikungunya will receive a detailed explanation of the study from the study research coordinator. Interested participants will be asked to sign the informed consent form before enrollment into the study.
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable Not applicable.

Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial The data will be confidential and will be disclosed only in conferences or scientific publications, with no disclosure to third parties and no data that could identify the participants. These data will be kept by the principal researcher in a safe place and for a period of 5 years at the Faculty of Health Sciences of Trairí/UFRN according to Resolution Nº. 466/12 of the National Health Council.
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site Authors declare no competing interests.
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators All data will be available for research time directly upon reasonable request to principal investigator. After the publication of the clinical trial, data will be available to any reader directly upon reasonable request to principal investigator, respecting the privacy and confidentiality of research participants.
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation According to Resolution No. 466/12 of the National Health Council, the investigators are responsible to any compensation to trial participation.
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions After the and of the study, investigators will perform a Symposium to publisher the trial results and all participants and scientific community will be invited. There are no publication restrictions in this trial.
	31b	Authorship eligibility guidelines and any intended use of professional writers There are no intended to use professional writers. All authors are previously described, and the eligibility will follow the ICMJE recommendations to best practice and ethical standards in the conduct and reporting of research.
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code Publication of this protocol in an open-access journal. All data will be available directly upon reasonable request to principal investigator
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates The consent form model followed the Brazilian model for informed consent and was approved by the responsible ethics committee.
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable Not apllicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.