Registered Reports

Effect of neuromodulation on pain and functional mobility in people with HTLV-1: randomized clinical trial protocol

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ABSTRACT | BACKGROUND: The main symptoms of myelopathy associated with human T-cell lymphotropic virus type 1 or tropical spastic paraparesis (HAM / TSP) are the presence of high intensity pain in the lower back, spasticity and weakness in the lower limbs, loss of balance and difficulties in locomotion. Pulsed Transcranial Magnetic Stimulation (rTMS) has been able to influence cortical plasticity, decreasing spasticity, increasing motor performance and promoting analgesia in several similar conditions. **OBJECTIVE:** To analyze the effect of neuromodulation by pulsed transcranial magnetic stimulation (rTMS) on pain and functional mobility in individuals with HAM/TSP. **METHODOLOGY:** A randomized clinical trial will be conducted in a sample made up of 40 participants randomly divided into two groups: Sham Group (SG) with 20 and Test Group (TG) with 20 patients. Individuals aged > 20 years, community walkers with or without orthosis, with chronic pain (≥ 6 months) in the lumbar region and/or lower limbs will be included. Individuals with epilepsy, cancer, pregnant women, patients with cardiac pacemakers, metallic implants in the brain or skull, users of illicit drugs and/or use of controlled medications in the last six months will be excluded. The protocol will be applied for 10 consecutive days with a follow-up period of eight months. Our hypothesis is that when using rTMs according to the proposed procedure, it will be possible to relieve pain and improve the functional mobility of these individuals with a long-lasting effect. **CONCLUSION:** We hope that rTMS is a promising treatment to reduce pain intensity and improve functional mobility in individuals undergoing active modality. We declare this protocol to be a promising resource for the treatment of htlv-1 individuals to reduce pain and improve functional mobility. Yes, this protocol has already been used in 6 patients. However, due to the pandemic, the study had to be discontinued. However, despite the small sample size and not being fully applied as suggested by the protocol, it was possible to notice a satisfactory result of the intervention. Thus, the application of this protocol can contribute to identify the result of this therapeutic modality in a safer way, as well as assist in the treatment of symptoms in this population, leading to a better quality of life.

KEYWORDS: Neuromodulation. Pain. Functional mobility. Tropical Spastic Paraparesis. Human T-Linphotropic Virus type 1.

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Introduction

HTLV-1 belongs to the Retroviridae family and affects approximately 5 to 10 million people worldwide.[1] Although a small number of individuals develop symptoms, they are complex, as they affect the neurological, rheumatic, dermatological and urogenital systems, negatively impacting the quality of life.[2-4] Since there is still no cure for this disease, it is necessary to identify resources that can interfere with the disease progression, reducing its rhythm and relieving its symptoms.[5] It is also necessary to identify less invasive and more effective therapies to control signs and symptoms.

One of the main effects in individuals with HTLV-1 is the occurrence of painful syndromes, which mainly affect the lumbar region and the lower limbs and tend to become chronic.[6] The mechanisms of pain are still unclear, but it is known that neuronal injury and musculoskeletal disorders contribute to the onset of this condition.[7] Chronic pain often has a negative impact on quality of life[8] and is associated with plastic changes in the Central Nervous System.[9,10]

Another phenomenon that causes a high level of suffering in this population is the loss of balance and dysfunctions in mobility.[11-14] These signs and symptoms lead to frequent occurrences of falls and difficulties in locomotion that prevent even going to treatment clinics.

There are few studies that demonstrate the effectiveness of pain treatments for people with HTLV-1, being very limited to the use of drugs similar to those used in people with HIV.[15,16] As there is still no cure, the treatment serves only to relieve pain symptoms.[15] However, the use of drug cocktails tends to produce adverse side effects. Therefore, it is relevant to conduct research on less invasive treatments, with less unwanted effects and more effective in reducing pain and improving mobility.

Among the treatments performed by physiotherapists, Pilates exercises[16], functional exercises[17] and Proprioceptive Neuromuscular Facilitation – PNF[18] demonstrate good results, but the protocols are prolonged, requiring three months for realization. Prolonged treatments hinder adherence, due to difficulties in locomotion and frequent urinary infections that affect this population, especially in patients with HTLV-1-associated myelopathy or tropical spastic paraparesis (HAM/TSP).

A study that used transcranial electrical stimulation with constant current (tDCS) demonstrated moderate pain relief in two sections, but not sustained over time.[19] However, the protocol proposed in the primary motor cortex (M1) with electric current may not have been the most suitable for this population.

Pulsed Transcranial Magnetic Stimulation (rTMS) was proposed by a group of researchers from Iran with the aim of reducing spasticity in this population[20] and presented beneficial results for this clinical sign, but also reduced the intensity of pain. However, the impacts of rTMS on functional mobility were not evaluated and the protocol applied was very different from what the literature recommends. rTMS has been better able to influence cortical plasticity, decreasing spasticity, increasing motor performance[9,21-23] and promoting analgesia[8,24] in several similar conditions, with promising results.

Therefore, with this protocol, we propose to analyze the effect of neuromodulation by Pulsed Transcranial Magnetic Stimulation (rTMS) on pain and functional mobility in people infected with HTLV-1; and, as secondary objectives, to verify the safety of the use of neuromodulation by rTMS in individuals infected with HTLV-1; to verify the immediate response to the use of neuromodulation by rTMS in individuals infected with HTLV-1; to verify through follow-up the medium-term effects of neuromodulation by rTMS in individuals infected with HTLV-1. Therefore, our hypothesis is that the application of this protocol can contribute to the treatment of pain and functional mobility in individuals with HTLV-1.

The protocol proposed in this article refers to the project registered under the number RBR-4zdtk9n on ReBEC (The Brazilian Clinical Trials Registry).

Methods / experimental design

This is a randomized clinical trial. The population will consist of individuals infected with HTLV, diagnosed according to the World Health Organization (WHO)

criteria, classified as symptomatic, defined or probable for HAM/TSP, registered at the HTLVida (HTLV Association of Salvador, Bahia, Brazil). To analyze the effects of rTMS, 40 individuals randomly assigned to two groups will participate in the study: a Sham Group (GS) and a Test Group (GT).

Participants will be randomized in blocks by a team member without contact with the evaluators and with the patients, according to the numbering from 1 to 6, with the help of the online virtual tool www.random.org. The secrecy of the allocation will be guaranteed through direct information from the member responsible for the randomization with the physiotherapist who will be responsible for the application of the therapeutic protocol carried out in another environment and who will not have any contact with the team responsible for the collection and with the data of the participants.

Selection of participants

Inclusion criteria

To be included in the protocol, the participant must: 1) be age > 20 years; 2) be a carrier of HTLV-1; 3) be a community walker with or without orthosis; 4) have chronic pain (≥ 6 months) in the lower back and/or lower limbs and 5) be able to sign the written consent form.

Exclusion criteria

Participants should be excluded if they: 1) have a history of epilepsy or cancer, or are pregnant women; 2) have a cardiac pacemaker and/or metallic implant in the brain or skull; 3) have used illicit drugs and/or alcohol in the past six months; 4) are taking controlled medications; and 5) are being accompanied in an exercise program in the 30 days prior to the intervention by rTMS.

Discontinuity criteria

There will be a discontinuity if: 1) the individual does not wish to continue due to discomfort or intolerance to the instruments of intervention and/or evaluation. Still, if the appraiser perceives any adverse effects; 2) if the participant withdraws consent at any stage of the study; 3) occurrence of events that may interfere with the results: epileptic seizures, traumatic brain injury, orthopedic trauma or infections of the nervous system, and changes in the approach to ongoing neurorehabilitation; 4) the individual have two consecutive absences to the proposed treatment.

Strategies to improve adherence to the intervention

Study participants will receive transportation to the research laboratory, intervention site and assessment site, as well as a meal voucher. At the end of the study, all participants in the "Sham" Group will receive treatment if a good clinical effect is obtained in the "Test" Group.

Study setup and participant schedule

Individuals who meet the requirements of the basic inclusion criteria will be identified in the clinical records. Potential participants will be invited to present the project and apply the anamnesis questionnaire to complement the eligibility criteria. Those who meet the eligibility criteria will be asked about their interest in participating in the research after presenting the objectives and procedures to which they would be submitted. Patients will be informed that they will be chosen at random to be allocated to the Test Group or the Sham Group. After the results of the study, if beneficial effects were evidenced for the Test Group, the Sham Group will also be treated according to the same protocol.

Clinical evaluation and complementary exams in the pre- and post- procedure phase

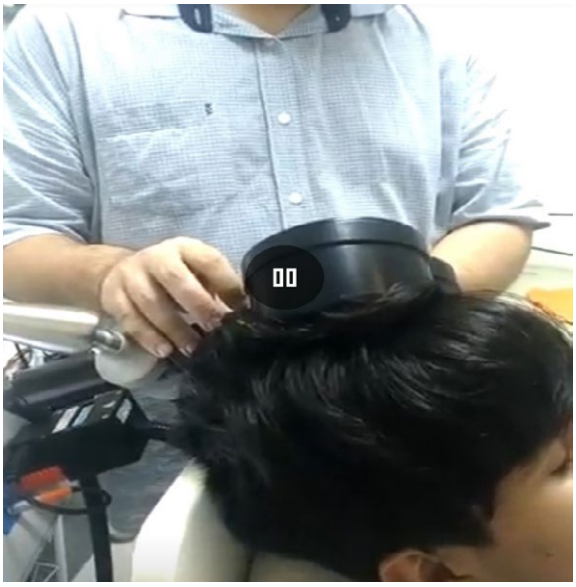
Participants will be subjected to a standardized assessment consisting of: application of the questionnaire by filling in sociodemographic and clinical data, application of the Brief Pain Inventory (BPI), application of the World Health Organization Quality of Life (WHOQOL-Bref) questionnaire and evaluation through the Timed Up and Go Test (TUG), performed by a single previously trained physiotherapist.

At baseline, a questionnaire will be applied to the sociodemographic and clinical data, the questionnaire WHOQOL-Bref for assessing quality of life, the BPI to assess the intensity of pain and the TUG to assess functional mobility. The BPI and TUG tests will be reapplied immediately after two weeks, eight weeks after the start of the protocol that will correspond to the follow-up period. The WHOQOL-Bref will be reapplied only eight months after the start of treatment.

Experimental procedures

The neuromodulation phase will be performed by a single physiotherapist at the Functional Stimulation Center (NESF) of the Federal University of Bahia, under the supervision of Professors João Zugaib and Cleber Luz. The rTMS protocol will be from 10Hz to 90% of the motor resting threshold with coil in 8 in the primary motor cortex aligned at 45o (forty-five degrees) with the sagittal plane (figure 1), 3000 pulses with 50 pulses in the pulse train and an interval of 25 seconds between trains.

Figure 1. Way of application and use of the coil in 8



Sessions will be held for five consecutive days in the first week, five days in the second week, one day per week for six weeks, and one session two and three months after the end of the six treatment sessions, in order to maintain the effects.

At the end of each session, participants will be asked about the presence of symptoms, including the application of VAS/P and the occurrence of falls in the period.

Blinding of participants will be guaranteed by using two coils, one of which will pass the electromagnetic current and the other of which will not be connected to the equipment. In the test group, participants will receive active stimulation according to the protocol, while the sham group will receive all procedures, however the disconnected coil is the one that will be in contact with the patient's skull. Since the equipment will be behind the participants, they will not be able to see which coil is being used, with the applying physiotherapist being the only one who knows which coil is applied (whether active or disconnected) to each participant.

Equipment

The rTMS will be performed by Magventure equipment. This MagPro R30 is an advanced high-performance magnetic stimulator designed for clinical use. This product is capable of performing repetitive Transcranial Magnetic Stimulation (rTMS) and works with many complex protocols in succession (up to 20,000 pulses).

- Biphasic waveform.
- Stimulation rates of up to 30 per second of pulses.
- Pulse trains up to 60 pps.
- Allows operation control through an internal computer and controls the synchronism of stimulus sequences.

- Stores flexible protocols.
- Friendly software.
- Enables quick set-up protocol and storage.
- Facilitates connection of external equipment (such as the EMG system) through in/out triggers.
- Displays feature reports.

Sample size

Sample calculation was performed with G-Power software, using an effect size of 0.3, an alpha of 5% ($p < 0.05$), and a study power of 80%. For the study, an estimated sample of 40 individuals, 20 participants in the Sham Group and 20 in the Test Group. The sample was expanded to 22 participants in each group, estimating a 10% loss to follow-up.

Study variables

Active rTMS and sham will be considered predictor variables.

The primary outcomes will be: pain intensity, measured with the instrument Brief Inventory of Pain following IMMPACT recommendations (http://www.immpact.org/sevensummits.html) and functional mobility measured with TUG.

Secondary outcomes will be: the impact of the protocol on the quality of life and the presence or absence of adverse effects.

Statistical analysis

Test results will be tabulated in the Microsoft Excel 2007 program and later analyzed by the Statistcal Package for Social Science program (SPSS version 21). To test the intragroup hypotheses, the paired t test or Mann Whitney will be applied, depending on the distribution of the variables. To test the difference between the groups, the ANOVA or Kruskal-Wallis test will be applied, also according to the distribution. A power of 80% and an alpha of 5% will be adopted. Missing data will be analyzed by intent to treat. Further tests for secondary outcomes will be defined later.

Discussion

Previous studies carried out with rTMS have demonstrated positive effects for treatment in other pathologies such as: stroke[25], multiple sclerosis26, fibromyalgia[27], depression[25,28] and Parkinson's disease.[29] However, in patients with HTLV-1, only one study has been found so far in Iran.[20]

According to the work developed[21] in patients with chronic stroke, stimulation on the brain's primary motor cortex, with high frequency rTMS, with 10 Hz, presented a significant result in the amplitude of the evoked motor potential (EPM), as well as a positive plastic change with better precision of motor performance. Even though it was applied twice a week, it was possible to notice an improvement in the response to cortical stimulation and in the movements developed by these patients.

A systematic review[22] also sought to assess the effect of cranial stimulation with rTMS in stroke patients. Although they have shown positive effects on the motor performance of patients with this pathology, they have not found the appropriate dose in view of the studies analyzed in their research. In fact, they identified the effects both in healthy individuals and in post-stroke individuals, but they believe that the effects are different when compared, therefore, more research should be conducted to more safely prove the effects and the best dosage. Likewise, another systematic review carried out[9] suggests that rTMS applied to the hemisphere affected by stroke is a safe technique and can be considered an effective approach for modulating brain function and contributing to motor recovery after stroke.

The work developed by O'Connell[30] studied the effect of rTMS on pain. This is a systematic review with the objective of evaluating the efficacy of noninvasive brain stimulation techniques in chronic pain. He evaluated different techniques, but the one that interests us most is the effect of rTMS. According to this study, single doses of high frequency rTMS to the motor cortex may have small short-term effects on chronic pain. The effects do not clearly exceed the predetermined threshold of minimum clinical significance. Low frequency rTMS is not effective in the treatment of chronic pain. Although the studies were conducted in different populations and with different objectives, the technique of transcranial stimulation in the motor cortex with the use of rTMS proved to be

effective for both improving motor performance and treating pain.

The only work on HTLV-1 patients found in the research was conducted in Iran.[20] It is a pre- and post-test study, with nine individuals with HAM/TSP who received rTMS for 5 consecutive days, with the following stimulation protocol: daily sessions of active high frequency rTMS for the motor area of the leg (20 trains of 10 pulses at 5 Hz and an intensity of 90% of the resting motor threshold for the biceps brachii muscle (i.e., a total of 200 pulses over 20 minutes)). As they identified in previous studies that 5 Hz stimuli were effective in reducing spasticity, they used the same frequency. Motor threshold was defined as the intensity that evoked potential evoked motors of 0.50 mV amplitude from peak to peak in at least 5 out of 10 consecutive stimuli and was determined once for each patient at the beginning of the study. Structurally, the motor area of the leg was positioned at the point of the midline around 1 to 2cm posterior to the vertex where it was located at the depth of the interhemispheric fissure. To stimulate the right hemisphere area, the current direction was in the portion of the coil, which rested in the leg part, from right to left. For the left side stimulation, the reverse procedure was performed. The middle point of the coil was positioned approximately 5cm in front of the apex, and the posterior spirals of the coil were reclined about 1 to 2 cm behind the apex. The MagPro X100 machine (Magventure Company, Farum, Denmark) was used, equipped with a commercially available double cone coil that was kept on the apex. All rTMS sessions were conducted with the patient in the supine position. According to this study, a statistically significant decrease in pain and spasticity in the lower limbs was identified. It should be noted that the decrease in spasticity was persistent even 30 days after the intervention; however, a reduction in pain was observed only 5 days after the procedure. There was no change in the quality of life, and muscle strength was detected.

In view of the effects presented with the application of rTMS, because it has been demonstrated safety and benefits, and in view of the scarcity of work in patients with HAM / TSP, we, therefore, seek to analyze the effects of this protocol in this population. However, some adjustments will be necessary. As comparative parameters, we rely on the work developed by Amiri et al., 2014[20] to make these changes and to compare the effects. In other words, the work of these authors was carried out on five consecutive days, with only nine patients, and the result was evaluated before and after the intervention.

The procedures and parameters used in our protocol will be different, as described at the beginning, but for comparison, ours will be performed with a coil in eight, the patient will be seated in a comfortable chair and not in the supine position, and the machine will be the MagPro R30 with different parameters.

In addition to the different parameters, in our protocol it is intended to apply the procedure to a larger population, which will be divided into two distinct groups, a Test and a Sham, and for a longer time of application and follow-up. The duration of the intervention will also be longer, applying for 10 consecutive days, followed by a three-month weaning protocol. Follow-up will be performed after the protocol is completed for up to six months in order to assess the duration of the effect. In addition, the impact on quality of life will also be assessed.

Ethical responsibilities

The project was approved by the EBMSP CEP (CAAE 96054818.5.0000.5544) and participants will only participate if they sign the Free and Informed Consent Term - TCLE (appendix 1) which was prepared according to the recommendations of Resolution 466/12 of the National Health Council. According to the literature, the passage of the pulsed electric current through the body does not produce any sensation. Stimulated people do not feel tingling, warmth, pain, vibration or discomfort. So far, studies have not shown any harm to humans, as long as there is respect for the low-intensity limits of the devices registered with ANVISA and the contraindications defined in the eligibility criteria. The project must be registered at http://clinicaltrials.gov.

Author's contributions

All authors participated in the drafting of the protocol with suggestions and approved the final version. Lucynara G. L Tambon and Katia Nunes Sá were responsible for the development of the project and submission to the research and registration ethics committee at REBEC-Brasil. Iago will participate as an undergraduate student and Dislene Silva will be a collaborating

researcher responsible for carrying out the experimental procedures. Erika Pedreira will be responsible for the blind evaluation of the participants. Cleber Luz will be responsible for randomization, allocation of participants and supervision of intervention procedures. Abrahão Baptista and Katia Nunes Sá will coordinate all phases of the research project.

Competing interests

No financial, legal or political interests competing with third parties (government, commercial, private foundation, etc.) were disclosed for any aspect of the submitted work (including, but not limited to scholarships, data monitoring advice, study design, manuscript preparation, statistical analysis, etc.). The author Lucynara G. L. Tambon was financed by FAPESB (Research Support Foundation of the State of Bahia) with a PhD scholarship under the number BOL0524/2019.

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