

Searching for the optimal Transcranial Direct Current Stimulation (TDCS) target combined with peripheral electrical stimulation in chronic low back pain: a protocol for a randomized controlled trial

Em busca do local ideal da Estimulação Transcraniana por Corrente Contínua (ETCC) associada à estimulação elétrica periférica na dor lombar crônica: um protocolo para um ensaio clínico randomizado controlado

En busca del sitio ideal de Estimulación Transcraneal de Corriente Continua (ETCC) asociado con la estimulación eléctrica periférica en el dolor lumbar crónico: un protocolo para un ensayo clínico controlado aleatório

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Abstract

Background: Low back pain (LBP) has been associated with severe impairments, primarily related to activities of daily living, functional ability and quality of life. A multimodal approach to pain management, such as transcranial direct current stimulation (tDCS) and peripheral electrical stimulation (PES), may improve outcomes in chronic LBP. However, the optimal cerebral target for stimulation still remains controversial. This pilot trial aims to investigate whether active stimulation could promote additional gains to the PES results in LBP patients. Our secondary objective is to investigate whether the stimulation of primary motor cortex and dorsolateral prefrontal cortex results in distinct clinical effects for the patients involved. **Methods:** Sixty patients with chronic low back pain will be randomized into one of three tDCS groups associated with PES: motor primary cortex, dorsolateral prefrontal cortex and sham stimulation. Each group will receive transcranial direct current stimulation at an intensity of 2 mA for 30 minutes daily for 10 consecutive days. Patients will be assessed with a Brief Pain Inventory (BPI), Roland Morris Disability Questionnaire (RMDQ), Medical Outcomes Study 36-item Short - Form Health Survey (SF-36) and electromyography at baseline, endpoint (after 10 sessions) and 1-month follow up. **Discussion:** This study will help to clarify the additive effects of tDCS combined with peripheral electrical stimulation on pain relief, muscle function and improvement in quality of life. Additionally, we will provide data to identify optimal targets for management of chronic low back pain.

Keywords: Low back pain; tDCS; TENS.

Resumo

Introdução: A dor lombar (DL) tem sido associada a deficiências graves, principalmente relacionadas às atividades da vida diária, capacidade funcional e qualidade de vida. Uma abordagem multimodal para o gerenciamento da dor, como estimulação transcraniana por corrente contínua (ETCC) e estimulação elétrica periférica (PES), pode melhorar os resultados na dor lombar crônica. No entanto, o alvo cerebral ideal para estimulação ainda permanece controverso. Este estudo piloto tem como objetivo investigar se a estimulação ativa pode promover ganhos adicionais para os resultados PES em pacientes com lombalgia.

Nosso objetivo secundário é investigar se a estimulação do córtex motor primário e do córtex pré-frontal dorsolateral resulta em efeitos clínicos distintos para os pacientes envolvidos. Métodos: Sessenta pacientes com dor lombar crônica serão randomizados em um dos três grupos ETCC associados a PES: córtex motor primário, córtex pré-frontal dorsolateral e estimulação simulada. Cada grupo receberá estimulação transcraniana por corrente contínua na intensidade de 2 mA por 30 minutos diários por 10 dias consecutivos. Os pacientes serão avaliados com um Brief Pain Inventory (BPI), Roland Morris Disability Questionnaire (RMDQ), Medical Outcomes Study 36-item Short - Form Health Survey (SF-36) e eletromiografia na linha de base, ponto final (após 10 sessões) e 1 acompanhamento por mês. Discussão: Este estudo ajudará a esclarecer os efeitos aditivos da ETCC combinada com estimulação elétrica periférica no alívio da dor, função muscular e melhora na qualidade de vida. Além disso, forneceremos dados para identificar os alvos ideais para o tratamento da dor lombar crônica.

Palavras-chave: Dor lombar crônica; ETCC; TENS.

Resumen

Introducción: El dolor lumbar (DL) se ha asociado con discapacidades severas, principalmente relacionadas con las actividades de la vida diaria, la capacidad funcional y la calidad de vida. Un enfoque multimodal para el manejo del dolor, como la estimulación transcraneal de corriente directa (ETCC) y la estimulación eléctrica periférica (PES), puede mejorar los resultados en el dolor lumbar crónico. Sin embargo, el objetivo cerebral ideal para la estimulación sigue siendo controvertido. Este estudio piloto tiene como objetivo investigar si la estimulación activa puede promover ganancias adicionales para los resultados de PES en pacientes con dolor lumbar. Nuestro objetivo secundario es investigar si la estimulación de la corteza motora primaria y la corteza prefrontal dorsolateral produce efectos clínicos distintos para los pacientes involucrados. Métodos: Sesenta pacientes con dolor lumbar crónico serán asignados aleatoriamente a uno de los tres grupos ETCC asociados con ESP: corteza motora primaria, corteza prefrontal dorsolateral y estimulación simulada. Cada grupo recibirá estimulación de corriente continua transcraneal a una intensidad de 2 mA durante 30 minutos al día durante 10 días consecutivos. Los pacientes serán evaluados con un Inventario Breve de Dolor (BPI), el Cuestionario de Discapacidad de Roland Morris (RMDQ), la Encuesta de Salud de Forma Corta (SF-36) del Estudio de Resultados Médicos (SF-36) y una electromiografía al inicio del estudio, punto final (después de 10 sesiones) y 1 seguimiento por mes. Discusión: Este estudio ayudará a aclarar los efectos aditivos de ETCC combinados

con estimulación eléctrica periférica para aliviar el dolor, la función muscular y mejorar la calidad de vida. Además, proporcionaremos datos para identificar los objetivos ideales para el tratamiento del dolor lumbar crónico.

Palabras clave: Dolor lumbar; ETCC; TENS.

1. Background

Chronic low back pain (cLBP) is a prevailing, disabling and challenging condition that is associated with an increase in disability adjusted for years of life (DALYs) (Carregaro, et al., 2020). Because it is more frequent in young adults, it generates a burden on health systems and society, since it is one of the main causes of decreased individual productive capacity of workers due to absenteeism, increasing spending on health services, including rehabilitation (Helfenstein Junior, Goldenfum & Siena, 2010; Meziat Filho & Silva, 2011; Carregaro et al., 2020). In order to promote pain reduction in this region and prevent relapses, non-pharmacological therapies have been proposed, among them the Peripheral Electrical Stimulation (PES) and the Transcranial Direct Current Stimulation (tDCS).

The pain neuromodulation of these electrotherapeutic resources occurs through different nerve pathways, because while PES generates electrical impulses by means of transcutaneous electrodes that will promote the depolarization of sensitive peripheral nerves (Albrecht, Goulart & Weis, 2015), tDCS uses electrical stimuli that cross the skull, with the intention of modulating the action of brain neurons (Luedtke, Rushton, Wright, Juergens, Mueller & May, 2011). Some studies have pointed out the efficacy of PES for the reduction of acute (Simpson, Fouche, Thomas & Bendall, 2013; Santana, Gallo, Ferreira, Duarte, Quintana & Marcolin, 2016) and chronic pain (Gibson, Wand, Meads, Catley & O'Connell, 2019), as well as tDCS in different types of pain in healthy individuals (Csifcsak, et al. 2009; Bachmann, et al 2010), and in clinical conditions involving chronic pain (Baptista, et al. 2019; Silva, et al. 2019).

Although there is evidence of synergistic effects regarding the association of PES and tDCS in pain modulation (Facci, Nowotny, Tormem & Trevisani, 2011; Faria, Santos, Rodrigues & Martins, 2009; Fregni, et al., 2011), little is known about the best cortical target for stimulation. Most studies have used the primary motor cortex (M1) as the locus of choice for pain control (Faria et al., 2009; Hazime, et al., 2015; Mori, et al., 2010), however, recent investigations suggest changes in morphological and functional activity beyond motor regions, involving changes in somatosensory, emotional and cognitive processing of pain,

which would include changes in the prefrontal cortex, insula, anterior cingulate cortex and somatosensory cortex (Schabrun, Chipchase, Jones & Hodges, 2013; Schabrun, Jones, Elgueta & Hodges, 2014). The dorsolateral prefrontal cortex (DLPFC) has been used as a therapeutic locus for inhibition of the descending mechanism of pain modulation in patients with chronic pain (Coppeters, et al., 2016; Niddam, Lee, Su & Chan, 2017; O'Connell, et al., 2013; Schabrun, Burns, Thapa & Hodges, 2018).

Considering the potential adjuvant effect of tDCS, the main objective of the present study is to verify whether active stimulation can promote additional gains in PES outcomes in pain relief, muscle function, and quality of life in patients with chronic low back pain, while the secondary objective is to investigate whether stimulation of M1 and DLPFC results in distinct clinical effects for the patients involved. In view of the reasons for the promising analgesic effects of DLPFC stimulation, we hypothesize that tDCS over DLPFC is superior to tDCS over M1 plus PES for the improvement of the studied outcomes. To the best of our knowledge, this is the first study comparing the effectiveness of DLPFC tDCS versus M1 tDCS combined with PES in chronic low back pain.

2. Methods

Design

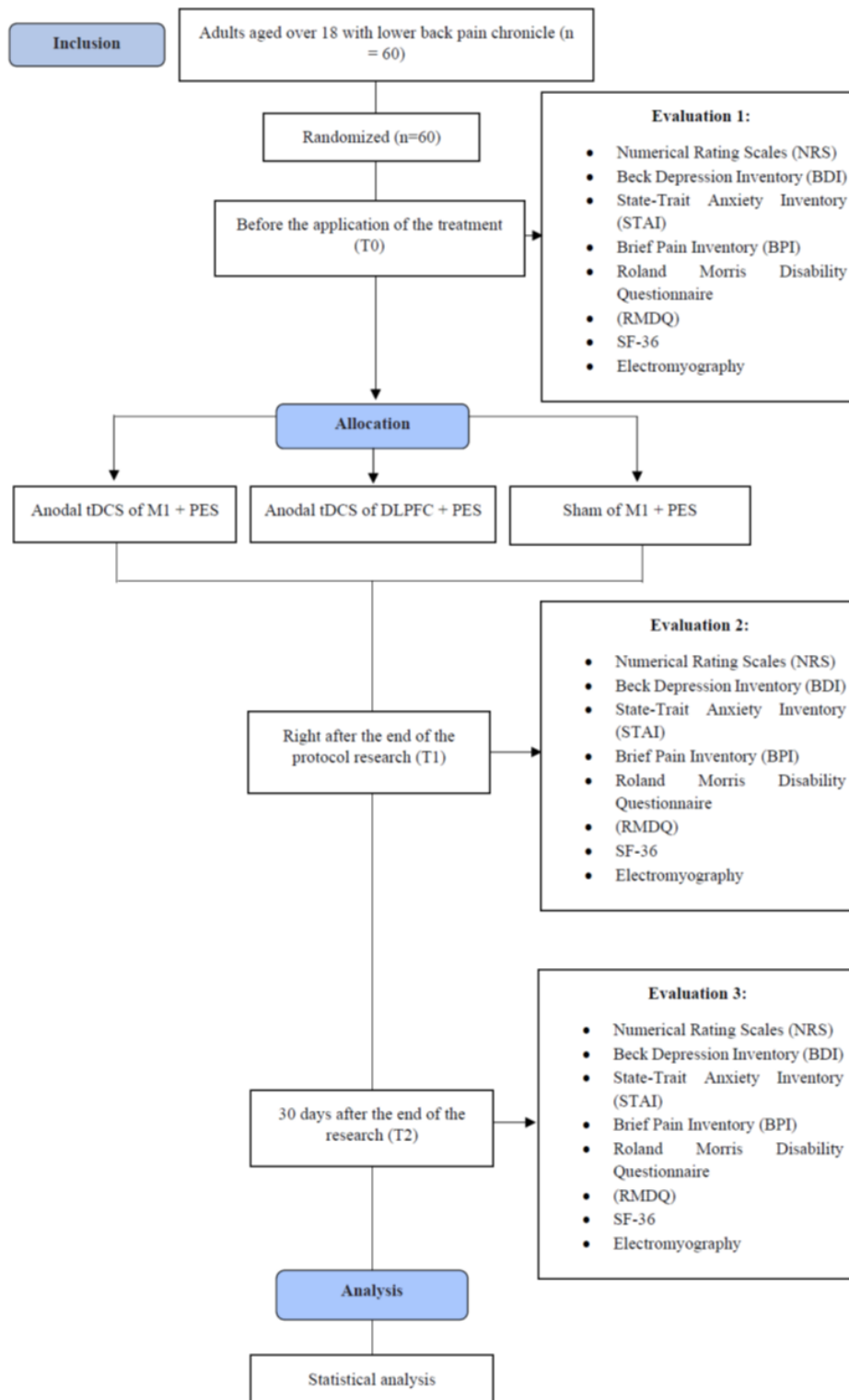
This is a pilot, sham-controlled, double-blind, randomized clinical trial (Figure 1) in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines (Chan, et al. 2013). The trial has been prospectively registered with the public platform clinical trials registry (NCT04496661).

Participants

The inclusion criteria will be the following: age over 18 years; diagnosis of chronic low back pain, lasting more than 6 months; pain intensity of at least 4 in 10 in Visual Analogue Scale (VAS); stable pharmacological treatment for at least one month before the study and throughout the study; and not having received physical therapy intervention in the 3 months prior to the start of this clinical trial. The diagnosis of chronic lumbar pain will be based on clinical and neurophysiological criteria, according to the European Guidelines on Low Back Pain (Konno & Sekiguchi, 2018). The exclusion criteria will be intense pain from

another origin, such as neuropathic pain; alcohol or substance abuse; associated diseases of the peripheral or central nervous system and contraindications for non-invasive brain stimulation.

Figure 1: Study design flowchart.



Source: Authors.

Recruitment

The study will be conducted in a Public Neuromodulation Unit, which provides specialized assistance to patients with chronic pain (cLBP). Participants will be recruited from hospitals and clinics, as well as through social media and support groups. Written and informed consent will be obtained from all participants and those interested in participating will have their records reviewed and will be contacted for inclusion in the study, according to the eligibility criteria.

Randomization and Blinding

Participants will be randomly allocated via an online generator (www.random.org) in one of three groups (1:1:1): anodal tDCS of M1 + PES; anodal tDCS of DLPFC + PES; Sham of M1 + PES. This sequence will be performed blindly, independently, and remotely by a blind investigator who will have no contact with other research procedures, and randomization will be hidden until the group is allocated.

The hidden allocation process will be performed using sequential, numbered, opaque and sealed envelopes. The outcome assessors, trialists and participants will be blinded to the performed procedures.

Attrition and Adherence

Attrition will be considered under the following conditions: (a) two consecutive or three alternating absences during treatment; (b) the inability to complete the post-test and follow-up; and (c) the development of any disabling condition preventing the participant's participation in the study. Regarding adherence strategies, up to two non-consecutive absences can be compensated the following week. Flexible therapy hours will also be offered, and the relatives of the patients will be directly contacted by telephone to confirm the dates of evaluation, thereby reinforcing treatment adherence (Brunoni, et al., 2011). Additional measures to avoid dropouts will also be applied, including periodic assessments of treatment satisfaction, discussion of difficulties in continuing treatment (for example, logistics of the trips to the laboratory) and attempts to resolve and avoid possible problems that may affect adherence to and continued participation in the study.

Outcomes

Participants will be evaluated by means of an initial visit shortly after their inclusion to the study by means of the eligibility criteria. After the screening, primary and secondary endpoint evaluations will be performed at baseline. These assessments will be repeated at the endpoint (at the end of the 10 sessions) and the follow-up (after 1 month). The safety assessment will be carried out at each session, collecting information about perceived sensations and possible reported discomfort or adverse effects.

At the initial visit, we will employ a structured assessment, including demographic data, diagnostic time, pain severity, symptoms of depression and anxiety. Pain severity will be assessed with Numerical Rating Scales (NRS), which refers to a subjective measure in which individuals classify their pain on an eleven-point numerical scale. The scale is composed of 0 (no pain) to 10 (worst pain imaginable) (Tu, et al., 2019). The Beck Depression Inventory (BDI) will be used to assess the severity of depression (Beck, 1961). The State-Trait Anxiety Inventory (STAI) was used to measure two different components of anxiety, state and trait (Spielberger, Gorsuch & Lushene, 1970).

The primary outcome of this study will be the Brief Pain Inventory (BPI) (Airaksinen, et al., 2006), which assesses multidimensional aspects of pain. It includes 15 items that evaluate the existence, severity, location, functional interference, applied therapeutic strategies and effectiveness of pain treatment. It is an instrument with adequate validity and reproducibility, commonly used in the evaluation of patients with chronic pain (Jensen, Turner, Romano & Fisher, 1999).

The secondary outcomes will include: Roland Morris Disability Questionnaire (RMDQ), which evaluates functional disability associated with chronic low back pain (Martinez, Grassi & Marques, 2011). Composed of 24 questions, with a variation of scores between 0 and 24 points: Zero point corresponds to a person without complaints and the maximum value (24 points) to a patient with very severe limitations; Medical Outcomes Study 36-item short-form health survey (SF-36), for evaluation of quality of life (Laguardia, Campos, Travassos, Najjar, Anjos, Vasconcellos, et al., 2103), in which the total score ranges from 0 to 100, in which higher scores indicate better health status; Surface Electromyography (EMGs) of the lumbar/multifidus (ML) and transverse abdominal (TrA) will be recorded using an 8-channel data acquisition system (model W4X8, Biometrics Ltd. , UK), bluetooth, with the following technical characteristics: hardware with 12-bit analog-to-digital (A/D) conversion board, 1000-fold gain amplifier, 20 to 500 Hz bandpass filter (2nd order

Butterworth), common mode rejection ratio (RRMC) >100 dB, signal noise rate <3 mV RMS, 109 Ohms impedance, surface, bipolar, active, simple differential electrodes, 20-fold pre-amplification, reference electrode and DataLOG software for signal collection and analysis with 1000 Hz sampling frequency. The protocol of EMG capture of the ML and TrA will be according to Schmit et al. (2016), with the electrodes positioned taking as reference a line connecting the upper-posterior iliac spine and the interspinous space of the first and second lumbar vertebra on both sides of the column to the ML and at a point located medially to the inguinal ligament, two centimeters medial and two centimeters caudal from the anterosuperior iliac spine on both sides of the pelvis to the TrA and the reference electrodes will be positioned in the right lateral malleolus to the ML and left to the TrA, with the volunteer in ventral and dorsal decubitus respectively. Each individual will perform three 15-second attempts in each position (rest and isometric contraction), requesting a maximum voluntary isometric contraction (CIVM), with verbal command "contract" in the fifth second and "relax" in the 10th second, being stimulated with the command "force, force, force" during the contraction. The five central seconds will be used to process the data, using the average values of Root Mean Square (RMS) normalized by the peak of the CIVM.

Safety

To control the adverse effects, patients will be asked about the sensations experienced during the session regarding "tingling", "burning", "headache", "drowsiness" and other inconveniences, which will be scored in intensity (1 - no, 2 - mild, 3 - moderate, 4 - strong), and also whether this effect is related to stimulation on a Likert scale of 1 (unrelated) to 5 (strongly related). If any damage or strong discomfort is identified, therapy will be discontinued and specialized medical assistance will be offered at no charge or cost to the participant. Any adverse effects will be recorded, along with the severity and duration of the symptoms and how the adverse effect was managed.

Intervention

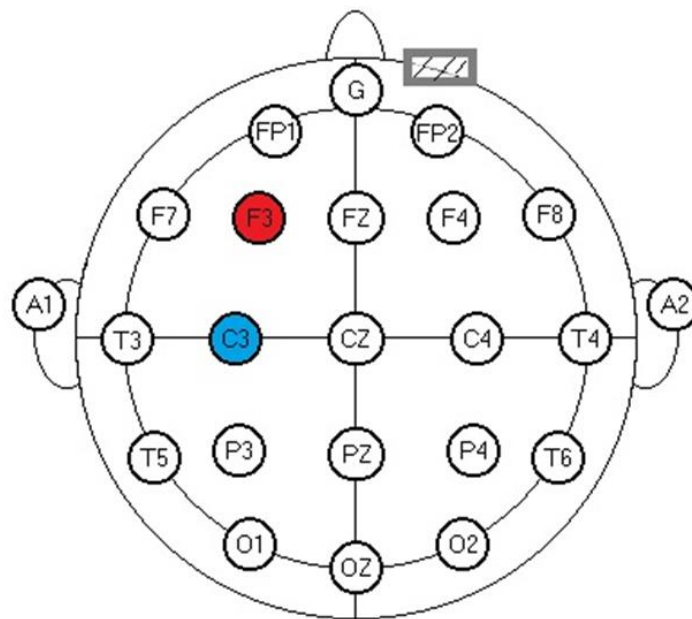
tDCS

Patients will be submitted to 10 treatment sessions, five days a week, for 30 minutes, paired to the same PES protocol. The direct current (2 mA) will be transferred through a neuro-stimulator (TransCranial Technologies, Hong Kong, China), with the use of electrodes

and 4x4 cm sponges moistened with 0.9% saline solution. The anodic electrode will be placed on C3 to stimulate the left primary motor cortex and on F3 to stimulate the left dorsolateral cortex according to the international 10-20 EEG system (Homan, Herman & Purdy, 1987). For sham stimulation, the anodic electrode will be positioned on the left primary motor cortex, but the current will be turned off automatically after 30 seconds. The reference electrode will be positioned in the supra orbital contralateral region for all groups.

To verify the chosen electrode configuration, we will perform a simulation of the current distribution and flow for the mentioned tDCS configuration (Figure 2) using SimNIBS 2.1 (SimNIBS software, <http://www.simnibs.org>) and MNI coordinates (Montreal Neurological Institute) (Saturnino, Antunes & Thielscher, 2105).

Figure 2. Simulation of the current distribution and flow for the tDCS configuration.



Source: Authors.

PES

The participants will be positioned in ventral decubitus position and submitted to continuous application of PES for 30 minutes, using a strong but comfortable intensity adjusted according to the sensitivity of each volunteer. Four self-adhesive electrodes with dimensions of 5 x 5 cm will be placed at the height between the T12 and S1 vertebrae in order to cover the entire lumbar area. A 20Hz frequency and pulse duration of 330ms will be

provided by means of two channels from an electro-stimulator (Neurodyn, Ibramed), according to Facci et al (2011).

Data analyses

This is a pilot clinical trial that may be useful for supporting a future large-scale randomised controlled clinical trial, provided that the here tested intervention is safe, feasible and effective. In this sense, a prospective calculation of sample size has not been performed. Based on previous studies involving non-invasive neuro-stimulation in patients with chronic pain, a sample size of 20 patients per group (60 in total) was estimated (Kodama, Takamoto, Nishimaru, Matsumoto, Takamura, Sakai S, et al. 2020).

Analysis of intention to treat will be employed and imputation methods (single or multiple) will be used to evaluate the dropouts. Comparisons of baseline characteristics between groups will be analyzed using the chi-square for categorical data and the Student t-test for continuous variables, with normality verified by the Shapiro-Wilk test. The analyses will be conducted using Multivariate imputation by chained equations (MICE, the R Foundation for Statistical Computing, Vienna, Austria) and Statistical Package for Social Sciences v21 (IBM, Armonk, NY).

For primary and secondary outcomes, we apply a mixed linear model with analysis of variance (ANOVA) for a split plot design: within-group (group; M1, DLPFC, sham); between-group (time, baseline, endpoint and follow up). If necessary, post-hoc comparisons will be made using Bonferroni's correction. The adverse effects will be calculated in terms of the proportion in each group and in each period, and will be analyzed by Fisher's exact test. The size of the partial eta-square effect (η^2) will be calculated for each measurement to quantify the standardized difference between the groups. P values below 0.05 will be considered as statistically significant.

Additional analysis will be conducted to investigate possible response predictors. We will conduct a linear regression model with stepwise method, which tested the influence of age, duration of illness, pain severity (VAS score) and baseline anxiety and depressive symptoms (STAT and BDI score, respectively).

3. Discussion

This work is a pilot, sham-controlled, double-blind, randomized clinical trial, developed to analyze the effectiveness of associated tDCS and PES stimulation in pain relief, improvement of muscle function and quality of life in patients with chronic back pain. Our secondary objective is to investigate whether stimulation of M1 and DLPFC results in different clinical effects for the patients involved.

Regarding the sample size, this study aims to provide useful information to support a future large-scale randomized controlled clinical trial if the intervention tested is safe, feasible and effective. In this sense, a prospective calculation of the sample size was not performed. Based on previous studies involving non-invasive neuro-stimulation in patients with chronic pain, a sample size of 20 patients per group (60 in total) was estimated (Kodama et al., 2020).

Preliminary studies show that different brain regions integrate information through several interconnected networks, so that changes in functional connectivity of the default mode network (DMN), salience network (SN), central executive network (CEN) and sensory-motor network (SMN) are related to the cLBP and other chronic pain conditions (Coppieters et al., 2016). Additionally, neuroimaging studies have demonstrated that patients with cLBP have a decreased activation of the anterior cingulate cortex, prefrontal cortex and accumbens nucleus.

As the anterior cingulate cortex and prefrontal cortex belong to the descending inhibitory system and the accumbens nucleus, involved in the dopamine system, releases m-opioids that act in pain relief, a reduced activation of these three brain regions may be related to a decreased functioning of the descending inhibitory system (Schabrun et al., 2018).

Similarly, it has been demonstrated that therapies for chronic pain affect pain-related brain activity, inducing changes in structural and functional activities, especially in CBP, as well as inducing changes in functional connectivity between the pain-related brain areas in patients with chronic disease. Examples are myofascial trigger point (MTrP) compression (Homan et al. 1987; Schabrun et al., 2014) and physiotherapy (Saturnino et al., 2105).

Although studies involving M1 stimulation are important, investigating the effects of tDCS associated with PES in DLPFC provides the possibility to clarify the knowledge about the role of this region in pain modulation (Niddam et al., 2107), as well as to point out new treatment routes for patients who are refractory to traditional therapy involving primarily motor regions. In general, the strengths of our study include the following: 1) to propose a new overview “alternative stimulation versus traditional stimulation” involving the primary

motor cortex in the management of chronic lumbar pain; 2) to quantify the synergistic effects resulting from the association of central and peripheral stimulation in pain control; 3) to conduct safe treatment, easy to apply and low cost.

The results of this study should be interpreted with caution, considering some limitations. One of them refers to the eligibility criteria, since we will only insert patients with chronic pain, which limits generalization to other conditions, such as patients with acute and subacute pain. Since there is evidence of neurophysiological changes, according to the phase in which the patient experiences pain, we have chosen to delineate only one of them, for greater experimental control. This choice, however, does not prevent future studies which can compare the effects of this therapy in patients under different phases of pain, in order to elucidate which patients are the better responders to the treatment.

Another relevant factor is that although we will analyze the efficacy of tDCS on M1 versus DLPFC associated with PES, we cannot guarantee that there is no overlap of cumulative effects of M1 stimulation on DLPFC and vice versa. Due to the limited focus inherent to the tDCS technique, overlapping effects are possible and should be considered in the planning of studies as possible intervening variables (Mhalla, et al. 2011). In this sense, it is important to note that we control and adjust our design to reduce these effects, such as the use of systematic techniques for locating cortical targets and orientation of the electrical current flow, the use of electrodes with reduced size, and computational modeling for individualized execution of the protocol and repetition of the process throughout all sessions. Thus, the conduct of this study may bring theoretical contributions to the development of new investigations in this area and provide relevant information for the clinical management of patients with cLBP.

4. Final Considerations

This article described a study protocol which aims to investigate whether tDCS active stimulation could promote additional gains to the PES results in LBP patients. The conduct of this study may bring contributions to the development and growing of investigations in this area and provide relevant information for the clinical management of patients with cLBP.

Study Status

The study was registered at ClinicalTrials.gov on 27 July 2020 (NTC04496661). Recruitment will start on November 2020 and will proceed until October 2022. Randomization will ongoing from November 2020 until October 2022 (60 participants randomized as of the end of October 2022). The final report will be prepared for 2022.

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