Background: Persistent pain in knee osteoarthritis (KOA) may generate sensitization of the afferent and central nervous system (CNS) pathways over time. Therefore, for patients with chronic pain derived from KOA, to associate therapies that address peripheral impairment, such as central and manual therapy and transcranial magnetic stimulation seems to be a promising strategy for pain reduction. Objectives: The purpose of this study is to unite rTMS and TM to control the pain of patients with knee OA and to examine the efficacy of this treatment protocol, assuming that this union would be more beneficial than the formally applied therapies isolated. Methods: This clinical trial with three arms interventions, controlled, triple blind and randomized, will allocate patients with KOA in groups (i) transcranial magnetic stimulation; (ii) sham transcranial magnetic stimulation + manual therapy and (iii) transcranial magnetic stimulation + manual therapy. Pain assessment will be performed using the visual analog scale of pain of 100 points, before and after the interventions, and for a maximum of 30 days after the single session. This session will involve the application of real or fictitious transcranial magnetic stimulation followed by manual or home therapy. Discussion: The study is in the recruitment stage and it is expected that after the application of the therapeutic protocol the group that performed the association has a more significant improvement in comparison to the others. Study registry: The protocol of this study was published on the Clinical Trials (www.clinicaltrials.org), with the registration number NCT03076294.

Keywords: Knee osteoarthritis; Chronic pain; Musculoskeletal manipulations; Transcranial magnetic stimulation.

INTRODUCTION

Knee Osteoarthritis (KOA) is a chronic, degenerative and inflammatory disease characterized by a degradation of the articular cartilage, thickening of the subchondral bone and formation of osteophytes. The persistent nociceptive stimulus resulting from the degenerative process in the knee joint causes sensitization of the afferent pathway of pain leading to plastic alterations at the segmental and central level. As a consequence of these changes, there may be symptoms such as expansion or reduction of pain threshold and allodynia.

Given this clinical picture of OA, the most common forms of treatment are analgesics and non-steroidal anti-inflammatory drugs (NSAIDs). These are widely used for the control of pain, but cause serious adverse effects after prolonged use and uncertainties regarding their efficacy. In this scenario, manual therapy (MT) is one of the physiotherapy techniques that can act in the peripheral aspect, normalizing the alterations of the afferent information of the somatosensory system. In addition, MT may act in the inhibitory descending control of pain, thus being able to act in the central aspect of the disease. However, due to the lack of studies on the theme to confirm the positive results found so far, TM is still recommended as adjuvant therapy despite being present as a first-line treatment for patients with knee OA.

In addition to MT techniques in pain control, repetitive transcranial magnetic stimulation (rTMS) is highlighted as it has been shown to be effective in reducing chronic pain in a number of pathologies. The rTMS is a tool used by physiotherapists of a painless and non-invasive character, being able to modulate brain activity. Since chronic pain promotes less cortical plasticity, the challenge of obtaining the most relevant combination of tools capable of interfering with central and peripheral pain processing is of utmost importance. For this reason, the purpose of this study is to join rTMS and TM to control the pain of patients with knee OA and to examine the efficacy of this treatment protocol, assuming that this union would be more beneficial than the formally applied therapies isolated.
METHODS

The protocol was developed according to the CONSORT guidelines.

Study design

This study is a clinical trial with three arms interventions, controlled, triple blind and randomized, for rTMS intervention, in which volunteers with knee OA are being recruited.

Registration of clinical trials

The protocol of the study was published on the Clinical Trials (www.clinicaltrials.org), with the registration number NCT03076294.

Study place

This study will be carried out in the Applied Neuroscience Laboratory (LANA) and the Kinesiotherapy and Manual Therapeutic Resources Laboratory (LACIRTEM), which are located in the Physiotherapy Department of the Federal University of Pernambuco (UFPE), Recife - PE. This project was approved by the ethics and research committee (CEP) of this institution (Approval number: 2.478.531). Researchers will be responsible for the assessment, reassessment and supervision of the intervention program.

Inclusion criteria

Study participants will be in the age group of 50 to 80 years, both gender, with diagnosis or medical report proving KOA for more than a year, who meet the criteria of the American College of Rheumatology for idiopathic knee osteoarthritis and present a pain level of at least 30 points on the visual analog scale (VAS) of pain from 0-100 points.

Exclusion criteria

The volunteers that present the following criteria will be excluded: (i) have a diagnosis of rheumatoid arthritis, osteoporosis, fibromyalgia, other neurological disease; (ii) have received opioid or corticosteroid injection in the past 30 days; (iii) are using any modified medication for chronic pain in the last month before participating in the study; (iv) report a history of knee surgery in the last six months; (V) are obese patients with grade II and III; (vi) present a cognitive deficit verified through the Mini Mental State Examination with adjusted cut-off point for literate subjects or (vii) have contraindications for the use of non-invasive brain stimulation, such as: metallic implant on the face or skull, history of convulsion, cochlear implant. Subjects with bilateral knee OA will have the most compromised knee (determined by the pain intensity of the patient) designated for evaluation and treatment.

Baseline characteristics

After recruitment and initial screening, details will be collected regarding personal and socioeconomic data, lifestyle, medications, identification of other diseases and anthropometric assessments.

Randomization and allocation

Once an authorization has been granted, the volunteers who met the eligibility criteria will be selected for the study. The randomization will be done by an external researcher (researcher 1), not involved in the various stages of the study, through a random numerical sequence generated in the site www.randomization.com. This sequence will be kept secret by opaque and sealed envelopes. Patients will be divided into three groups: (i) group A (rTMS), submitted to a rTMS session; (ii) group B (sham rTMS + MT), submitted to a fictitious rTMS session followed by MT and (iii) group C (rTMS + MT), submitted to a rTMS session of high frequency followed by MT.

Experimental procedures

A second researcher will be responsible for the evaluation procedures, a third one for the execution of TM and a fourth researcher for the application of rTMS, and also will maintain, throughout the study, the blindness of the patient and the researcher 2 and 3 regarding to the type of stimulation (real or sham).

The rTMS session will be held at LANA and the MT session at LACIRTEM, both for approximately 20 minutes. Patients will be evaluated in at least four moments: T0 - before the first intervention (real or sham rTMS); T1 after the first intervention and before the second intervention (MT); T2 – after the second intervention (MT) or rest; and T3 – daily evaluations through telephone contact, for a maximum of 30 days or until returning to baseline pain level. When there is no manual therapy the volunteer will remain in dorsal decubitus for approximately 20 minutes to preserve the blinding of the researcher 2.

Repetitive transcranial magnetic stimulation (rTMS) sessions with high frequency

In the sessions of rTMS, participants remain seated in a comfortable chair with headrest and armrests. The rTMS of the motor cortex will be performed with a coil coupled to a magnetic stimulator. Prior to the initiation of rTMS, the resting motor threshold (RMT) of the first dorsal interosseous muscle contralateral to the knee with greater pain will be determined. The RMT will be defined as the lowest TMS intensity required to produce an amplitude of motor evoked potential greater than or equal to 50 μV in at least 5 of 10 trials. In the therapeutic protocol will be provided 24 trains of stimulus at 10 Hz lasting five seconds each train. The interval between the trains will be 45 seconds, totaling 1200 pulses for approximately 20 minutes. The intensity used will be 90% of the RMT. The stimulation parameters adopted are based on protocols already used for...
treatment of chronic pain\textsuperscript{13,14}, but adapted to the need of this research, regarding the time, feasibility and comfort of the patient and according to the safety criteria recommended for the technique\textsuperscript{15}.

The sham rTMS will be performed using the sound recording of the stimulation, but the stimulator will remain off and the inactive coil will be positioned at the same location as a real stimulation. To control the possible adverse effects of stimulation after each rTMS session patients will respond to a questionnaire and declare their perception of stimulation as real or sham.

Manual therapy sessions

The MT sessions (25 minutes) will be performed shortly after the rTMS for the volunteers who participated in group A or C. For the patients in group B, i.e. that only performed the rTMS, will be advised to remain at rest, lying on the stretcher in dorsal decubitus, during the 30 minutes to preserve the blinding of the evaluator.

The sessions will begin with manipulations or mobilizations necessary to the volunteer. This need will be verified by the therapist responsible for the intervention. The therapy will then continue with a masstherapy protocol\textsuperscript{16}. In this protocol will be performed the mobilization of soft tissues with moderate pressure in the region of the quadriceps and hamstring muscles and around the patella for 20 minutes. The MT will be performed by a professional trained in the area of manual therapy who will not know what type of stimulation (rTMS sham or active) the subject will be submitted until the time of manual therapy.

For the evaluation of the primary outcome (pain), the following measures will be performed:

\textbf{Visual Analog Scale of pain}

It is the scale commonly used to evaluate pain, composed of 100 millimeters to quantify the level of pain, in which each millimeter symbolizes a point, zero indicating no pain, and 100 indicating the worst possible pain. VAS is recommended as the main endpoint in chronic pain studies\textsuperscript{17} and it has already been established that a decrease by at least 30 points represents a minimal clinically important difference (MCID)\textsuperscript{18}. MDCI it consists of the smaller variation in a clinical outcome perceived by the patient and that results in a relevant change in his state of health\textsuperscript{19}.

\textbf{Pressure Algometry}

It will be performed in the T0, T1 and T2 evaluations. It is a technique that aims to quantify through physical stimuli (pressure on the nociceptors) the capacity for perception and pain tolerance. It will be used with the patient lying in the dorsal position in order to measure the pressure pain threshold (PPT) at eight points located in and around the patella. In addition, two control points will be adopted, one in the anterior tibial muscle (five centimeters distal to the anterior tuberosity of the tibia) and another in the extensor carpi radialis longus (five centimeters distal to the lateral epicondyle of the humerus)\textsuperscript{20}. The point of the extensor carpi radialis longus will also be used to evaluate the presence of central sensitization in the volunteers of this study, since the low PPT at this site, far from the affected area, suggests a central sensitization\textsuperscript{21}.

For secondary outcomes the following measures will be carried out: (i) Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), (ii) Timed Up and Go Teste (TUG) and (iii) range of motion (ROM).

WOMAC is a self-administered, validated\textsuperscript{21} and specific questionnaire for osteoarthritis, with three dimensions in which are evaluated pain, joint stiffness and physical incapacity during daily life activities. This scale allows specific assessment of the disease becoming an instrument of use for clinical research. The Likert scale scores vary from 0 to 4, and the higher the score, the worse the three aforementioned outcomes\textsuperscript{21}. It will be done in the T0 evaluation and through phone contact 72 hours after the last intervention (T5).

TUG, is a reliable test to quantify functional mobility in frail elderly\textsuperscript{24}. It quantifies in seconds the functional mobility by means of the time that the subject performs the task of getting up from a chair, walking 3 (three) meters, turning, returning to the chair and sitting again. In the test the volunteer starts from the initial position with the back on the chair. The timing shall be initiated after the starting signal and shall stopped only when the subject is back again in the initial position\textsuperscript{25}. The timing of this test will be done through the Wiva\textsuperscript{a} Mob, a non-invasive analysis tool for the study of conditions that affect movement, walking and postural stability. The system uses an inertial sensor, connected through Bluetooth to a computer, that will be positioned in the waist of the volunteer with a special ergonomic belt that does not influence the execution of the motor gesture. This measure will be performed in T0, T1 and T2.

The range of motion is a measure that evaluates functionally the degree of amplitude of the knee joint through the Wiva\textsuperscript{a} Mob. In this evaluation the sensor will be positioned, with an ergonomic belt, above the lateral malleolus of the evaluated leg. From the moment the sensor will be connected through Bluetooth to the computer, the volunteer will be asked to perform knee extension movement in the sitting position and knee flexion in the ventral decubitus position. This measurement will be performed at T0, T1 and T2.

Sample size

The calculation of sample size will be performed using the G*Power program, considering a 5% alpha and a 80% beta.

Statistical analysis

The normality of the data will be verified with the Shapiro-Wilk test. Parametric data will be expressed as mean and SD, using the t-test for independent samples to compare
the groups and the paired t-test to compare the times. For the analysis of repeated measurements, the analysis of variance will be used with a post hoc LSD test. Non-parametric data and discrete variables will be expressed through medians with interquartile ranges. The Mann-Whitney test will be used to compare the groups, and for comparison of moments the Wilcoxon test will be applied. In all tests, the results will be considered statistically significant when α values are <0.05.

DISCUSSION
The aim of this clinical trial is to evaluate the effect of the association of manual therapy and repetitive magnetic stimulation of high frequency on pain control in patients with knee osteoarthritis. The study is guided by scientific evidence based on practice for the use of manual therapy and magnetic stimulation for this condition.

Upon completion of data gathering, it is expected that the group of volunteers with a combination of rTMS and MT have a more effective improvement compared to those isolated therapies in reducing pain levels, as well as improving functional and physical capacity and range of motion, and decreasing stiffness of subjects with knee OA. Furthermore, it is expected that the lower levels of pain, joint stiffness and improved physical capacity after an association of rTMS and MT are more durable compared to those isolated therapies for these subjects. The data will be published after the conclusion of the study.

PROGRESS OF THE CLINICAL TRIAL
Data is currently being collected.

AUTHORS CONTRIBUTION

CONFLICT OF INTEREST
The authors declare no conflict of interest.

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