RESEARCH PROJECT

TREATMENT OF DEPRESSION IN THE ELDERLY WITH REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION (RTMS) USING THETA-BURST STIMULATION (TBS): RANDOMIZED, DOUBLE-BLIND, SHAM-CONTROLLED, CLINICAL TRIAL

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Treatment of Depression in the Elderly with repetitive transcranial magnetic stimulation (rTMS) using theta-burst stimulation (TBS): study protocol for a randomized, double-blinded, controlled trial

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ABSTRACT

Background: Recurrent transcranial magnetic stimulation (rTMS) is a consolidated procedure for the treatment of depression, with several meta-analyses demonstrating its efficacy. The theta burst stimulation (TBS) method is a modification of the usual rTMS protocol, with short bursts of stimulation at high frequencies, with the bursts themselves being applied 5 times per second. As a new intervention method, there are still few studies evaluating its efficacy in treatment of major depression. However, a recently published meta-analysis has pointed to benefits of this therapeutic modality. To date, there are no studies published with this method for the treatment of geriatric depression.

Methods/design: The proposed study is designed as a double-blind clinical trial to assess the efficacy of rTMS theta-burst in the treatment of major depressive disorder in the elderly, in a sample of 108 individuals. Patients will be randomized to two groups: the experimental (TBS) and comparative (sham) group. Inclusion criteria include a diagnosis of Major Depressive Episode and a minimum age of 60 years. The coil will be positioned in the dorsolateral prefrontal cortex, with intermittent TBS mode on the left and continuous TBS on the right. There will be 20 consecutive sessions. Outcome measures will be at eight occasions: before the intervention (baseline) and after 1, 2, 4, 6, 8 and 12 weeks of onset. The main clinical result will be measured using the Hamilton Depression Scale (HDRS), comparing the initial scores with those obtained at the end of 6 weeks after the intervention. As secondary outcomes, we will use the Global Clinical Impression Scale (CGI), the CIRS (Cumulative Disease Assessment Scale), the Geriatric Depression Scale (GDS), the intermediate scores obtained on the HDRS scale and the variations in serum BDNF concentrations. As parameters of tolerability and safety, the incidence of adverse events and the occurrence of manic and / or hypomanic symptoms will also be assessed by the Young Mania Scale (YMRS).

EXPECTED RESULTS: TBS stimulation will prove to be a safe, well-tolerated and effective intervention for the treatment of major depression in the elderly, becoming a more therapeutic option, particularly useful for patients with poor response or contraindications to the use of antidepressants.

Trial registration: NCT0484292 Registered on https://clinicaltrials.gov/ct2/show/NCT04842929

KEYWORDS: depression; major depressive disorder; elderly; antidepressant; Repetitive transcranial magnetic stimulation (rTMS), theta-burst (TBS).

Introduction

With the increase in life expectancy and, consequently, the proportion of elderly people in the population, the morbidity of this age group will be increasingly relevant in terms of public health. As in other age groups, major depressive disorder (MDD) is a major problem for the elderly. Several studies demonstrate that MDD also worsens the prognosis of cardiovascular and cerebrovascular diseases, the main causes of morbidity and mortality in the elderly. For example, it is known that MDD, besides being an independent risk factor for cardiovascular disease [1,2,3,4], it is also associated with other risk factors such as arterial hypertension [5,6], diabetes mellitus [7] and smoking [8,9]. In addition, clinical trials in patients with cardiovascular diseases have demonstrated that antidepressant use decreases mortality [10],while the severity and persistence of depression in patients who had acute myocardial infarction increased mortality over subsequent years [11]. Finally, the presence of MDD is also associated with decreased cognitive and functional capacity [12]. In this way, the treatment of depression in the geriatric population is important not only from the psychiatric point of view, but also clinical and functional.

The treatment of choice for geriatric unipolar depression is with antidepressants. The therapeutic response is considered to be similar to adult depression, remission rates that stabilize at 60-70% after more than three antidepressant treatments, and therefore approximately 30% of patients are resistant to pharmacological interventions[13]. However, there are not many clinical trials focusing specifically on the elderly population - in fact, much of the evidence for elderly antidepressant drug therapy is extrapolated from adult clinical trials or post-hoc analyses of these trials, focusing on the elderly subgroup[14]. Interestingly, a clinical trial that recruited only patients over 75 years did not demonstrate superior efficacy of citalopram over placebo in the treatment of depression[15]. Still in the pharmacotherapy of geriatric depression, important issues are the side effects, drug interactions and restrictions of use of antidepressants in this age group. For example, the elderly are more sensitive to anticholinergic effects (constipation, urinary retention) characteristic of tricyclic antidepressants and the noradrenergic (dry mouth, tremor) effects of "dual inhibitors"[16]. Medications for therapeutic potentiation of antidepressants also have important side effects, such as lithium (intoxication by decreasing renal clearance, dehydration) and antipsychotics (weight gain, extrapyramidal symptoms) [16]. For these reasons, the therapeutic adherence to pharmacological treatment for depression in this age group is usually low [17]. Among the biological treatments, we highlight electroconvulsive therapy (ECT) and repetitive transcranial magnetic stimulation (rTMS). Both are treatments approved for depression and effective in the geriatric age group [18,19], however they have some issues that limit their use. ECT is associated in some cases with cognitive deficits in the long term and its application requires sedation - in fact, ECT is usually reserved only for cases of severe, refractory and / or psychotic depression [20].

The rTMS is a consolidated treatment for depression, with several meta-analyses demonstrating its efficacy [21,22]. However, there are few studies that have specifically evaluated the efficacy of rTMS in the geriatric population [23-27]. The rTMS may have some advantages over medications for the treatment of MDD in the elderly population. First, rTMS offers few

side effects, with headache being the most common complaint[28]. The most serious adverse event is a seizure; however, using the safety parameters, it is an extremely rare event, with few reports of cases in the literature[29]. Additionally, the risk of drug interaction observed with the use of antidepressants and other medications of continuous use is null, a situation very common among depressed elderly people. Also, rTMS does not negatively interfere with patients' cognitive function, and may even improve it in some aspects[30]. Theta burst stimulation (TBS) is a method of rTMS that more closely mimics the natural rhythms of activity in the neurons of the brain and uses short bursts of stimulation at high frequencies, with the bursts themselves being applied 5 times per second[31]. Its main advantage against conventional rTMS is the shorter time of section (3 to 12 minutes, against 20-30). One non inferiority trial showed the same efficacy of the conventional rTMS[32]. No controlled studies with TBS have been performed in the treatment of geriatric depression; however, recent studies with the method have shown good prospects for the treatment of major depression in adults with meta-analyses demonstrating a possible clinical superiority over conventional rTMS [33-38]. In addition, the session time in which the patient stays in the machine during TBS is much shorter, which facilitates patient compliance.

We want to evaluate if TBS is a therapeutically effective alternative, and also with few side effects, for this geriatric population with depression. This may bring short-term clinical gains for depressed elderly patients who do not tolerate antidepressants or have been refractory to antidepressants.

Methods/design

Design and population

The study will be a randomized, double-blind, sham-controlled clinical trial in which volunteers will be recruited at the Clinical Hospital of the Medical School of University of São Paulo. They will be allocated to one of the groups: active TBS or sham stimulation. Participants will receive 20 consecutive work days of TBS and will return at the end of 4, 6, 8 and 12 weeks for one single session, evaluation of clinical outcomes. Those who do not present clinical improvement and have been allocated to the sham group may choose to receive 20 days of active stimulation after the end of the trial.

Randomization and allocation of participants

The randomization will be in block, in which there will be permutation in the order and size of the blocks. The randomization will be generated through the website *www.randomization.com* by a researcher who will not be directly linked to the research. Patient allocation will be done through sealed, opaque and standardized envelopes. After the patient signs the informed consent form, the envelope will be opened and the envelope will be allocated to the treatment, in a coded form. The envelope will be identified with a random number that will be assigned to each patient.

Inclusion and exclusion criteria

Patients older than 60 years, with initial HDRS greater than 17, who have MDD. The exclusion criteria will be: other mental disorders (alcohol or drug addiction, psychotic disorders, dementia, bipolar disorder); presence of serious neurological or clinical diseases; presence of severe suicidal ideation and CIRS (Cumulative Illness Rating Scale) score> 7, characterizing a set of clinical morbidities that could impair adherence to the research protocol. In addition, specific contraindications to the use of rTMS will also be excluded, such as: metal implants, epilepsy or electronics in the cephalic segment. Patients who are receiving antidepressants will have a wash-out of five half-lives of the medications prior to entry into the study. Patients receiving benzodiazepines will be included since receiving a maximum dose of 10mg of diazepam or equivalent. Other psychoactive drugs will be accepted as long as the doses of the medications have been stable for at least 6 weeks.

Blinding

The study will be double-blind, evaluators and patients will not be aware of the randomized treatment until the end of the study. The blinding will be done with a sham coil, which consists of a coil that reproduces the sound that the true coil does, but without generating the magnetic field. A person only intended to apply the rTMS session will do the procedure and will not be involved with the evaluations or with the evaluators, this person will be also blinded. A blinding scale will be applied to evaluators, applicators, and volunteers to evaluate if the blinding was effective.

Interventions

The coil will be positioned in the prefrontal dorsolateral cortex, with intermittent TBS (TBSi) mode on the left and continuous TBS (TBSc) on the right (F3 and F4 positions determined by the 10–20 Electroencephalographic International System). 1800 pulses will be used on each side, totaling 11 minutes 39 seconds of total duration. TBS will have the following parameters: in cTBS bursts of three pulses at 50 Hz (20-ms interval between stimuli) will be applied continuously for 120 s total in the right DLPFC and iTBS bursts of three pulses at 50 Hz (20-ms interval between stimuli) will be applied for 2-s duration repeated every 10 s for a total time of 570 s also totaling 1800 pulses in the left DLPFC, both with 120% of motor threshold. We will use a magnetic stimulator device (MagVenture©) in study mode for double-blind trials. The coil has a side that is active and the other is sham. The applicant of TMS will be blinded too (after placing the coil over the patient's head and entering his number, the device tells if the position is correct or if you have to turn it, but the applicant does not know externally what is the sham side of the coil). The sham produces the same sound as the real one. We also put on the head electrodes that give stimulus to mimic the real magnetic coil (both groups receive this). There will be

20 consecutive sessions, one per day, except on weekends and holidays, totaling around 4 weeks. A day of stimulation with the same technique will be done in the 6th week, 8th week and 12th week.

Clinical variables

We will use the MINI questionnaire for the diagnosis of psychiatric disorders, applied by an experienced psychiatrist. It is translated and validated into the Portuguese language[39]. The demographic and clinical profile of the patients will be evaluated by: gender, age, schooling, socioeconomic status, clinical comorbidities, use and dose of antidepressants and other psychoactive drugs.

The main outcome will be measured using the HDRS scale. The primary evaluation will be done at the end of 6 weeks from the start of the first day of TBS. As secondary outcomes we will use the GDS (Geriatric Depression Scale), Cumulative Illness Rating Scale (CIRS), the global clinical impression scale (CGI), Positive and Negative Affect Scale (PANAS), Montgomery-Asberg Depression Rating Scale (MADRS), and Edinburgh Handedness Inventory (EHI). All scales have already been translated and validated into Portuguese[40]. Outcomes will be measured on 7 occasions: baseline after 1, 2, 4, 6, 8 and 12 weeks of study entry. The presence of adverse effects and the Young mania (YMRS) questionnaire will also be evaluated to detect manic and / or hypomanic cycling.

Cognitive Assessments

The cognitive battery will be applied by experienced neuropsychologists. For cognitive assessments they will be exploratory, secondary outcomes will be measured on the baseline, on the 20th day of the session and the addenbrooke cognitive examination will also be reapplied on the 12th week. We will use the Addenbrooke's Cognitive Examination - Revised Version (ACE-R), Ravlt - Word List, Rey's complex figure, Stroop Test (violet version); Wais III - Subtest Codes; Trail Making A and B and WASI - Vocabulary and Matrix Reasoning subtest.

Biomarkers

BDNF (brain-derived neurotrophic factor) is implicated in the pathophysiology of depression. Recent meta-analyses have shown that depressed patients have lower serum levels of BDNF than normal subjects [41,42]. The samples will be collected in dry tubes, centrifuged within two hours after collection, then separate the serum and refrigerate it in eppendorfs at -70oC in liquid nitrogen. The samples will therefore be stored in a cryogenic bank. They will be collected at the beginning of the study and in the 6th week.

Cerebrospinal fluid (CSF) samples will be collected by means of a lumbar puncture during the evaluation procedures before the intervention begins. They will be used for the investigation of beta-amyloid peptide (Aβ1-42) and Tau protein (total and phosphorylated). These determinations will allow

the analysis of the interaction between the presence of Alzheimer's disease pathology and the therapeutic response to the TBS intervention.

Cortical excitability will be measured using an EMT device with a circular coil, positioned at 45º from the skull, in M1. This procedure will involve the application of a magnetic pulse generated by the EMT device, on the surface of the skull corresponding to the hand area of the right and left primary motor cortex. A surface electromyograph will be placed in the region of the abductor pollicis brevis muscle to measure the motor response of the hand.

Evaluation of sensitivity thresholds according to the Quantitative Sensitivity Test (TQS): This assessment is made by the psychophysical method that quantifies the positive and negative phenomena of exteroceptive sensitivity transmitted by the thin or thick fibers of the peripheral nervous system. It makes it possible to determine the thresholds for detecting general sensitivities and pain, and generates painful stimuli that make it possible to diagnose the occurrence of hyperalgesia or hyperpathy. The TQS device was developed by Fruhstorfer et al. (1976) and Dyck et al. (1978), in order to quantify the sensitivity exams in clinical practice. At the beginning of the test, the stimulator temperature (thermode) is maintained in the thermal adaptation range (31 (C to 36˚C). The perception of the hot or cold stimulus and the pain of hot or cold stimuli is determined by increasing or decreasing the temperature of the thermometer. The cutaneous receptors, that is, the free nerve endings, which, in turn, trigger action potentials in the thin myelinated A-delta and / or unmyelinated C fibers, which are transmitted to the long tracts of the spinal cord.

Diffuse Nociceptive Inhibitory Control (CIND) or Conditioned Pain Modulation (MCD) CIND is a term used to demonstrate a reduction in pain, in response to the application of painful stimuli outside the area of pain. In general, heterotopic painful stimuli tend to decrease the pain induced by harmful stimulation, applied extra-segmentally. Studies show that the application of harmful heat to a part of the body, such as the arm, ends up resulting in a decreased response to stimuli painful in a heterotopic region, using the legs as an example. CIND was developed and formulated describing a specific inhibitory mechanism mediated by the brain stem. Researches based on human beings, using a pain that inhibits other pain, admitted to adopting the term CIND, extending it to the psychophysical domain, and describing patterns of behavior that may belong to various neural mechanisms. The volunteers will be submitted to the same test stimulus: heat pain evoked by a suprathreshold stimulus with a thermode (30x30, Medoc) for five seconds on the thigh, on the right and left leg, with a maximum temperature of 49 ° C. The thermode is placed on the right thigh and then on the left thigh of the volunteer, instructed to press the mouse button when the temperature reached causes the onset of a hot pain. To verify the supra-painful stimulus, the temperature found as the LdorQ of the volunteer and the previous LdorQ is added by 2 ° C, in the Medoc machine we select the suprathreshold stimulus and set it so that the stimulus lasts 5s, and is at a temperature of 2 ° above the LdorQ , the volunteer is then invited to describe his pain to the respective stimulus with a VAS scale> 70/100 mm, if the VAS reported by the volunteer is less than 70, we repeat the stimulus gradually increasing the temperature by 1 in 1 ° C, until he reports a VAS of at least 70/100

millimeters. The tests will be done before starting the TBS sessions and in the 4th week.

Actigraphy consists of a wrist device equipped with an accelerometer, a microprocessor and an internal memory, which are capable of detecting and storing the movement record. It is used in the evaluation of sleep disorders such as diseases of circadian rhythm, insomnia and excessive daytime sleepiness. We will use the actigraphy on the left wrist of the volunteers 1 week before the beginning of the research and for another 4 weeks after the studyThe objective is to assess sleep changes associated with the clinical response to magnetic stimulation.

Pupil Examination (PLR) the participant will do a test lasting about 20 minutes in which a camera phone will record the size of your pupil during this period while you will hear some sounds. The exam is painless and without side effects.

Sample size calculation:

Based on the clinical trial of Li[43], which demonstrated an efficacy favoring bilateral TBS in depression of 52.5% for the active group and 17.4% for the sham group, for a two-tailed p 0.05 and a power of 90%, the total sample size Is 86 subjects. Considering a rate of friction of approximately 25%, we estimated the final sample size in 108 patients.

Statistical analysis

Statistical analysis will be performed with the Stata 16 SE program for Mac OS X. All analyzes will be made on the intention to treat principle (ie the data of all participants will be included in the analysis) in which lost data will be allocated according to the last observation carried forward principle and/or mixed data. Analyzes will be considered significant at $p < 0.05$. We will use parametric tests to analyze the main outcomes, which are allowed by the sample size. Number of previous admissions, presence of clinical comorbidities, refractoriness (measured by the Massachusetts General Hospital scale - MGH-S)[44] will be analyzed as ordinal data. For the main outcome we will use a repeated measures analysis, having HDRS scores as Dependent variable and TBS as independent variable at week 8. Secondary analyses of the other scales and biomarkers will be performed in the same way, replacing HDRS as a dependent variable.

Study Flow Chart

We show below the flowchart for each patient throughout the study. It is worth remembering that TBS will be applied 23 times: 20 consecutive sessions (week 0 through week 4), 6th week, 8th week and 12th week. Still, patients who receive *sham* stimulation and who are still depressed may receive active stimulation at the end of the study.

Table 1. Study schedule

	Triage	Baseline	Week						
			1	2	3	4	6	8	12
Assessment of eligibility	X								
Structured interview (MINI)	X								
Consent form	X								
Theta-burst stimulation (active/sham)			D	D	D	D	W	W	W
Clinical interviews	X		X	X		X	X	X	X
Adverse effects			X	X		X	X	X	X
Blood collection for serum biomarkers		X					X		
Neuropsychological evaluation		X					X		X
Cerebrospinal fluid collection		X							

"D" and "W" represent interventions performed daily and weekly, respectively.

Ethical aspects and safety

The rTMS is very safe when used properly and has few adverse effects, and as mentioned above, the most common is headache. Applications will always be made in a hospital setting with a physician present. We will evaluate patients 23 times over 12 weeks - so that we can quickly identify any worsening of the clinical picture and perform early intervention.

The study is approved by the Research Ethics Committee (CAAE: 80215117.5.0000.0068). All enrolled subjects will consent to participate through an Informed Consent Form.All the procedures described present minimal risk. If a volunteer presents a risk of major suicide, the same will be excluded from the study, adopting the standard procedure for the management of this type of patient. Participants may have access to their data and may leave the study at any time, without prejudice to any treatment they may perform within the institution. The data will be collected, analyzed and published in order to preserve the anonymity of the individual. In addition, the study will be conducted in accordance with all requirements of the Research Ethics Committee and also based on the recommendations established in the Declaration of Helsinki (1964), as amended in Tokyo (1975), Venice (1983) and Hong Kong (1989). As a benefit, participants will be able to participate in a clinical trial to treat their clinical condition. This

will be possible even if they receive sham stimulation, as they may receive active stimulation at the end of the study if they still have severe depressive symptoms.

Discussion

Here we provided the study protocol of a randomized controlled trial (RCT) that will evaluate the efficacy of TBS for the treatment of geriatric depression. To the best of our knowledge, this is the first study in this field. The participants will receive 23 sessions of bilateral TBS, comprising first inhibitory stimulation delivered by cTBS in the right DLPFC followed by excitatory stimulation delivered by iTBS in the left DLPFC, totalizing 3600 pulses. We performed sample size calculation based on the effect size found in the most similar clinical trial found in literature [45]. There are no specific treatments using neuromodulation for depression in the elderly. This study aims to answer this question. We will enroll patients with different degrees of refractoriness and the TBS as the only treatment for depression (the antidepressants will be wash-outed). , which will significantly increase the external validity of our results. These data could contribute to the analysis of some predictors of response as well.

We expect that TBS will be statistically superior to sham treatment for depression as assessed through the Hamilton Depression Rating Scale (HDRS). Other expected secondary outcomes consist of: TBS will be superior to sham treatment for improvement of depressive symptoms by the GDS (Geriatric Depression Scale), the MADRS (Montgomery-Asberg Depression Rating Scale), and the Global Clinical Impression Print Scale (CGI). Regarding serum markers, we expect that the TBS group active vs. sham will show a significant increase in BDNF levels. From the neurocognitive point of view, we expect that both groups will perform similarly.

Conclusions

This study will investigate the efficacy of TBS for the treatment of major depressive disorder in elderly patients using a randomized, sham-controlled design. The biomarker investigation will contribute to the understanding of the neurobiological mechanisms of depression and their relationship with the treatment. This trial will contribute valuable information to the treatment of depression in the elderly.

Author´s contributions:

LV is responsible for initiating and managing the trial, conceived and designed the essay, analyse the data and wrote the manuscript. PJCS, WG, AB, OF performed the statistical analyzes, LS, RB, CM, JL are responsible for the clinical evaluation.LT, HC, RV, RM responsible for the neuropsychological evaluation. PO responsible for the collection of CSF, KM responsible for collecting

cortical excitability,CIND andMCD. BP, BT responsible for collecting Pupil Examination.. VS is responsible for the application of rTMS. All authors contributed, read and approved the final manuscript.

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Conflicts of Interest

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest

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