UNIVERSIDADE LA SALLE
Postgraduate Program in Health and Human Development
Research Line: Pathological Process

Research Project

Association of low doses of naltrexone and Transcranial Direct Current Stimulation in fibromyalgia: randomized clinical trial, double blinded, controlled with placebo

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Canoas
2019

ABSTRACT

Fibromyalgia (FM) is a syndrome of chronic pain, which its physiopathology seems to involve alteration on the cortical system responsible for the processing of pain. Currently, the treatment for fibromyalgia became a big challenge, inasmuch as the available medicines present adverse effects that limit the adhesion of the same. Objectifying to modulate these altered circuits, Association of low doses of naltrexone and Transcranial Direct Current Stimulation (tDCS) have showed promising results for its capacity of reducing the pain in these patients. Besides that, the use of low doses of naltrexone at FM showed analgesic effects, which looks like interesting according to the pharmacodynamics profile of this medicine, being the probable mechanism of action the *up regulation* of opioids receptors and consequently the increase of endogenous opioids. Aiming to evaluate if the previous use of low doses of naltrexone potentiate analgesic effect induced by the tDCS in patients with fibromyalgia; it is proposed to evaluate the changes on the level psychophysical and neuroendocrine through evaluation with psychophysical pain tests, and levels of neurotrophins and serum cytokines. It will be conduced a randomized clinical trial, double blind, parallel, controlled with sham and placebo. It will be included 92 women between 18 and 65 years with confirmed diagnosis of fibromyalgia and pain evaluated as bigger than six in the Visual Analog Scale (VAS) at the last three months. All patients will sign an Informed Consent Questioner. Each patient will be randomized to receive 21 days of low doses of naltrexone or placebo, followed by 5 consecutive sessions of tDCS or sham-tDCS. We will evaluate the changes on pain after intervention, and we will study your association with the psychophysical profile of pain and serum neurotrophins, that might have predictive response function.

Key Words: fibromyalgia, low doses of naltrexone, Transcranial Direct Current Stimulation

INTRODUCTION

The chronic pain is a maladaptive process that manifests as a dysfunction of the nervous system. It causes considerable negative impact on the individual and the society, it onerous the health system affecting more than 20% of global population, allied to the incapacity, work departures and early retirement (Saastamoinen et al., 2012; Hecke, Torrance and Smith, 2013). Although the multiples mechanisms physiopathogenics that unleash and sustain this process are known, it is not clear the real impact of the therapeutic strategies on the mechanisms of neuroplasticity on the neuromatrix of pain. Among the conditions of chronic pain of hard treatment there is the fibromyalgia, characterized by musculoskeletal generalized pain, accompanied by fatigue, sleep alterations and humor (Wolfe, 2016). Sleep disturbances, depression e symptoms of fatigue, constitute the fibromyalgic syndrome (Russel and Raphael, 2008), that affects between 1-2% of the population, being more frequent in women (Bannwarth, 2009; Mas et al., 2008; McNally, Matheson and Bakowsky, 2006). Fibromyalgia courses with a deep impact on the activities and productivity in the daily life of the individual (Hawley and Wolfe, 1991; Martinez et al., 1995). More than one-third of the patients are forced to reduce the work journey or the level of work physically exigent, involving additional costs to the society in general. At USA, for example, 15% of population with fibromyalgia is retired due to disability (Russell, 2011).

The physiopathology model more accepted considers that there is an imbalance between the nociceptive process and the physiologic control of pain (Yunus, 2007). According to this model, there is a global decrease on the inhibitor routes of pain; allowing, that way, the stimuli of low intensity or non-nociceptive to be processed on pre-cortical structures and cortical involved on the affective and cognitive process of pain, increasing the painful perception (Burgmer et al., 2009). Based on this theory, the therapeutic approaches, aiming the modulation of the central nervous system, can be beneficent. Anticonvulsant drugs, that block up the sodium channels, for example, phenytoin, topriamate, carbamazepine, lamotrigine, increases the motor threshold; and agonists GABAergics, such as diazepam, reduce the signal of intracortical facilitating neurons potentiating the intracortical inhibition (Chen et al., 1997; Manganotti et al., 1990; Ziemann et al., 1996). Based on clinical works that demonstrate reasonable evidence, the antidepressant and anticonvulsant are recommended options for the fibromyalgia treatment (Arnold, 2006; Harris and Clauw, 2008). However, the use of anticonvulsants induces the depression of the central nervous system (CNS), leading the patients to present somnolence, mental confusion or imbalance. These central side effects are frequent (Chizh et al., 2007), because of this it is necessary the investigation of new options of treatment, wheter pharmacological or not pharmacological.

A therapeutic option that is still in study for the treatment of fibromyalgia is the use of low doses of naltrexone (Younger et al., 2013). Antagonist of the opioid receptors, naltrexone is used on the treatment of dependence on opioids and alcohol (Haber et al., 1997). Its structure and action mechanism are similar to the antagonist opioid, naloxone. However, naltrexone shows a greater bioavailability on oral and greater time of half-life (Verebey et Mulé, 1975). Naltrexone acts blocking opioids receptors leading to a compensatory increase on the production of endogenous opioids that activate the kappa opioids receptors. The activation of kappa receptors induces the anti-inflammatory effect, decreasing the IL-6 levels and neutrophils migration (Dan Segal et al., 2013).

Another mechanism potential for the effects of the use of low doses of naltrexone, happens by the antagonism on non-opioids receptors, such as *Toll like Receptor* 4 (TLR4) (Brown and Panksepp, 2008), found on macrophages. The blocking of TLR4 inhibits the release of cytokines pro-inflammatory, P substance, nitric oxide, excitatory amino acids and TNF conducing to negative regulation of the expression of the chemokine receptor and the adhesion molecule (Jarred et al., 2014).

Besides these mechanisms, studies in animals (Tempel, Gardner e Zukin, 1985) shows that the daily administration of naltrexone induces up-regulation of opioids receptors, reaching its high effect in 8 days of treatment. The therapy increased by 1,9 times the concentration of encephalic opioids receptors. The "*up-regulation*" induced by naltrexone happens, mainly, in receptors of subtype mu and delta, without changing significantly the density or affinity of kappa or sigma receptors. In the expected form, the chronic therapy with naltrexone increases the analgesia induced by morphine, that turns back to its basal approximately 6 day after the suspension of naltrexone.

Therefore, the use of low doses of naltrexone seems to be an interesting therapeutic from the pharmacodynamic point of view e also related to the adverse effects. Moreover, considering that most of fibromyalgics patients respond just partially to the treatment and that its neurophysiological effect is poorly known, a greater understanding of the effect of the therapeutics on the neuromatrix of pain, constituted by multiples centers of cortical and subcortical domain, could provide a better base of understanding to the diagnostic and therapeutic process.

Considering the importance of the searching of new therapeutic options for the treatment of Fibromyalgia, non-invasive techniques of cerebral stimulation can represent a promising focus of study. A neuromodulator technique has been studied for the treatment of chronic pain is the transcranial direct current stimulation(tDCS) (Boros et al., 2008; Floel et al, 2008; Fregni et al., 2006a; Fregni et al., 2006b; Hummel and Cohen, 2005; Wagner et al., 2007; Nitsche et al., 2003a; Nitsche et al., 2003b). It has been shown that this technique induces significant currents on cortical areas that induces alterations on the cortical excitability. These changes on excitability can be explained by synaptic changes and direct effects on the neuronal spontaneous activity (Boros et al., 2008). The changes of long duration on the excitability resemble in long term to the potentiation and depression, such as alterations of intensity of glutamatergic synapses (Boros et al., 2008; Nitsche et al., 2003a; Nitsche et al., 2003b; Nitsche et al., 2001; Nitsche et al., 2000). The duration of the effects depends on the time of the stimulation and can remain for more than one hour after stimulation (Medeiros et al., 2012). Because the mechanisms of action of tDCS induces a alteration on the neuronal spontaneous activity, the use of this technique combined to the drug effects on the matrix of pain can amplify the therapeutic effects.

tDCS modulates the cortical excitability by the application of a continuous current of low intensity (1-2mA) directed to the scalp by cathodes and anodes electrodes. The current reaches the cerebral cortex, producing hyperpolarization or depolarization of the potential of axonal membrane. Evidences have shown that this method of neuromodulation can change neural cortical e subcortical network (Medeiros et al., 2012). The use of tDCS on the treatment of pain has as theoretic and empiric support the reducing of pain and changing of neurophysiological report of the painful experience (Fregni, Freedman and Pascual-Leone, 2007; Zaghi et al., 2011). The tDCS stimulating the motor cortex is a non-invasive technique, of low cost and easy application and it has demonstrated efficacy on the treatment of pictures that curses with chronic pain. These properties characterize it as a promisor technique on the therapeutic scenario of many kinds of pain.

The tDCS effects are from dependent polarity, whose anodic stimulation induces cortical excitability and the cathodic stimulation, reduces. The effects are explained by the depolarization or hyperpolarization of the membrane, respectively. The kind of answer is bound to the stimulated area (Raghavan, Eldabe and Strachan, 2008). This effect is additive to the repetition of the stimulation courses. The lasting effect is due to the increase of the pre-synaptic *activation* and positive regulation of the synaptic mediated tonus by NMDA receptor, depending on protein synthesis, on modifications on the cyclic AMP intracellular and on calcium intracellular influx. These processes are part of the *long-term potention,- LTP* and *long-term depression - LTD* (Liebetanz et al., 2006). Experimental studies developed on a partnership with Brazilian laboratory demonstrated that, in animal models, the analgesia promoted by tDCS is mediated by opioid pathways, noradrenergic, serotoninergic, adenosinergic and canabinoids, on central and peripheral circuits (unpublished data). It is about, therefore, of a non-pharmacological technique, that acts modulating different endogenous systems to promote therapeutic effects.

As explained, the fibromyalgia courses with an alteration on the nociceptive system. The tDCS, by means of various mechanisms, could play a role by lowing the pain on those patients, being its clinical significance still a study subject. In consideration to the involvement of the opioid system both in the physiopathology of fibromyalgia, and on the tDCS action mechanisms, we propose to realize a “conditioning” of this system using naltrexone. As previously explained, low doses of naltrexone induces *up-regulation* of the opioids receptors. This induction would let the endogenous opioid system (responsible for the inhibition descending of pain, among others) with more exposition receptors, ready to be activated by tDCS.

To understand the effect of different therapeutic approaches on the neuroplasticity cerebral processes, added to the resources that operationalize this measure by physiological parameters, evaluation of the inflammatory marker levels, such as interleukins and neurotrofines like BDNF seems to be complementary. Besides the advantages to the patients and public safes, this is study may provide a new therapeutic option, which effect on the neurobiological processes in real time is still incipient on clinical research. In the study of pain, this association of different therapeutic modality allows to understand the complex integration of different structures that constitute the pain matrix, in reference of perception, modulation and therapeutic.

On the process of markers evaluation, it may be bound to the treatment course, directly or indirectly, once that the painful episodes courses with stress and IL-1 is a critic mediator of stress adaptive answer. It induces the activation of the hypothalamic axis adrenal hipophysis, at least in part, by changing on the hypothalamic noradrenergic neurotransmission. This way is mediated by IL-1β, that activates proto-oncogenes *c-fos* on the cellules producers of corticotrophin releasing hormone(CRH) of the paraventricular nuclei, by the spinal noradrenergic projections. Besides that, the peripheral IL-1 can stimulate the nucleus of the lonely tract, the ventrolateral medulla and the *locus ceruleus* to secrete noradrenaline, which, in turn, increases hypothalamic IL-1by microglia. This relation between cerebral IL-1 and the noradrenergic system seems to be bidirectiona. IL-1 also induces hyperalgesia and depressive symptoms, even in the absence of inflammation (Markus et al., 2003; Lorton et al., 2008). The BDNF is a neurotrophin that regulates the integrity and differentiation of neurons during its development, is also involved in many functions on the adult life, including the neuronal plasticity process. The BDNF expression on the CNS I modified by many impairments, such as stress, ischemic, hypoglycemia, depression, etc. It also can work in adaptive essential mechanisms, playing a crucial role on the synaptic potentiation process of long duration, neuroplasticity mechanism fundamental to unleash and sustain the pain memory process. The growth of BDNF increases the LTP, while the reduction of its levels attenuates this phenomenon. With this, it is observed that chronic painful condition depends on a long time process (Patterson et al. 1996; Kossel et al., 2001).

Considering what was exposed, the hypothesis of this study is that the previous use of low doses of naltrexone potentiate the analgesic effects of tDCS, by positive regulation of opioids receptors in female fibromyalgic patients.

OBJECTIVE

Primary Objective: evaluate the effect of low doses of naltrexone followed by tDCS for the treatment of pain in patients with fibromyalgia.

Secondary Objectives:

1. Measure the effect of low doses of naltrexone followed by tDCS on pain of patients with fibromyalgia, evaluated by Visual Analogue Scale
2. Study if the effect of this association present some impact on the quality of life and psychological factors of these patients, evaluated by the Fibromyalgia Impact Questionnaire, Beck Depression Inventory, State-Trait Anxiety Inventory, Pain Catastrophizing Thought and Profile of Chronic Pain
3. Study if this association induces changes on the nociceptive system, when evaluated by Pain Pressure Threshold (PPT) and Conditioned Pain Modulation
4. Evaluate if the effect of this association induces changes in possible serum biomarkers of neuroplasticity (BDNF) and cytokines.

MATERIAL AND METHODS

Design: Randomized clinical trial, double-blind, parallel, controlled.

Randomization and blinding: randomization table will be generated by a website (www.sealedenvelope.com), creating a list of randomization, using randomization in blocks with size equal to 8.The codes of randomization will be placed in sealed brown envelopes, it will be randomized in four groups:

1. tDCS + Placebo
2. tDCS + low doses of naltrexone
3. tDCS-*Sham* + Placebo
4. tDCS-*Sham* + low doses of naltrexone

Evaluators and patients will be blinded. The blinding will be kept in wall stages of the study. To evaluate the conservation of the tDCS blinding, at the end of 5 (five) sessions the patient will be inquired about the type of intervention that believes to have received (tDCS active or sham) and about the degree of safety on the answer, using a standardized questionnaire. The same will be realized to evaluate the blinding of naltrexone.

Follow-up

The patients will be evaluated for one week after the last intervention, to rate the effects after stopping the use of naltrexone and tDCS.

<u>Inclusion Criteria:</u> Provide an informed consent to participate on the study; women with age between 18 and 65 years; medical diagnoses of fibromyalgia according to the American College of Rheumatology criterion (2010); know how to read and write; pain evaluated as bigger than six at the last 3 months on the Visual Analogic Scale; treatment of chronic use stable on the last 3 months;

Exclusion Criteria: Be using opioid drugs; pregnancy or non-use of contraceptive method; history of alcohol or drugs abuse on the last 6 months; historic of neurologic pathology; history of cardiac arrhythmia and use of drugs that change the vascular answer (adrenergic blockers, vasodilators); history of cranial traumatism moderated or severe; history of neurosurgery; systemic decompensated disease, and chronic inflammatory disease (Lupus, rheumatoid arthritis, Sjogren Syndrome, Reiter Syndrome); history of hypothyroidism non compensated; personal history of cancer, passed or in treatment.

Evaluation: after the realization of the Informed Consent Questioner, it will be applied the following proceeds:

- Sociodemographic Questionnaire
- Visual Analogue Scale for Pain (VAS)
- Beck Depression Inventory (BDI-II)
- Fibromyalgia Impact Questionnaire (FIQ)
- State-Trait Anxiety Inventory (STAI)
- Pain Catastrophizing Scale (PCS)
- Blood samples for BDNF (Brain Derived Neurotrophic Factor)
- Pain Pressure Threshold (PPT)
- Conditioned Pain Modulation (CPM) task

As the randomization, the participant will receive 21 days of treatment with low doses of naltrexone (or placebo) and more 5 days in sequence of low doses of naltrexone combined with tDCS, 5 sessions of allocated intervention. During each session, the patient will be inquired about the perception of the pain with the Visual Analog Scale and about the presence of adverse effects, according to a standardized questionnaire. At the day of the last allocated session, the patient will be submitted to the same initials questionnaires and evaluations, except the demographic questionnaire.

Measurement of Outcomes

Measurement of Outcome by clinical parameters: Pain – The pain will be measured by the **Visual Analog Scale (EAV)** of 100 mm, whose zero corresponds to no pain and 100 to a lot of pain

CPM, *Conditioned Pain Modulation*: it will be measured as a difference on the pain score between two tests of painful stimulus, first applied on *baseline* and also, concomitantly with the conditioning painful stimulus produced by the non-dominant hand immersion on the water with temperature between zero and 1,5°C for 30 seconds.

Pain Pressure Threshold (PPT): measured using the electronic algometer with a rubber probe with 1 cm^2 applied on the right forearm. The researcher will touch the rubber probe slowly increasing the pressure, instructing the patient to report verbally as soon as feel the pain first sensation.

Laboratory Outcomes

It will be measured before the first allocated intervention session, and at the end of the last session, and it will be included the BDNF levels. The blood will be centrifuged, the supernatant will be aliquot and stored in a freezer at the research room at Clínicas Integradas Unilasalle, for posterior analysis, that will be realized by the ELISA technique, according to the manufacturer instructions.

Interventions

Low doses of naltrexone: the biggest clinical trial published until now (Younger et al., 2013) using low doses of naltrexone in patients with fibromyalgia, used a dosage of 4,5 mg VO each day. This dosage has been previously descripting in pilot studies (Younger and Mackey, 2009) and observational on fibromyalgia (Noon et al., 2016). Therefore, the pharmacological intervention will be consisted by the use of low doses of naltrexone (4,5mg lonely daily dose), for 26 days, being 21 days just naltrexone and 5 days subsequent combined to tDCS.

Naltrexone's placebo: the placebo will be produced by a manipulation pharmacy. It will be a capsule of the same color as naltrexone; however, the excipient utilized will be amid.

tDCS: The proceed will begin with the placing of a anodal electrode on the superjacent scalp of the primary motor cortex (contralateral to the dominant cortex), the cathode will be on the contralateral supra-orbital area. The size of the electrodes will be 35cm². The utilized current will be 2 mA applied for 20 minutes. A stimulator of constant current moved by battery will be used (tDCS device Soterix 1X1) (Fregni et al., 2006a, Fregni et al., 2006b). It will be done 5 sessions of stimulation, as reported in previously publications for the Fibromyalgia analgesia (Valle et al., 2009).

tDCS sham: the current will be applied just for 30 seconds. The patients can perceive the same sensation of the initial stimulation, but they will not receive current for the remaining period. Analogously to tDCS, it will be realized 5 sessions of sham stimulation.

tDCS Potential Adverse Effects: It will be used a standardized questionnaire of adverse effects.

Statistical Analysis

The comparison between the groups of average of the variable at *baseline* will be realized a one-way ANOVA, when the variables present normal distribution or equivalent test for statistics non-parametric. The comparison of the variables outcomes over the time will be done repeated measures ANOVA on a mixed linear model from fix effect, with adjust to the levels of *baseline* and possible confounders. Having the intervention group as factor and time as repeated measure to the outcome variables. It will be used the Bonferroni *post hoc* test to multiples comparisons to detect differences between groups in any of the measurements moments. The level of significance will be $P<0.05$, with respective adjusts to multiple comparisons. The analysis will be processed using SPSS 20.0 version (SPSS, Chicago, IL).

Ethics: The study follows the established conditions at 466/12 Resolution from Conselho Nacional de Saúde (CNS) and will be registered on the international platform www.ClinicalTrials.gov.

MAIN SCIENTIFIC, TECHNOLOGICAL OR FROM INOVATION CONTRIBUTIONS OF THE PROPOSE

As bigger goal, we look up to strengthen the activity of academic cooperation between the Post-graduation Program in Health and Human Development with excellence global centers of this investigation area. The concretization of this study can have applicability in other conditions mentioned above to understand physiological, physiopathological aspects, predict and evaluate outcomes until then only inferred by means of depressive and anxiety symptoms. Besides that, we look for contribution with the development of post-graduation and research group involved, collaborating both qualitatively and quantitatively with the scientific and technological development of the country. It is intended to help on the fortification of the international competitiveness of the Brazilian research by innovation and regional development, in a local, regional and international development policy. In addition to enable a improvement on the patient care that suffer with pathologies that demand high costs from the Brazilian health public system.

DETAILED BUDGET

Prof. Andressa already own all equipment at your disposal to execute the project, the materials that has to be acquired are going to be provided by external research edicts or from own financing.

Spend – Consumption Material (Values are described in Reais)

Specification	**Quantity**	**Unit Cost**	**Total Cost**
Kit ELISA BDNF human	01	4.800,00	4.800,00
Kit ELISA IL1-beta human	01	4.800,00	4.800,00
Saline 9% 250 Ml	92	1,70	156,40
Alcohol PA	1	68,50	68,50
Cotton	2	5,95	11,90
Rechargeable batteries for the tDCS– AA with 4 units	2	84,00	168,00
Prints of questionnaires and TCLE	1000	0,20	200,00
TOTAL VALUE			10.204,80

Capital – Permanent Material (Values are described in Reais)

Specification	**Quantity**	**Unit Cost**	**Total Cost**
Notebook	1	R$ 1.800,00	R$ 3.100,00
Pressure Algometer (Algomed)	1	R$ 13.000,00	R$ 13.000,00
Total	R$ 16.100,00		

ACTIVITY SCHEDULE

Year/ Activity	**Schedule divided by trimester**			
2017	**1º**	**2º**	**3º**	**4º**

Patients call and application of the inclusion and exclusion criteria				X
Randomization and data collect				X
Data typing				X
2018	**1º**	**2º**	**3º**	**4º**
Patients call and application of the inclusion and exclusion criteria	X	X	X	X
Randomization and data collect	X	X	X	X
Data typing	X	X	X	X
2019	**1º**	**2º**	**3º**	**4º**
Patients call and application of the inclusion and exclusion criteria	X	X	X	X
Randomization and data collect	X	X	X	X
Data typing	X	X	X	X
Statistics Analysis			X	X
2020	**1º**	**2º**	**3º**	**4º**
Write and Submission of scientific articles and reports.	X	X	X	X

All activities are occurring according what was planned

BIBLIOGRAPHIC REFERENCES

Arnold, L.M., Biology and therapy of fibromyalgia. New therapies in fibromyalgia. Arthritis Res Ther, 2006. 8(4): 212.

Bannwarth B, Blotman F, Roué-Le Lay K, Caubère JP, André E, Taïeb C. Fibromyalgia syndrome in the general population of France: A prevalence study. Jt Bone Spine. 2009;76:184-187.

Beck A, Steer R, Brown G. Beck Depression Inventory-II.; 1996.

Boros, K., et al., Premotor transcranial direct current stimulation (tDCS) affects primary motor excitability in humans. Eur J Neurosci, 2008. 27(5):1292-300.

Brown, N., Panksepp, J., 2008. Low-dose naltrexone for disease prevention and quality of life. Med. Hypotheses 72 (3):333–337.

Burgmer, M., et al., Altered brain activity during pain processing in fibromyalgia. Neuroimage, 2009. 44(2): 502-8.

Buysse, DJ, Reynolds CF, Monk TH, Berman SR KD. Pittsburgh Sleep Quality Index (PSQI). Psychiatry Res. 1989;28:193-213.

Chen, R., et al., Effects of phenytoin on cortical excitability in humans. Neurology, 1997. 49(3): 881-3.

Chizh, B.A., et al., Effects of oral pregabalin and aprepitant on pain and central sensitization in the electrical hyperalgesia model in human volunteers. Br J Anaesth, 2007. 98(2):246-54.

Collins S, Moore R, McQuay H. The visual analogue pain intensity scale: What is moderate pain in millimetres? Pain. 1997;72(1-2):95-97.

Dan Segal, A., John, K., Nilesh, C. Low dose naltrexone for induction of remission in Crohn's disease. Funct. Bowel Disord. 2013; 28, 23–34.

Fagerlund AJ, Hansen OA, Aslaksen PM. Transcranial direct current stimulation as a treatment for patients with fibromyalgia: a randomized controlled trial. Pain. 2015;156(1):62-71.

Floel, A., et al., Noninvasive brain stimulation improves language learning. J Cogn Neurosci, 2008. 20(8): 1415-22.

Fregni F, Boggio PS, Lima MC, et al. A sham-controlled, phase II trial of transcranial direct current stimulation for the treatment of central pain in traumatic spinal cord injury. Pain. 2006a;122(1-2):197-209.

Fregni F, Gimenes R, Valle AC, et al. A randomized, sham-controlled, proof of principle study of transcranial direct current stimulation for the treatment of pain in fibromyalgia. Arthritis Rheum. 2006b;54(12):3988-3998.

Fregni, F., S. Freedman, and A. Pascual-Leone, Recent advances in the treatment of chronic pain with non-invasive brain stimulation techniques. Lancet Neurol, 2007. 6(2):188-91.

Haber, H., Roske, I., Rottmann, M., Georgi,M., Melzig,M., 1997. Alcohol induces formation of morphine precursors in the striatum of rats. Life Sci. 60 (2):79–89.

Hawley, D.J. and F. Wolfe, Pain, disability, and pain/disability relationships in seven rheumatic disorders: a study of 1,522 patients. J Rheumatol, 1991. 18(10):1552-7.

Harris, R.E. and D.J. Clauw, Newer treatments for fibromyalgia syndrome. Ther Clin Risk Manag, 2008. 4(6):1331-42.

Hecke, oV., Torrance, N., Smith, B.H., Chronic pain epidemiology and its clinical relevance. Br J Anaesth, 2013. 111(1):13-8.

Hummel, F. and L.G. Cohen, Improvement of motor function with noninvasive cortical stimulation in a patient with chronic stroke. Neurorehabil Neural Repair, 2005. 19(1):14-9.

Jarred, Y., Luke, P., David,M., 2014. The use of low-dose naltrexone (LDN) as a novel antiinflammatory treatment for chronic pain. Clin. Rheumatol. 33 (4):451–459.

Kaipper MB, Chachamovich E, Hidalgo MPL, Torres ILDS, Caumo W. Evaluation of the structure of Brazilian State-Trait Anxiety Inventory using a Rasch psychometric approach. J Psychosom Res. 2010;68(3):223-233.

Kossel, A., et al., A caged Ab reveals an immediate/instructive effect of BDNF during hippocampal synaptic potentiation. Proceedings of the National Academy of Sciences of the United States of America, 2001. 98(25):14702-14707.

Liebetanz, D., et al., After-effects of transcranial direct current stimulation (tDCS) on cortical spreading depression. Neurosci Lett, 2006. 398(1-2): 85-90.

Lorton, D., et al., Proinflammatory cytokines and sickness behavior in rheumatic diseases. Curr Pharm Des, 2008. 14(13):1242-60.

McNally, J.D., D.A. Matheson, and V.S. Bakowsky, The epidemiology of self-reported fibromyalgia in Canada. Chronic Dis Can, 2006. 27(1):9-16.

Manganotti, P., et al., Cortical excitability in patients after loading doses of lamotrigine: a study with magnetic brain stimulation. Epilepsia, 1999. 40(3):316-21.

Markus, R.P., et al., Melatonin nocturnal surge modulates nicotinic receptors and nicotine-induced [3H]glutamate release in rat cerebellum slices. J Pharmacol Exp Ther, 2003. 305(2): 525-30.

Martinez, J.E., et al., Psychological aspects of Brazilian women with fibromyalgia. J Psychosom Res, 1995. 39(2):167-74.

Mas AJ, Carmona L, Valverde M, Ribas B. Prevalence and impact of fibromyalgia on function and quality of life in individuals from the general population: results from a nationwide study in Spain. Clin Exp Rheumatol. 2008;26(4):519-526.

Medeiros, L.F., et al., Neurobiological effects of transcranial direct current stimulation: a review. Front Psychiatry, 2012. 3:110.

Nitsche, M.A., et al., Pharmacological modulation of cortical excitability shifts induced by transcranial direct current stimulation in humans. J Physiol, 2003a. 553(Pt 1):293-301.

Nitsche, M.A., et al., Modulation of cortical excitability by weak direct current stimulation--technical, safety and functional aspects. Suppl Clin Neurophysiol, 2003b. 56:255-76.

Nitsche, M.A. and W. Paulus, Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J Physiol, 2000. 527 Pt 3:633-9.

Nitsche, M.A. and W. Paulus, Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. Neurology, 2001. 57(10):1899-901.

Noon K, Sturgeon J, Kao M, Darnall B, Mackey S. (418) A novel glial cell inhibitor, low dose naltrexone, reduces pain and depression, and improves function in chronic pain: A CHOIR study. J Pain. 2016 Apr;17(4S):S79.

Patterson, S.L., et al., Recombinant BDNF rescues deficits in basal synaptic transmission and hippocampal LTP in BDNF knockout mice. Neuron, 1996. 16(6):1137-45.

Pesce RP, Assis SG, Avanci JQ, Santos NC, Malaquias J V, Carvalhaes R. [Cross-cultural adaptation, reliability and validity of the resilience scale]. Cad Saude Publica. 2005;21:436-448.

Raghavan, S., S. Eldabe, and R. Strachan, Novel trends in pain management – Neuromodulation. Current Anaesthesia & Critical Care, 2008. 19:344-348.

Russell, I.J. and K.G. Raphael, Fibromyalgia syndrome: presentation, diagnosis, differential diagnosis, and vulnerability. CNS Spectr, 2008. 13(3 Suppl 5): 6-11.

Russell, I.J., Future perspectives in generalised musculoskeletal pain syndromes. Best Pract Res Clin Rheumatol, 2011. 25(2): 321-31.

Saastamoinen, P., Laaksonen, M., Kaaria, SM., Lalluka, T., Leino-Arjas, P., Rahkonen, O., Lahelma, E., Pain and disability retirement: A proscpective cohort study. Pain, 2012. 153(1):526-531.

Schestatsky P, Stefani LC, Sanches PR, et al. Validation of a Brazilian quantitative sensory testing (QST) device for the diagnosis of small fiber neuropathies. Arq Neuropsiquiatr. 2011;69(6):943-948.

Tempel A, Gardner EL, Zukin RS. Neurochemical and functional correlates of naltrexone-induced opiate receptor up-regulation. J Pharmacol Exp Ther. 1985;232(2):439-44.

Valle A, Roizenblatt S, Botte S, et al. Efficacy of anodal transcranial direct current stimulation (tDCS) for the treatment of fibromyalgia: results of a randomized, sham-controlled longitudinal clinical trial. J Pain Manag. 2009;2(3):353-361.

Verebey K, Mulé SJ (1975) Naltrexone pharmacology, pharmacokinetics, and metabolism: current status. Am J Drug Alcohol Abuse 2(3–4):357–363.

Wagner, T., et al., Transcranial direct current stimulation: a computer-based human model study. Neuroimage, 2007. 35(3):1113-24.

Wolfe F, Smythe H a, Yunus MB, et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. Arthritis Rheum. 1990;33(2):160-172.

Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Hauser W, Katz RL, Mease PJ, Russel AS, Russel IJ, Walitt B. 2016 revisions to the 2010/2011 Fibromyalgia Diagnostic Criteria. Semin Arthritis Rheum. 2016;46(3):319-329.

Younger J, Mackey S. Fibromyalgia symptoms are reduced by low-dose naltrexone: a pilot study. Pain Med 2009;10:663–72.

Younger, J., Noor, N., McCue, R., & MacKey, S. (2013). Low-dose naltrexone for the treatment of fibromyalgia: Findings of a small, randomized, double-blind, placebo-controlled, counterbalanced, crossover trial assessing daily pain levels. Arthritis and Rheumatism, 65(2):529–538.

Yunus, M.B., Fibromyalgia and overlapping disorders: the unifying concept of central sensitivity syndromes. Semin Arthritis Rheum, 2007. 36(6):339-56.

Zaghi, S., et al., Assessment and treatment of pain with non-invasive cortical stimulation. Restor Neurol Neurosci, 2011. 29(6): 439-51.

Ziemann, U., et al., Effects of antiepileptic drugs on motor cortex excitability in humans: a transcranial magnetic stimulation study. Ann Neurol, 1996. 40(3):367-78.

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

NOME DO ESTUDO: Efeitos da combinação de baixas doses de naltrexona e Estimulação Elétrica Transcraniana na fibromialgia: ensaio clínico randomizado, cego, controlado com placebo.

Número do protocolo:________________________________

Instituição: Universidade La Salle – Clínicas Integradas

Pesquisador Responsável: Dra. Andressa de Souza – 51 981975718

Você está sendo convidado para participar, como voluntária, em uma pesquisa. Após ser esclarecida sobre as informações a seguir e retirado todas as suas dúvidas sobre a pesquisa, no caso de aceitar fazer parte do estudo, assine ao final deste documento, que está em duas vias. Uma delas é sua e a outra é do pesquisador responsável.

1. OBJETIVO DO ESTUDO

Avaliar o efeito do tratamento da dor por meio da utilização do medicamento naltrexona e da aplicação de corrente contínua de baixa intensidade sobre a cabeça (ETCC - figura 1), à pesquisa de marcadores de resposta em pacientes com fibromialgia. Os efeitos destas intervenções serão avaliados por meio de exames de sangue, percepção da dor por estímulos leves que produzem as sensações de calor e a pressão. Haverá perguntas sobre os seus sentimentos, nível de dor e pensamentos que lhe aparecem na cabeça durante o tratamento.

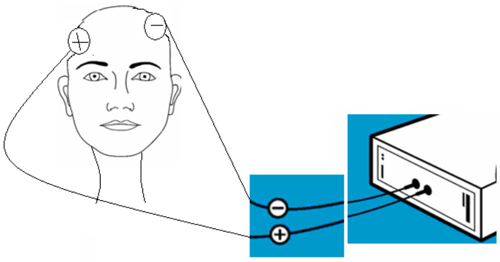

Figura 1. ETCC.

2. EXPLICAÇÃO DOS PROCEDIMENTOS

Para participar da pesquisa, será necessário que a senhora responda várias perguntas antes, durante e após os procedimentos. O estudo ocorrerá ao longo de sete visitas. A sua participação é voluntária. Se concordar, serão aplicados os questionários e daremos início ao estudo. Na continuação, serão explicados os procedimentos realizados em cada visita:

Na primeira visita serão realizadas: coleta de sangue, questionários e testes da sensibilidade à dor. A coleta da amostra de sangue avaliará a produção de marcadores sanguíneos relacionados a sensação de dor. O sangue será coletado antes de se iniciar os procedimentos na primeira visita. O volume de sangue será de 10 ml a cada coleta, o equivalente a duas colheres de sopa. Depois, serão realizados questionários para verificar a qualidade do sono, características de sintomas de tristeza, nível de dor, ansiedade e os pensamentos relacionados à dor. Nos testes de senbilidade à dor, será colocado um equipamento que produz estímulos leves de sensações de calor e de pressão, através de um aparelho que será posicionado no seu braço. Nesta primeira visita você receberá um pote com 26 cápsulas do medicamento naltrexona, que a senhora deverá utilizar uma cápsula por dia, pela manhã. A senhora deverá utilizar esse medicamento por 21 dias e retornar para avaliação no 22º dia. Se a senhora sentir qualquer incomodo com o uso do medicamento, deverá entrar em contato imediatamente com o pesquisador do estudo. Esta visita terá duração aproximada de uma hora.

Na segunda visita, serão realizados os mesmos questionários e testes da primeira visita, além da coleta de sangue. Finalmente, será realizada a primeira sessão com a estimulação trancraniana de corrente contínua (ETCC), com aplicação de uma corrente elétrica fraca na sua cabeça por 20 minutos, como será explicado no item Sessões de ETCC. Após a estimulação serão feitos testes para avaliar a dor ou desconforto e pesquisa de aparição de efeitos adversos. Estima-se que o tempo para cada uma destas visitas seja de uma hora.

<u>Na terceira à quinta visita</u> será realizada a sessão de ETCC e a pesquisa de aparição de efeitos adversos. Estima-se que o tempo para cada uma destas visitas seja de 40 minutos.

<u>Na sexta visita</u>, serão realizados os mesmos questionários e testes da primeira visita, além da coleta de sangue. Será realizada a sessão com a estimulação trancraniana de corrente contínua (ETCC). Após a estimulação serão feitos testes para avaliar a dor ou desconforto e pesquisa de aparição de efeitos adversos. Estima-se que o tempo para cada uma destas visitas seja de uma hora.

<u>Na sétima visita</u> ocorrerá sete dias após a última dose do medicamento e última sessão de ETCC, então serão realizados os mesmos questionários e testes da primeira visita, além da coleta de sangue, afim de verificar os efeitos após cessar o uso do tratamento. Estima-se que o tempo para cada uma destas visitas seja de 40 minutos.

3. MEDICAÇÃO - NALTREXONA

A naltrexona é um medicamento que em baixas doses tem sido estudada para o tratamanento da fibromialgia. Neste estudo você poderá receber a medicação verdadeira, naltrexona 4,5mg, ou placebo. Nem o participante da pesquisa, nem os profissionais responsáveis pela condução dos testes saberão qual tipo de tratamento.

4. SESSÕES DE ETCC

Neste estudo, as sessões serão realizadas conforme o protocolo. Será composto por dez sessões, nas quais iremos utilizar eletrodos ("borrachas umedecidas") que serão colocados na sua cabeça, através dos quais passarão uma corrente elétrica de baixa intensidade. No grupo "sham", a sessão será realizada com os mesmos equipamentos que não emitirão nenhum estímulo. Se concordar em participar do estudo, terá que cooperar em todas as etapas do mesmo. Nem o sujeito de pesquisa, nem os profissionais responsáveis pela condução das sessão de ETCC saberão qual tipo de tratamento (ativo ou "sham") a senhora estará recebendo.

3. GRUPOS DE PESQUISA

Após um sorteio utilizando um site na internet, você será alocado em um dos 4 grupos de tratamento:

1. ETCC + Medicação verdadeira
2. ETCC + Placebo
3. ETCC-*Sham* + Medicação verdadeira
4. ETCC-*Sham* + Placebo

5. POSSÍVEIS RISCOS E DESCONFORTOS

Um possível desconforto poderá ser sentido, por algumas pessoas, na coleta de sangue, pois implica uma picada que poderá gerar uma mancha roxa no local, que desaparecerá em poucos dias. Durante a aplicação da estimulação poderá ocorrer vermelhidão, sensações de coceira, leve formigamento no local onde serão colocados os eletrodos. Com os questionários você poderá se sentir desconfortável ao responder alguma pergunta pessoal ou sobre o seu estado de saúde e qualidade de vida. Nos testes de sensibilidade à dor você poderá sentir um desconforto na região local do braço e apresentar alguma vermelhidão, que deverão desaparecer em pouco tempo. Em relação ao uso do medicamento, você poderá apresentar os seguintes efeitos adversos: nausea, cefaleia, visão turva e alterações do humor, que podem ocorrer em aproximadamente 1% da população.

6. POSSÍVEIS BENEFÍCIOS DESTES ESTUDOS

Você poderá não beneficiar-se diretamente da participação neste estudo pois, embora a naltrexona e a ETCC ETCC visem diminuir a dor e melhorar a qualidade de vida, 5 sessões de ETCC podem diminuir a dor mas por um tempo de duração limitado a semanas. Porém, com os resultados deste estudo poderemos obter informações importantes sobre o quanto esta terapia poderá beneficiar outros pacientes com quadros de dor semelhantes ao seu, ou você mesma num futuro próximo.

7. EXCLUSÃO DO ESTUDO

O investigador responsável poderá ao longo do estudo considerar o seu afastamento da pesquisa, caso seja verificado que você não preenche adequadamente os critérios necessários ou seja verificado que a pesquisa possa adicionar outros riscos para você .

8. DIREITO DE DESISTÊNCIA

Sua participação é totalmente voluntária, e você pode desistir de participar a qualquer momento da pesquisa, sinta-se à vontade. Sua decisão de não participar ou de deixar a pesquisa depois de iniciada não prejudicará a atenção recebida nas clínicas integradas da La Salle.

9. PRIVACIDADE

Os pesquisadores se comprometem em manter a confidencialidade dos dados. Todas as informações obtidas deste estudo poderão ser publicadas com finalidade científica, preservando os dados de identificação dos participantes.

10. CONTATO DOS PESQUISADORES

Caso você tenha alguma dúvida poderá entrar em contato com o pesquisador responsável por este estudo: Profº Dra. Andressa de Souza, através do telefone 981975718. Ou, poderá contatar o Comitê de Ética e Pesquisa da Universidade La Salle, pelo e-mail: cep.unilasalle@unilasalle.edu.br

11. RESSARCIMENTO DE DESPESAS

Você não terá despesas com a sua participação na pesquisa e não será remunerada por ela.

12. CONSENTIMENTO

Este termo de Consentimento Livre e Esclarecido será assinado em duas vias, uma para você e uma via será arquivada pelo pesquisador. Desta forma, declaro ter lido – ou me foi lido – as informações acima antes de assinar este Termo. Foi-me dada ampla oportunidade de fazer perguntas, esclarecendo plenamente minhas dúvidas. Por este instrumento, torno-me parte, voluntariamente, do presente estudo.

Nome do participante: ____

Assinatura do participante: ____

Nome do pesquisador: ____

Assinatura do pesquisador: ____

Porto Alegre, _______ de ________________________ de _____.