Efficacy and Safety of rTMS Plus Rehabilitation for the Improvement of the Upper Extremity in Stroke (ERES)

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Title of the project	**Pilot Study to Evaluate the Efficacy and Safety of rTMS Associated With Rehabilitation for the Improvement of the Functionality of the Upper Extremity in Stroke**
Start of the study	15/October/2019
End of the study	15/April/2021
Research Program	Non invasive stimulation
Type	Study
Classification	Research

Summary:

The rehabilitation of the upper limb after a stroke is a challenge due to its complexity and the important cerebral representation of it, particularly of the hand. Repetitive transcranial magnetic stimulation (rTMS) is a tool that can broaden the effect of rehabilitation and thus appears to be observed in different studies performed in patients in chronic phase. However, we have little data on its usefulness before 6 months after the stroke. The variability in the presentation and the fact that it is a phase where the motor deficit of the upper limb coexists with other deficits and medical problems partly explain the lack of specific studies.

We present here a preliminary study on the efficacy of rTMS associated with the rehabilitation program of the paretic upper extremity due to a stroke in comparison with sham rTMS. Patients (with moderate to mild involvement) will be randomly distributed in the two study groups and will be evaluated both clinically and neurophysiologically before and after the sessions to try to show if there is a positive effect safely.

Introduction :

Stroke is the leading cause of acquired disability in the world (Donnan et al, 2008). Although in recent years there has been a real revolution in treatments in the acute phase of ischemic stroke, up to 60% of patients who have suffered it show some alteration of manual dexterity at 6 months (Lai et al. 2002). Rehabilitation plays a positive role in improving the functionality of patients, but it is very unlikely that a patient who does not recover manual functionality can perform, for example, the same work that was previously performed (Kwakkel et al, 2002).

Different rehabilitation techniques have been added in recent years to the catalog of what has been classically called "conventional treatment" in order to maximize its effectiveness (Claflin et al, 2015) and one of them is the use of non-invasive stimulation. Non-invasive stimulation includes transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS). The latter manages to induce an electric current that leads to neuronal depolarization through rapid changes in the magnetic field induced by a coil. The objective is to modulate the cortical excitability and induce functional plasticity that allows a better motor learning when the specific motor tasks of the rehabilitation treatment are performed (Reis et al., 2008).

Generally, non-invasive stimulation has been based on two principles: of increasing the excitability of the affected hemisphere (which is translated at the level of rTMS in performing a stimulation at frequencies greater than 5 Hz) or of reducing that of the healthy hemisphere (with stimulation frequencies equal to or less than 1 Hz) to minimize intracortical inhibition that may exert on the affected hemisphere (Takeuchi 2012). Besides the question of the type of stimulation, another determining factor is its dosage: There is a presumption that more intensity and longer duration is usually associated with a greater effect, although this in turn could increase the risk of side effects with seizures, headache or nuchal pain, as well as greater operational difficulties. In this sense, consensus has been established through different guidelines for applying the techniques in a safe manner (Wassermann et al, 1998).

The majority of studies that have evaluated the use of rTMS for the improvement of the upper limb have been performed in chronic patients with inhibitory stimulation contralateral to the lesion. We can say that in this case, based on the published studies, there is a level of evidence B in relation to this assumption. (Lefaucheur et al 2014, Emara et al 2010). However, some studies have also been conducted with fewer patients in acute and subacute phases with different results (Seniow et al 2012, Sasaki 2013, Zheng 2015) and even a few works with high frequencies in the injured hemisphere (Khedr 210 et al. al, Emara et al 2010). Another issue addressed by these studies is to know which is the best of the therapies to be associated with the stimulation and the degree of synergy of both activities (Avenanti et al 2012, Seniow et al 2012).

In relation to the location of the lesions, some studies suggest that the benefit of the effect would be greater in the case of subcortical lesions than in those cases of cortical involvement (Ameli et al 2009, Emara et al 2009); less information we find about what are the neurophysiological characteristics that indicate a greater response.

In summary, rTMS is a tool that can be useful to improve the response of rehabilitation treatment of upper limb paresis after a stroke, although this seems more evident in the case of chronic patients. We do not know, however, which are the most correct parameters and the best rehabilitation to be applied jointly, as well as knowing the type of patients that will have a greater benefit. In our particular case we want to obtain data that indicate the efficacy of low-frequency rTMS contralateral to the lesion associated with our rehabilitation treatment protocol in acute / subacute patients (less than 6 months of evolution).

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Outcomes :

- Primary outcome:
- To evaluate the efficacy of low-frequency rTMS contralateral to the lesion in patients with stroke in the subacute phase (<6 months), associated with rehabilitation treatment in the improvement of functionality of the paretic upper limb.
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- Secondary outcome:
- To analyze the presence of neurophysiological differences between patients who have received rTMS associated with rehabilitation of the upper limb and patients who have undergone such treatment after sham stimulation in the subacute phase.
- Establish the clinical and neurophysiological elements that may indicate that patients respond better to rTMS plus rehabilitation of the upper extremity in subacute phase
- Evaluate the safety of rTMS associated with rehabilitation in subacute patients with stroke.

Hypothesis :

Low-frequency rTMS contralateral to the injury in patients with stroke in the subacute phase (<6 months) improves the rehabilitation performance of the upper limb in a safe manner

Material and Methods:

1) DESIGN
The study presents a randomized design (rTMS vs simulated stimulation) in patients with a single stroke of less than 6 months of evolution and unialteral involvement, who have a brachial paresis with scores on the Fugl Meyer scale (FM) ≥ 22 in the upper limb. The different clinical evaluations (previous and result of the intervention) will be carried out blindly with respect to real or simulated rTMS realization. To do this, patients will be selected who come to our center on an admission or outpatient basis.
The intervention phase will last 3 weeks (daily sessions from Monday to Friday), completing a final of 15 sessions. In each session EMTr would be performed first and immediately the rehabilitation treatment of the upper limb based on the protocol of our center (1 specific hour, within the integral program). Evaluations will be made before the intervention, at the end of the intervention and one month later.

• Patients: Patients with a stroke (ischemic-hemorrhagic) that conditions a unilateral limitation (brachial monoparesis or hemiparesis) and that presents a moderate or mild deficit (motor score on the FM scale ≥ 22 at motor level of the upper extremity) .To Participate in the study the patients must sign an informed consent and be > 18 y.o. Patients with epilepsy or those with electrical devices in their body or metallic ones in the brain, as well as patients with craniotomy without cranioplasty, will be excluded from the study. All patients whose medical conditions prevent them from complying with the rehabilitation protocol will be excluded

• rTMS: Patients will be distributed randomly in real or sham rTMS before the specific rehabilitation treatment. To do this, a Magstim Super Rapid magnetic stimulator (Magstim Company, Whitland, Wales, UK) equipped with a double cone coil was used to position it on the cranial cortex. Simulated stimulation will be performed by placing the same coil without being connected, but maintaining the characteristic noise of the stimulation (all this assembly will be kept out of the patient's visual field). The rTMS intensity is calculated over 90% of the motor threshold, evaluated by EMG of surfaces, of the first dorsal interosseous of the hand without motor involvement. From this intensity, adjustments can be made depending on the tolerance. This system has been previously carried out in different studies of ours and other groups for different pathologies, proving safe and tolerable. For rTMS 1500 pulses of 1 Hz frequency will be used at the sub-threshold intensity commented on the optimal score in M1 of the unaffected hemisphere (in relation to the first interosseous dorsal muscle). The simulated rTMS will be applied during the same time. The patient will be in a sitting position while the technique is performed.

• Rehabilitation treatment of the upper limb: The rehabilitation treatment protocolized in our center will be followed within the comprehensive stroke treatment program. According to this protocol, there would be differences between a moderate patient (FM upper extremity motor between 22 and 45) and mild (FM upper limb motor greater than 45).

- Moderate: Active mobility work, proprioceptive treatment, exercises with reality virtual and biofeedback and use of robotic systems with multiple repetitions.
- Mild: Work of active mobility, proprioceptive treatment, exercises with reality virtual and biofeedback, as well as restrictive therapy.

In any case, to compensate for the potential variability of rehabilitative work, the therapist will be blind to the condition of real or simulated stimulation of the patient.

- Clinical evaluation: A specific clinical evaluation will be carried out before, at the end of the treatment and a month after the same. In this evaluation the FM, Block Test, 9- HPT and ARA Test scale will be evaluated. In turn, spasticity in the muscle groups of the upper extremity will be evaluated using the modified Ashworth scale (Bohanson & Simth 1987) and an analogue numerical scale (from 1 to 10) according to the patient's assessment. In turn, demographic data (sex, age) and stroke characteristics (classification, location, NIHSS) will be registered in the first visit.

- Neurophysiological evaluation: The neurophysiological evaluation will be carried out before the first session and after the end of the intervention phase. The evaluation will be performed with the patient seated, using Ag-AgCl bipolar surface electrodes and a routine electrodiagnostic device using bipolar Ag-AgCl surface electrodes and a CED Spike electrodiagnostic device (CED Micro 1401 analog-to digital system). The motor evoked potentials of the first dorsal interosseous of hand hands will be evaluated, calculating the motor threshold, the recruitment curve and the paired impulse curve. For this, stimuli will be performed by Magstim Super Rapid EMT (Magstim Company, Whitland, Wales, UK) equipped with a focal coil to position it on the cranial cortex. The minimum threshold will be considered to be the motor threshold for at least 5 evoked potentials of at least 50 µV in 10 stimuli.

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- Statistical analysis: Changes in the clinical scales (FM and ARA Test) between the two groups will be compared by means of nonparametric tests (Mann-Whitney T test) or, if the normality (Kolmogorov-Smirnov) is not rejected, the TTest test. In addition, the response variables (in these three tests) will be related to various demographic, neurophysiological variables and the characteristics of their disease), using the test to obtain a confidence of 95% and a power of 80%, it is estimated that the sample size it must be at least 10 subjects in each group (the objective of the study will be a minimum of 24 subjects to improve the statistical weight).

2) LIMITATIONS

The present study shows a series of limitations, most of them intrinsic to the difficulty of the object of the same and to the characteristics of the rehabilitation treatment. The aim of the study is to find indications of the efficacy of rTMS in the subacute phase for the improvement of the functionality of the upper extremity in stroke, which allows us to consider studies of a larger sample size and a more homogeneous sample.

- Strokes show great variability in etiology, location and response to rehabilitation treatment. We will try to perform a subanalysis of all these factors, although the sample size will not allow us to reach definitive conclusions.
- The radiological variables will be analyzed in a qualitative way, given the diverse origins with different characteristics of the patient's image tests
- The rehabilitative treatment, although it is protocolized, presents a variability marked by the necessary individualization (since we maintain the usual treatment of our center). This limitation is tried to compensate with the condition of blind for the condition of stimulation of the patient on the part of the therapist.
- The rhythm of patient recruitment can be variable given the characteristics of the patients who enter our center according to the stroke plan (patients with an important affectation, many of them severe and very severe in relation to the upper limb, and who in principle, it is unlikely that they can benefit from rTMS).

Pla de Treball:

Recruitment of patients for the study: 15 month period

Duration of the study: 18 months

- 1st month:
Start-up of the study, assessing in an initial patient the mechanics of evaluation and intervention measures in a coordinated manner. Randomization plan for patients. Before
start the study will register the same in the trials.gov page
-2nd to 15th month:
Carrying out of the study, with the realization of the first clinical and neurophysiological evaluation of each patient the week before performing the rTMS and the week after the end of the stimulation. A new clinical evaluation will be carried out at 4 weeks (± 1 week)
- 14th to 18th month:
Analysis of the data and starting of their dissemination.

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