



Cairo university
Faculty of physical Therapy
Research Ethical Committee

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To: Dr: Engy Badreldin Saleh

الباحثة : انجي بدر الدين صالح

القسم : ع.ط لاضطرابات الجهاز العصبي العضلي وجراحتها

عنوان البحث:

Effect of repetitive transcranial magnetic stimulation on upper limb motor function and cortical excitability in stroke patients.

نحيطكم علما بموافقة لجنة أخلاقيات البحث العلمي علي خطة البحث المقدمة و تعتبر هذه الموافقة
سارية اعتبارا من تاريخها.

و يرجى ملاحظة أنه يجب إخطار اللجنة على الفور في حال وجود أي آثار سلبية غير متوقعة عليه قد
تؤثر على موافقة اللجنة.

رئيس لجنة أخلاقيات البحث العلمي

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INTRODUCTION

Stroke is the leading cause of acquired adult disability worldwide and the fourth most common cause of death in developed countries. It is the third leading cause of death after heart disease and cancer, and it is a leading cause of disability in the eastern world. Of those who survive a stroke, 90% have a neurological deficits which are disabling than fatal. Stroke is usually considered a disease of the elderly, but nowadays it can occur at any age and their consequences in terms of lost productivity and poor quality of life are even greater in younger patients than in older ones. Despite the abundance of numerous neurorehabilitative treatments, approximately 80% of stroke survivors still suffer from persistent motor dysfunction after stroke (**Du et al, 2016**).

Stroke survivors usually show significant residual neurological deficits that impair function. Upper limb dysfunction hemiparesis specifically, is a very common and significant disability that affects daily living and increases the burden on these patients and their families. Restoring functional use of the upper extremity is a key goal and a priority for stroke patients. Proper outcome assessments at the activity and participation levels are necessary to determine the appropriate selected rehabilitation intervention that could result in changes that are important to the daily life of individuals living with stroke (**Hatem et al, 2016**).

Recovery of motor function after stroke depends mainly on the sustained capacity of the adult brain for plastic changes. This cortical excitability or cortical plasticity based on the concept of functional interhemispheric balance between the two motor cortices (**Kubis , 2016**). Various motor-related regions contribute to

motor recovery after a stroke. One of these motor-related regions, is the contralateral primary motor cortex (M1) contributes to the motor recovery of the upper extremity after a stroke (**Favre et al, 2014**).

The substantial changes that occur in the cortical reorganization of the brain ischemic areas and of more remote areas play an integral role in the recovery of motor dysfunction post stroke. The injured ischemic motor cortex has a reduced cortical excitability at the acute phase and a suspension of the topographic representation of affected muscles, while the contralateral motor cortex has an increased excitability and an enlarged somatomotor representation. The contralateral cortex exerts a transcallosal interhemispheric inhibition on the ischemic cortex. This results from the imbalance of the physiological reciprocal interhemispheric inhibition of each hemisphere on the other, contributing to worsening of neurological deficit (**Zhang et al , 2017**).

Series of repetitive transcranial magnetic stimulation studies on stroke have been trying to understand the relationship between hemiparetic upper limb motor recovery and cortical reorganization post stroke (**Tang et al , 2015**) . Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive stimulation to induce electrical currents in the brain tissues which can modulate cortical excitability of motor areas and enhance recovery. (**Du et al., 2018**). The application of repetitive transcranial magnetic stimulation depend on multiple parameters, such as stimulus-train length, stimulation frequency, number of pulses delivered, their temporal pattern and the targeted region . All of these parameters may differentially affect the responses of the intended target neurons to rTMS (**Matheson et al., 2016**).

Low-frequency repetitive transcranial magnetic stimulation (LF-rTMS) of the contralesional hemisphere is a safe procedure that suppresses local cortical activity of the non-affected cerebral cortex (**Li et al, 2016**). The primary motor cortex (M1) forms a main part of the motor cortices and contributes to the high order control of motor recovery of the hemiparetic upper limbs in stroke patients. It was assumed that the induced inhibitory effect of LF-rTMS on the non-lesional hemisphere can cause direct increase in the neural activation of the lesional hemisphere which can consequently regain the cortical interhemispheric balance and eventually can produce functional improvement in post-stroke patients with upper limb hemiparesis (**Blesneag et al,2015, Du et al, 2018**).

Statement of the Problem:

- Is there a significant effect of the contralesional low frequency repetitive transcranial magnetic stimulation (LF-rTMS) on cortical excitability modulation and consequently on the upper limb motor performance in stroke patients?
- The recommended minimum number of contralesional low frequency repetitive transcranial magnetic stimulation (LF-rTMS) sessions that can induce significant cortical excitability changes in relation to the conventional therapeutic physical therapy interventions in stroke patients?
- The recommended maximum number of contralesional low frequency repetitive transcranial magnetic stimulation (LF-rTMS) sessions that can induce significant cortical excitability changes before reaching a plateau in relation to the conventional therapeutic physical therapy interventions in stroke patients?

Purpose of the study:

- To assess and analyze the effect of contralesional low frequency repetitive transcranial magnetic stimulation (LF-rTMS) on cortical excitability and consequently its impact on the upper limb motor performance in stroke patients.
- To determine the recommended minimum and maximum number of contralesional low frequency repetitive transcranial magnetic stimulation sessions (LF-rTMS) in conjunction with the conventional physical therapy rehabilitation program that can induce significant impact on cortical excitability by analyzing the sequential rate of change in cortical excitability in response to contralesional (Lf-rTMS) stimulation in stroke patients.

Significance of the study

Stroke is a global disease with high rates of long-term disability. It is estimated that 25% to 74% of the 50 million stroke survivors worldwide require some assistance or are fully dependent on caregivers for activities of daily living (ADL) post stroke. (**Veerbeek et al, 2011**). It affects aspects of a person's physical, emotional, and social life. Although stroke is a lesser cause of disability than heart disease, the population of stroke survivors continues to increase, in part because of a fall in mortality rates. This consequently increases the societal burden because of the monetary load and costs of care applied upon the care givers, in-patient hospitals and family members. Upper limb motor rehabilitation is a priority that can be achieved by adopting a cohesive and multidisciplinary approach toward

clinical management and rehabilitation to minimize long-term stroke-related disability (**Santisteban et al, 2016**).

Upper limb motor impairments post stroke result in reduced functional mobility, motor or sensory dysfunctions as well as problems with balance, coordination, postural control, and walking mechanics resulting in increased financial and social burden of stroke patients and their families. These long-term sensorimotor impairments, is usually due to the patients' incapability to execute movements of the affected arm or hand independently. Impairments of the upper extremity post stroke are usually due to direct damage to the primary motor cortex, the primary somatosensory cortex, secondary sensorimotor cortical areas, subcortical structures, and/or the corticospinal tract (**Raghavan , 2015**).

Research in cortical excitability or cortical plasticity modulations highlighted the significance of such processes in the potential enhancement of motor recovery after cerebrovascular stroke. The modules involved in cortical reorganization post stroke can potentiate the results of clinical rehabilitation of various motor impairments in stroke patients. Non-invasive brain stimulation with inhibitory repetitive transcranial magnetic stimulation (rTMS) of the contralesional hemisphere may aid in relieving a post-stroke interhemispheric excitability imbalance, which could improve functional recovery (**Van et al, 2017**) Abnormal cortical excitability and interhemispheric imbalance in stroke patients assumes that, the increased excitability of the contralesional hemisphere applies excessive interhemispheric inhibition onto ipsilesional cortical hemisphere . This excessive imbalanced inhibition impede the neuroplasticity in these areas and limit the gains in motor recovery that can be achieved through rehabilitation (**Boddington & Reynolds 2017**).

Null Hypothesis:

- There is no significant effect of using contralesional low frequency repetitive transcranial magnetic stimulation (LF-rTMS) on cortical excitability and consequently on the motor performance of the affected upper limb in stroke patients.
- There is no change in the sessional values of cortical excitability in response to contralesional low frequency repetitive transcranial magnetic stimulation (LF-rTMS) thus the recommended minimum and maximum number of LF-rTMS sessions that can show significant changes in cortical excitability cannot be determined in stroke patients.

Delimitations:

This study was delaminated to:-

- Forty hemiparetic stroke patients of both genders who met all the inclusion criteria were recruited in this study from outpatient clinic, Faculty of Physical Therapy and outpatient clinic in the Neurology department, Faculty of Medicine, Cairo University.
- Their age ranged from 50 and 65 years
- All patients experienced single ischemic stroke for at least three months but not exceeded for six months.

- All patients were referred from a neurologist and the diagnosis was confirmed with non-contrast computed tomographic (CT) or magnetic resonance imaging (MRI) scans of the brain.
- The selected patients were randomly assigned into two equal groups (control group (GA) and study group (GB)), The randomization was done by random generator using permuted blocks of different sizes(Randomized Controlled Trial).
- All patients were selected with mild to moderate motor impairment verified according to the national istitutes of health stroke scale (NIHSS) (score 1-15) and modified ashworth scale (MAS) (1 or 1+).
- Fugl-Myer upper extremity assessment scale (FMA-UE) and hand grip dynamometer were used to assess the upper limb motor function for each patient in both groups (before and after treatment).
- Single pulse TMS was used to assess cortical excitability represented in measuring the active motor threshold from the contralesional (CAMT) and the ipsilesional (IAMT) primary motor “hot spot” for each patient in both groups (before and after treatment).
- Single pulse TMS was used to assess the sequential change in cortical excitability represented by the sessional measurement of (CAMT) and (IAMT) for all patients in both groups.
- Patients participated in the study were not informed whether they are in the Control group(GA) or in the Study group(GB) (Single blind study).
- The treatment sessions for all patients in both groups was conducted daily, five times per week for two consecutive weeks.
 - The control group (GA) were treated by a conventional physical therapy upper limb rehabilitation protocol (**Lie et al,2015**).

- The study group (GB) were treated with the conventional physical therapy upper limb rehabilitation protocol in addition to the contralesional low frequency repetitive transcranial magnetic stimulation (LF-rTMS).

Limitations:

An Effort was made to minimize the effect of the possible limitations which are:

1. The psycho-physiological status of the patients; all the patients were interested and motivated during all the sessions.
2. The transportation of all patients from the Outpatient clinic, Faculty of Physical Therapy, Cairo University was comfortable and without any effort or extra load on the patient as much as possible.
3. Each patient was assessed using single pulse TMS at the neurophysiology lab at Kasr El Aini, teaching Hospital, Cairo University, at a time suitable for each patient and without any list of waiting as much as possible.

Basic assumption:

It was assumed that:

- The sample of this study were carefully selected to represent all the subacute stroke population.
- Patient's motivation & cooperation were the same throughout the assessment and treatment procedures for each patient.

- All other factors which may influence the outcomes such as noise, distraction....etc during the assessment and treatment sessions were controlled.
- All risk factors of stroke would be controlled to avoid any recurrent stroke or instability of their medical state like blood pressure, glucose and cholesterol level that was achieved with their physicians.

Data Analysis and Statistical Design:

A- Descriptive statistics:

The mean value and standard deviations for upper limb motor function findings represented in **Fugl-Myer Upper Extremity Scale (FMA-UE)**, **Hand grip dynamometer** and Findings of cortical excitability represented in **Contralesional Active Motor Threshold (cAMT) and Ipsilesional Active Motor Threshold (iAMT)** obtained from MagstimRapid² stimulator system were compared for both groups (Control group (GA) and Study group (GB)).

B- Inferential statistics:

- **Student t Test** was used to compare different numerical variables represented in mean values and standard deviations of the patients **chronological features as Age (in years) and duration since onset of stroke (in months)** between both groups ((GA) and (GB)).
- **Student t Test** for independent samples test was also used to compare different numerical variables represented in mean values and standard deviations that were obtained from MagstimRapid2 stimulator system (

cAMT , iAMT) for cortical excitability and upper limb motor function findings (Fugl-Myer assessment- Upper Extremity (FMA-UE), Hand grip dynamometer) between both groups ((GA) and (GB)) (Pre treatment findings).

- **Chi-square (χ^2) Test** was performed to compare the **categorical data** of the patients' main features as gender, smoking history, within and between groups (control group (GA) and study group (GB)). **Fisher's Exact Test** was used instead when the expected frequency is less than 5.
- **Paired t Test** for independent samples test was used to compare the post to pretreatment change between both groups, represented in the mean values and standard deviations obtained for the recorded post to pretreatment difference in cortical excitability (cAMT , iAMT) and upper limb motor function findings ((FMA-UE), Hand grip dynamometer) .
- The mean values of the **Sequential rate of change in cAMT and iAMT** findings over the 10 therapeutic sessions were assessed by comparing the CAMT and the IAMT mean values of each session in relation to the previous session findings for each patient in both groups
- **Paired t Test** for independent samples test was used to compare the mean sessional values (sequential change) and the mean difference in the sessional rate of change of the **cortical excitability findings** represented by cAMT and iAMT between group control group (GA) and study group (GB).
- The alpha point of 0.05 was used as a level of statistical significance (when P = 0.05 is usually classed as “significant”, P = 0.01 as “highly significant”, and P = 0.001 as “very highly significant”) (**Betty and Jonathan, 2003**).

- All statistical calculations were done using computer program IBM SPSS (Statistical Package for the Social Science; IBM Corp, Armonk, NY, USA) release 22 for Microsoft Windows.