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EFFECT OF TWO NONINVASIVE BRAIN STIMULATION TECHNIQUES ON POST STROKE UPPER LIMB MOTOR FUNCTIONS

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ABSTRACT

Background and Purpose: Recovery of upper limb motor function in patients after stroke is essential for independent activities of daily living, The upper limbs contribute to most ctivities of daily living We designed this randomized double-blind, sham-controlled trial to examine the effect of two noninvasive brain stimulation techniques on recovery of functions in the upper limbs after stroke. ***Methods***: Forty-two chronic hemiplegic stroke patients were randomly allocated across 3 groups to undergo 24 sessions, 3d/wk of intervention combined with standard physiotherapy for motor functions of upper limb, Group (A) comprised 18 subjects who received 1-Hz rTMS, Group B comprised 13 subjects who received tDCS. Group C comprised 11 subjects who received Sham1-Hz rTMS.. Outcome measures were assessed by the Fugl-Meyer assessment (FMA)., grip strength, and stroke-specific quality-of life scale. at the baseline and after intervention. ***Results***: Significant improvement from baseline was noted following intervention in rTMS and tDCS groups, in the FMA, and SSQOL in upper limb motor functions. The rTMS group showed significantly improvements than the other two groups in handgrip strength. ***Conclusions***: Noninvasive brain stimulation combined with standard physiotherapy can be more beneficial in improving upper limb functions after stroke,

However, more studies are required to clarify the functional motor changes caused by noninvasive brain stimulations.

KEYWORDS: Stroke, rTMS, tDCS, Limb function, stroke, rehabilitation, Spasticity.

INTRODUCTION

Spasticity is a common and potentially incapacitating complication that affect the upper limb after stroke and may contribute significantly to functional loss and reduction in the quality of life in addition to economic and caregiver burdens.[1] It is estimated that nearly half of the patients with stroke develop moderate or severe spasticity, especially involving the affected upper limb.[2,3]

Reduction in cortical excitability of the damaged hemisphere is a well-recognized consequence after stroke.[4–6] Importantly, the level of excitability of the affected hemisphere correlates with motor function and predicts recovery.[7–9] Accordingly, increasing the level of excitability of the damaged hemisphere is thought to enhance stroke recovery.[10] Noninvasive brain stimulation (NBS), including repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) have shown promise for modulating cortical excitability and harnessing neuroplasticity in stroke patients to promote motor recovery. Inhibitory rTMS administered in the contralesional motor cortex at a frequency of <1 Hz is a strategy that has shown potential to disrupt this possible maladaptive transcallosal pathway.[11] tDCSrepresents a single polarity, Anodal stimulation is excitatory, while cathodal stimulation is inhibitory.[12,13] Both anodal stimulation of the damaged primary motor cortex (M1) and cathodal stimulation of the non lesioned M1 (the latter intended to restore the balance of interhemispheric excitability) have been shown to improve function of the hemiparetic upper extremity in patients after stroke.[14] Under the mechanism of long-term depression (LTD), 1-Hz rTMS has been found, primarily, to reduce contralesional cortical excitability and, secondarily, increase ipsilesional activity.[15] Transcranial magnetic stimulation uses a rapidly changing magnetic field to induce an electrical current in the brain. The stimulating current evokes action potentials in cortical axons, triggering the release of neurotransmitters.[16] When applied in a repetitive manner, TMS is able to promote both short- and long-term neuroplasticity, The neurophysiologic mechanism underlying the effect of rTMS on neuroplasticity is only partly known. It is believed that rTMS induces modifications of membrane proteins, alterations of morphology, and modifications of synaptic transfer. rTMS induce Long-term plasticity which may result from long-term potentiation (LTP, enhanced signal transmission efficacy between neurons), or long-term depression (LTD, reduction in synaptic transmission efficacy) at the synaptic level.[15]tDCS induce neuroplasticity which intend to be similar to LTP or LTD.[14]It is believed that anodal tDCS facilitates synaptic efficacy that is similar to LTP while cathodal tDCS reduces synaptic efficacy. Only a few studies have investigated the lasting effects on corticospinal excitability.[17,18] Assessment of the effects of NBS on corticospinal excitability and motor recovery, is needed. In the current randomized sham-controlled study, we applied 1-Hz rTMS to the contralesional M1 and additional rTMS to the ipsilesional M1 in hemiplegic patients. We aimed to assess the effect of two noninvasive brain stimulation techniques on post stroke upper limb motor functions

METHODS

Participants were recruited via contacting with physical therapists and screening outpatient clinics in Majmaah hospitals. Forty-two patients were recruited for this study comprising 10women and 32men aged 40 to 85 years. All subjects fulfilled the inclusion criteria of. (1) ischemic or hemorrhagic lesion within 1 hemisphere, as verified by MRI; (2) 4 to 15 months after the first-ever stroke; (3) muscle tone at the wrist with a modified Ashworth scale (MAS) score between 1and 3;(4) no history of seizure attack, dementia, cognitive impairment, or other neurodegenerative diseases; and (5) absence of aphasia, spatial neglect, visual field deficit, or emotional problems. Potential participants were excluded if they had (1) a history of seizure or cerebral aneurysm, (2) used anti spastic drugs within 6 months before enrollment, (3) previous surgery involving metallic implants, (4) unstable vital signs, (5) other neurological diseases, and (6) aphasia.

All patients gave their written informed consent before the experiment. The protocol was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and approved by Majmaah University Research Ethics Committee. Each patient received 24 sessions of stimulation (3 days per week for 8 weeks), of either real or sham 1-Hz rTMS over the contralesional M1, or transcarainal direct current stimulation (t DCS) over the ipsilesional M1.

Experimental Design

This study was a randomized, double-blind, sham-controlled trial and was carried out to investigate the efficacy of noninvasive brain stimulation on the upper limb motor functions and the quality of life of patients with chronic stroke. As shown in figure 1, 165 participants with stroke were screened for eligibility by telephone and 57 were eligible and physically screened. Of these 57, 15 were excluded because they had mild spasticity (MAS score _1) and the remaining 42 were randomly allocated across group A,|B and C. The randomization procedures were generated by a neutral administrator of hospital, Group A comprised 18 subjects who underwent 1-Hz rTMS. Group B comprised 13 subjects who underwent tDCS. Group C comprised 11 subjects who underwent Sham1-Hz rTMS.

All subjects continued the same conventional physical therapy program regardless of the group they were assigned. The program was composed of activities to improve strength, flexibility, transfers, posture, balance, and coordination and provide sensory stimulation. These activities provided various types of exercises focusing mainly on upper limb movements, including movements of the shoulder, elbow, wrist, hand, and fingers. Physical therapy was provided for approximately 30 minutes (3 days per week for 8 weeks).

We performed transcranial magnetic stimulation using Magstim Rapid2 (Magstim) with a 70-mm figure-of-eight coil; 1-Hz rTMS trains for 20 minutes, consisting of 1200 pulses at 90% of rTMS were applied over the motor representation of the first dorsal interosseus (FDI) in the contralesional side. We used a placebo coil (Magstim). For the anodal tDCS procedure, a 1 mA direct current was applied for 20 minutes (BrainSTIM Transcranial Stimulator, EMS, Italy) via a 5×5-cm anodal electrode positioned over the hotspot of the FDI muscle of the affected hemisphere. The cathodal electrode (5 × 5 cm) was placed at the contralateral supraorbital region. For sham rTMS, a coil disconnected from the stimulator unit was held over the scalp while a second coil, connected with the stimulator, was positioned behind the patient’s head, for 20 minutes, without touching the scalp. Thus, no current was induced in the brain, but the patients were exposed to acoustic stimulation (from the second coil). Participants were seated on a standard chair with their backs resting against the back of the chair. The test hand was placed on the armrest of the chair with the shoulder in approximately 0◦ degree of flexion and abduction, elbow in approximately 90◦ of flexion, and the forearm in pronated position. The same chair was used throughout visits. Finally, location of the hotspot for each participant was marked on the scalp directly using a waterproof marker.

Outcome measures

The National Institute of Health Stroke Scale and the Barthel Index score were used to assess neurological impairment and disability at enrollment. The outcome measures were obtained at baseline and after the interventions for all groups by an experienced assessor who was familiarized with the scales and tests used in this study and who was unaware of the group assignment.

The Fugl-Meyer assessment is considered standard for evaluating the motor function recovery.[19] Here, the upper extremity motor section of the Fugl-Meyer assessment was applied to measure the improvement in upper limb motor function in 33 items on a 3-point rating scale (maximum score, 66 points).[20] Maximum passive range of motion of the paretic wrist joint was measured with a goniometer.

The stroke-specific quality-of-life scale (SSQOL) was used to provide an assessment of the health-related quality of life specific to patients with stroke. The scale is a self-report scale (reference to the past 2wk) containing 49 items distributed into 12 domains (energy, mobility, upper limb function, work/productivity, language, self care, social roles, mood, vision, family roles, thinking, personality), graded on a 5-point scale. The total score (maximum 245) and the upper-extremity function scores (maximum of 25) were considered for the analyses. The questionnaire was translated with back translation and validated into Arabic language that can be used for patients.

Maximal grip strength represents an important aspect of hand function after stroke. Grasp and pinch grip dynamometry were **performed** using a digital dynamometer (Biometrics Ltd).[21] Scores were recorded in kilograms, averaged over 2 trials, and normalized to the unaffected hand.

Statistical Analysis

An independent researcher who was blinded to group assignment performed database management and statistical analysis. Monitoring of adverse effects was carried out by the treating physical therapists. Descriptive analyses were performed to present the demographic and clinical characteristics of the 3 groups. For categorical and continuous variables, chi-squared and t tests were used, respectively, to evaluate the differences between groups in the distribution of the patient’s characteristics at baseline and the demographic data. For the following outcome measures: UE-FMA, range of motion, SSQOL total, and upper-extremity SSQOL., t tests were used as post hoc comparisons when applicable and the paired t test was used for comparisons between the baseline and post intervention data.

RESULTS

Demographic data and clinical characteristics are depicted in Table 1. All 3 groups shared the same overall characteristics (*P*>0.05).All of the patients demonstrated good tolerance for the rTMS sessions, with no adverse side effects observed during the study. All participants completed all the study procedures and no one withdraw from the study (see fig:1).

Table 2 lists the descriptive data for all outcome measures before and after the interventions In our study, group A& B showed significant improvement in UE-FMA, wrist ROM and UE-SSQOL. However, only participants in r TMS group showed improved pinch and grasp scores.

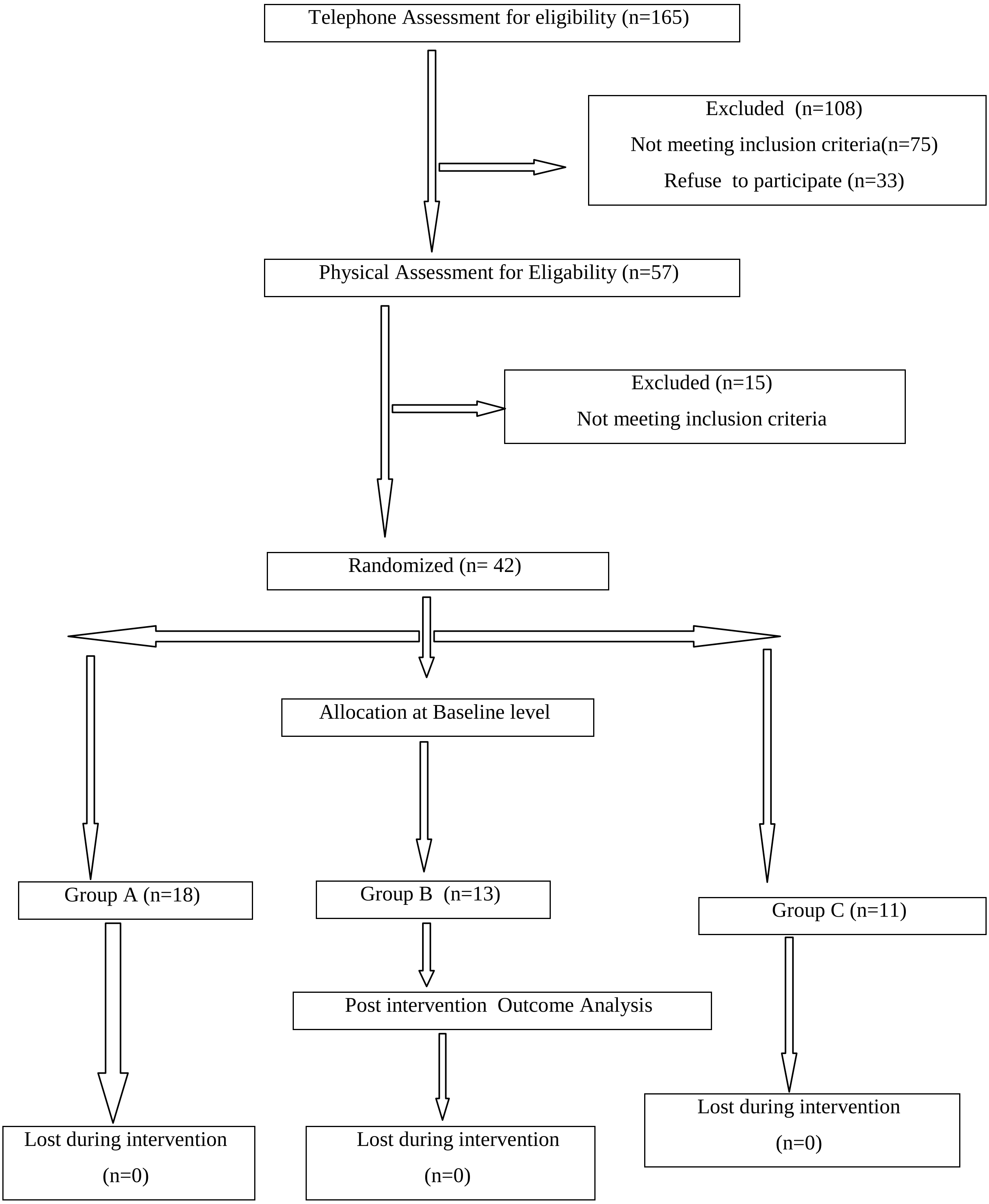
Table (1) Demographic Data and Clinical Characteristics of All Patients

VARIABLE	**Group A (n=18)**	**Group B (n=13)**	**Group C (n=11)**
Male/female	14/4	10/3	8/3
Age	64.3±11.2	66.7±12.4	63.3±11.7
Ischemic/hemorrhagic	12/6	9/4	7/4
poststroke (months)	7.8±1.7	8.1±1.5	8.2±1.6
NIHSS	14.2±3.5	11.1±3.3	12.3±3.5
Br stage, proximal	3.1±1.4	2.4±1.1	2.8±1.7
Br stage, distal	2.7±0.7	2.6±1.3	2.7±1.6

Table (2) Outcomes measured before (baseline), after (post intervention) for all 3 groups (A,B and C)

	Group A		**Group B**		**Group C**	
	Baseline	**Post**	**Baseline**	**Post**	**Baseline**	**Post**
UE-FMA score	26.4±12.6	28.2±11.3*	27.2±10.6	29.1±10.1*	26.7±10.6	26.9±11.5
Wrist ROM	55.4±12.1	67.4±16.4*	60.2±11.1	65.4±14.4*	54.3±14.1	54.4±15.3
SSQOL total score	181.2±27.0	190.4±28.1	177.2±26	187.2±28.1	173.6±28.0	173.8±29.1
UE-SSQOL score	17.8±2.2	19.7±3.5*	16.2±4.2	18.8±5.2*	15.8±2.2	16.1±3.7
Grasp dynamometry	0.47 ± 0.24	0.48 ± 0.29	0.44 ± 0.26	0.49 ± 0.27*	0.43 ± 0.21	0.43 ± 0.52
Pinch-grip dynamometry	0.6 ± 0.3	0.63 ± 0.4	0.55 ± 0.2	0.63 ± 0.4*	0.57 ± 0.3	0.57 ± 0.5

FMA indicates Fugl-Meyer Assessment, UE-SSQOL score indicates stroke-specific quality-of-life scale



Fig(1) Flow chart illustrates recruitment, group allocation, and post intervention analysis

DISCUSSION

This study examined the effectiveness of adjunct inhibitory rTMS with physical therapy and the adjunct facilitatory anodal tDCS when combined with Physical therapy to enhance recovery of motor function of upper extremities in chronic stroke patients. Our results demonstrated the effects of these adjunct treatments which have produced more profound effects than unilateral single inhibitory rTMS or facilitatory tDCS in facilitating motor performance of upper extremities. Other studies that used rTMS alone as the single treatment modality have described the anti-spasticity effect of inhibitory or excitatory rTMS with upper motor neuron dysfunction. In several cases of chronic spastic hypertonia (more than 5y after stroke in a stable state), the repeated consecutive application of inhibitory rTMS to the non-lesional hemisphere for 1 week significantly reduced spasticity in the affected limbs.[22] In a report of children with cerebral palsy and spastic quadriplegia, excitatory rTMS applied to the lesional hemisphere for 2 weeks improved spasticity in the spastic limbs.[23] Similarly, Centonze et al[24] showed that the application of excitatory rTMS to the lesional hemisphere for 2 weeks improved spasticity in the affected lower limb in patients with multiple sclerosis. The benefits of rTMS as an additional therapy to motor training for treating motor function have also been demonstrated by Kakuda et al.[25]

Several clinical studies have reported recently that the application of low-frequency rTMS to the contralesional hemisphere improved motor function of the affected upper limb in poststroke patients.[26,27,28] One possible mechanism for the improvement of UE-FMA score in groups (A&B) is reduction of interhemispheric inhibition from the stimulated hemisphere induced by low-frequency rTMS, and facilitatory anodal t DCS with Physical therapy which resulted in neural activation of perilesional areas.

Some researchers have shown that the application of intensive rehabilitative approaches produced functional reorganization in the lesioned hemisphere.[29,30,31] Therefore, we speculate that the combined application of low-frequency rTMS and physiotherapy facilitates functional reorganization in the damaged hemisphere more significantly compared with the use of only one of the two interventions alone. In contrast, the results of this study suggest that low-frequency rTMS applied with physiotherapy can reduce spasticity of the hemiparetic upper limb. In a study investigating the effects of low-frequency rTMS on motor function and spasticity of the affected upper limbs in 64 post-stroke patients, It was reported that consecutive application of 1 Hz rTMS over the contralesional hemisphere reduced spasticity in the affected upper limbs.[32] As it is reasonable to consider that the improvement in spasticity can lead to motor functional recovery in spastic hemiparetic post-stroke patients, we speculate that the underlying mechanism of motor functional improvement in the affected upper limb seen in our patients after the combination treatment includes not only functional neural reorganization in the damaged hemisphere, but also the reduction of spasticity on the affected upper limb.

According to the model of interhemispheric competition, excessive inhibition of the damaged hemisphere by the contralateral hemisphere may also contribute to the physiopathology of spasticity. We hypothesized that in our study, the inhibitory rTMS was primarily responsible for the decreased contralesional cortical excitability and, secondarily, the enhanced ipsilesional activity, leading to an enhancement in descending corticospinal projections and, therefore, reduced clinical spasticity. These hypotheses of the underlying mechanisms of the antispastic effect of inhibitory and excitatory rTMS are generally accepted by researchers.[33,34] Without additional neurophysiological studies to investigate the cortical excitability inthehemispheres, we can only speculate on the neuronal mechanisms that may underlie the observed effects.

FMA involves and coordination and dysmetria measurement, which is a more integral motor function assessment than merely testing strength. These results may be attributable to the projection of different movement component so various activated motor areas in the brain, as concluded by a number of previous fMRI studies. These earlier studies revealed that increasing complexity of movement led to increased activity in the bilateral superior parietal areas and contralateral inferior parietal areas[35], a component of the human mirror neuron system.[36] In this way, modulating the contra lateral hemispheric motor area prior to modulating the damaged hemispheric motor areas would facilitate motor planning and hand dexterity, resulting in bilateral interaction in accordance with the mirror neuron system. A superior after effect as registered in the Group (A) was achieved through reducing abnormal hemispheric inhibition and promoting a shift of cortico motor laterality back to the affected motor cortex.

Upper extremity motor function was significantly improved in group (B) which indicates that tDCS had a beneficial effect for these subjects. This result agrees with previous reports that tDCS increased motor performance assessments of the shoulder, elbow, and wrist, and lower limb assessments of stroke patients.[37] Together, these results suggest that conventional physical therapy with tDCS provides non-specific input to the motor cortex, facilitating changes in neural activation and synaptic plasticity which promote functional recovery, and enhance voluntary activities such as ADL by increasing the activity of the cerebral cortex in damaged brain areas.[38] Therefore, the application of tDCS could facilitate cortical repair by brain reorganization, and have great clinical benefits through improvements of impaired cortex and motor dysfunction of stroke patients. A variety of stimuli delivered to the cerebral cortex may enhance neural plasticity and motor learning. Application of tDCS combined with physical therapy may be more beneficial than functional training for improving the limb functions and activities of daily living of patients with chronic stroke. Further studies are needed to generalize these findings, to investigate a variety of physical therapies with concurrent tDCS, and to consider patients' quality of life as well as independence of ADL. Limitations of our study includes the small number of participants that precludes further large scale generalization of results. The relatively short time of intervention and what would be the results of longer application of treatment. Long follow up after stopping the trial is needed to examine the durability of effects. Future studies are needed to examine these questions.

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