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Therapeutic Efficacy of Low Frequency Transcranial Magnetic Stimulation in Conjunction with Mirror Therapy for Sub-acute Stroke Patients

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The purpose of the current study was to investigate the effect of repetitive transcranial magnetic stimulation (rTMS) in conjunction with mirror therapy on the balance function of patients with sub-acute stroke hemiparesis. This study was conducted with 36 subjects who were diagnosed with a hemiparesis due to stroke. Participants in the experimental (19 members) and control groups (17 members) received rTMS and sham rTMS during 10 minute sessions each, which were carried out five days per week for four weeks. This was followed by the mirror therapy over 30 minute sessions, which were carried out five days per week for four weeks. Motor recovery was assessed by balance index, dynamic limits of stability, Berg balance scale, and time up go test. The change values of the balance index (−2.06 ± 1.99 versus −0.41 ± 1.11), dynamic limits of stability (3.68 ± 2.71 versus 1.17 ± 2.38), and time up go test (−7.05 ± 5.64 score versus −3.35 ± 5.30 score) were significantly higher in the experimental group than in the control group ($p < 0.05$). At post-test, balance index (4.08 ± 1.14 versus 5.09 ± 1.04), dynamic limits of stability (13.75 ± 0.60 versus 11.73 ± 3.53), and time up go test (23.89 ± 4.51 versus 28.82 ± 3.07) were significantly higher in the experimental group than in the control group ($p < 0.05$). In the experimental group, significant differences were found in the pre- and post-test scores for the balance index, dynamic limits of stability, Berg balance scale, and time up go test ($p < 0.01$). In the control group, a significant difference was observed between the pre- and post-test only for the Berg balance scale and time up go test ($p < 0.05$). These findings demonstrate that the application of 1Hz rTMS in conjunction with mirror therapy can be helpful in improving the balance function of patients with sub-acute stroke hemiparesis, and this may be used as a practical adjunct to routine rehabilitation therapy.

Keywords : transcranial magnetic stimulation, stroke, mirror therapy

1. Introduction

In the patients with post-stroke hemiparesis, it has been reported that the risk of fall is as high as 5 times during their first year of stroke onset; this is indicating the clinical importance of balance impairment [1]. In addition, balance impairment may cause further pathological problems such as hip fractures and debilitation of functional ability [2]. Suitable physical actions during daily living may be an inevitable option for the maintenance of postural stability and functional movement. However, the defects in visual, vestibular, and somatosensory systems of the patients with post-stroke hemiparesis may critically reduce their ability to maintain static and dynamic balance during various movements, which contribute to the declining of their physical activity [3]. Stroke rehabilitation should focus on recovery of the balance function, thereby assuring that the patient is able to independently perform daily activities, including walking, without any safety problems [4]. Providing visual feedback during functional performance is considered as a beneficial adjunct to therapy and is commonly used in the field of stroke rehabilitation to facilitate functional recovery and to improve postural control [5]. Mirror therapy has frequently been performed to increase the effect of physical interventions which are used to improve postural alignment, physical functions, the level of daily activities, and participation in daily life situations after stroke [5]. It may also be helpful in improving postural stability and providing safety by minimizing the injury risk. Such a mirrored environment may increase the efficacy of the exercise therapy to a great extent, especially for active individuals with relatively

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high functional levels [6]. When patients are in front of a mirror watching their own reflections, they are able to immediately recognize errors in their postures and movements, which greatly help in correcting themselves [5]. Recent studies in stroke rehabilitation have reported that mirror therapy is beneficial for the functional movements of the upper and lower limbs [7] and for controlling of postures [5, 8, 9]. However, it remains unclear whether the symptoms can be enhanced by mirror therapy while performing specific therapeutic activities. The majority of studies have been conducted to determine the effect of mirror therapy for patients with sub-acute stroke hemiparesis, by observing the motions of their unaffected limbs [10, 11].

The rTMS was introduced by Barker *et al.* in 1985, and it has since gained recognition as a safe, relatively painless, and noninvasive method for mapping the cortical motor representation in both the normal and pathologic cases [12]. The rTMS has been used in the measurement of central nerve system adaptation and its relationship to changes in neural control and function [12]. It can modulate the excitability of the motor cortex beyond the period of stimulation [13]. However, no study has been conducted on mirror therapy and rTMS together to investigate their effects on stroke patients. The purpose of this study was to determine the effects of rTMS applied in conjunction with mirror therapy, in the sub-acute stroke patients.

2. Materials and Methods

A total of 36 patients with sub-acute stroke hemiparesis volunteered to participate in this study. They were randomly allocated to either an experimental group (EG=19) or a control group (CG=17). Although 48 subjects were initially recruited, 12 (EG: 5 and CG: 7) were excluded due to lack of regular participation in the treatment sessions. Consequently, the data of 36 subjects were used for statistical analysis (Table 1). Inclusion criteria were as follows: (1) stroke onset duration of > 6 months, (2) no neurological deficits in the cerebellum or the brainstem, (3) no hemineglect or visual field deficits, (4) no cognitive problems (> 24 points in the Mini-Mental State Examination) [14], and (5) independent walking (with or without walking aids). In this study, we used a pre- and post-test design with randomized controlled groups. All subjects were randomly assigned to either the EG or the CG. Subjects were randomized by blindly drawing one card out of an envelope containing two cards that were each marked as EG and CG. This study was single-blinded; although the subjects and their therapists were aware of their groups, the person in charge of the outcome measurements and data analysis was not aware of the group to which each patient was assigned. Subjects in the experimental group received mirror therapy and repetitive transcranial magnetic stimulation (rTMS) for a total of 40 min (mirror therapy: 20 min, rTMS: 20 min) per day, with a 10-minutes of rest period in the middle of the session. Subjects of the experimental group received training five days per week for four weeks. Subjects in the control group received sham therapy and rTMS for a total of 40 min (sham therapy: 20 min, rTMS: 20 min) per day on the same days.

Table 1. General and medical characteristics of subjects.

	EG (n = 19)	CG (n = 17)
Sex (Male/Female)	10/9	9/8
Age (years)	60.00 ± 7.80	57.35 ± 9.38
Height (cm)	165.20 ± 5.33	163.30 ± 8.46
Weight (kg)	61.40 ± 5.75	63.40 ± 6.40
Time since onset (months)	1.95 ± 0.62	1.65 ± 0.86

EG, experimental group; CG, control group
Values are expressed as mean ± SD

For rTMS equipment, a 70 mm coil and a Magstim Rapid (Magstim, Wales, UK) were used. One Hz rTMS was applied for 20 minutes to the hotspot of the lesional hemisphere in 10 second trains, with 50 second intervals between the trains [13]. Mirror therapy was conducted using the study of Sütbeyaz *et al.* with modification. Subjects were in a semi-seated position on a bed, while the mirror board (60 × 90 cm) was positioned between the legs perpendicular to the subject's midline, with the nonparetic leg facing the reflective surface [10]. Subjects observed the reflection of the nonparetic leg while flexing and extending the hip, knee, and ankle at a self-selected speed under supervision but without additional verbal feedback. The control group performed the same exercise for the same duration, but the reflecting side of the mirror was covered with white fabric.

Quantitative data (Balance Index [BI] and Dynamic Limits of Stability [DLOS]) of balance function were obtained by means of a balance measurement system. Balance function related to functional ability in clinical aspects was assessed using the Berg Balance Scale (BBS), and walking function of the subjects was assessed using time up go (TUG) test. All measurements were performed before and after 4 weeks of training.

BI and DLOS scores were obtained by means of a balance measurement system (Biodex Balance Master, New York, USA). This system incorporates a specific monitor and a movable force platform, which provides up to 20° of surface tilt in a 360° range of motion, with a visual feedback system. Data measured in the platform were digitalized using computer software (Biodex, Version 3.1, Biodex Medical Systems) to attain objective measurements of balance.

BI refers to the subject's ability to maintain the vertical axis of body weight within the suitable range of balance center in the platform's angle of tilt. A low score of BI implies excellent balance ability [15]. DLOS refers to the maximum angle that the subject's body can achieve from the vertical axis without collapsing. The score ranges between 0 and 100, with a higher score implying greater balance ability to perform the task [15]. For the measurement of BI and DLOS, subjects were asked to stand upright in barefoot, with both arms comfortably placed along the trunk on the platform, and to look straight ahead with the eyes open over a period of 20-sec.

Before testing, subjects were allowed a 1-min practice to become accustomed to the equipment measurement procedures. BI was determined by adjusting the center of the body weight to the balance center of the platform; DLOS was measured by shifting the center of the body weight to the targets arranged at a regular interval from the balance center of the platform. BI and DLOS have a strong internal consistency and acceptable intrarater ($r = 0.82$) and interrater ($r = 0.70$) reliabilities [15]. The value was averaged over 3 trials with a 1-min rest interval.

Berg balance scale has been widely used to measure the quality of balance performance related to the functional movement in clinical settings [16]. It consists of 14 items (9 balance and 5 motor activities) which assess the static sitting and standing balance, as well as anticipatory balance during daily activities such as turnings, transfers, reaching, and retrieving objects from the floor. BBS consists of a 5-point scale ranging from 0 (unable to perform) to 4 (normal performance). The scores on each item are summed up to a maximum total score of 56. The BBS has been shown to have excellent intrarater and interrater reliabilities (ICC = 0.99 and 0.98 respectively) and strong internal consistency (Cronbach alpha = 0.96) [16]. A higher total score represents better balance. The score is categorized according to 3 grades as follows: (1) 0-20 points, wheelchair bound; (2) 21-40 points, walking with assistance; and (3) 41-50 points, independent [16].

The time up go test has been commonly used as a clinical outcome measurement to assess the walking and functional abilities of the elderly. It measures the time taken by a subject to perform the steps in the following order: stand up from a standard-height chair with arm rests, walk a distance of 3 m (with an assistive device, if needed), turn around, walk back to the chair, and sit down on the chair [17]. The subjects were asked to complete the exercise as rapidly and safely as possible. TUG has excellent intrarater ($r = 0.99$) and interrater ($r = 0.98$) reliabilities [18] as well as acceptable concurrent validity, because it correlates well with the data obtained from more extensive measures of balance, gait performance, and functional abilities [17]. Subjects can be categorized according to 4 levels of mobility based on the time taken to complete the test as follows: (1) normal mobility (< 10 sec), (2) good mobility (< 20 sec, ability to go out alone or being mobile without walking aids), (3) limited mobility (< 30 sec, unable to go outside alone or requiring walking aids), and (4) dependent mobility (> 30 sec, dependent on aid for most activities and mobility in daily living) [17, 18]. In general, a score of ≥ 15 sec has been recognized to indicate high risk of falls [18].

Differences in general characteristics between the experimental group and the control group before therapy were compared using independent t-tests and chi-square tests. Comparisons were made on the balance before and after training within each group, by using the paired samples t-test. Comparisons were made on the pre- and post-test differences in balance between the experimental group and the control group, by using the independent samples t-test

Table 2. Comparison of pre and post functions between the groups.

	EG (n = 19)		CG (n = 17)	
	Pre-test	Post-test	Pre-test	Post-test
BI (score)	6.14 ± 1.25	4.08 ± 1.14*[a]	5.49 ± 0.66	5.09 ± 1.04
DLOS(score)	10.08 ± 2.73	13.75 ± 0.60*[a]	10.56 ± 4.38	11.73 ± 3.53
BBS(score)	40.74 ± 10.61	56.74 ± 10.96*	42.53 ± 11.64	53.06 ± 9.63*
TUG(seconds)	30.95 ± 4.27	23.89 ± 4.51*	32.18 ± 3.75	28.82 ± 3.07*

BI, Balance index; DLOS, Dynamics limits of stability; BBS, Berg balance scale; TUG, Time up and go test; EG, experimental group; CG, control group
Values are expressed as mean ± SD
*significant difference from pre-test, $p < 0.05$
[a]significant difference in gains between two groups, $p < 0.05$

The statistical software, SPSS 18.0 (SPSS Inc., Chicago, IL, USA), was used for statistical analysis. The level of significance was chosen as 0.05.

3. Results

All subjects signed a written informed consent agreement before participating in this study. Table 1 summarizes the detailed demographic and clinical information of the subjects. There were no statistically significant differences in age ($t = 0.92$, $p = 0.36$) and onset duration ($t = 1.21$, $p = 0.24$) between the 2 groups. The values of BI, DLOS, BBS, and TUG test of the experimental and control groups are summarized in Table 2. The change in the values of BI, DLOS, and TUG test differed significantly between the two groups ($p < 0.05$). In addition, significant differences in the post-test BI, DLOS, and TUG test were observed between the two groups ($p < 0.05$). In the experimental group, significant differences were found in the pre- and post-test scores for the BI, DLOS, BBS, and TUG test, ($p < 0.01$), whereas in the control group, a significant difference was observed only between the pre- and post-test for the BBS and TUG test ($p < 0.05$).

4. Discussion

This study was conducted to investigate the effect of rTMS applied in conjunction with mirror therapy for the improvement of balance ability in the patients with sub-acute stroke. After four weeks of program, significant improvements in balance ability were observed between the experimental group and control group.

This result supports the primary hypothesis of this study that the application of rTMS in conjunction with mirror therapy would improve the balance ability of stroke patients. To the best of our knowledge, our study is the first study to investigate the effects of rTMS applied in conjunction with mirror therapy on balance ability.

In this study, the balance functions of patients with sub-acute stroke hemiparesis were provided by 2 quantitative variables, BI and DLOS, which were measured using specific equipment. These variables measure the ability to maintain postural stability when subjects stand on stable or unstable surfaces. The values of BI and DLOS reflect the level of proprioceptive acuity of neuromuscular mechanisms that affect the dynamic postural stability of the whole body [15]. BBS and TUG test, which represent the balance ability related to functional mobility [19], were selected as the main outcome measures to support the clinical benefits of mirror therapy on balance function. These assessment tools have been commonly used in clinical settings because of their convenience of use [19].

In this study, quantitative measurement of BI and DLOS showed that the EG significantly improved balance function, as compared with the CG. These parameters represent the ability to maintain postural stability without collapsing while standing upright on stable or unstable surfaces, and they reflect the efficiency of proprioceptive function in the neuromuscular system, which controls the posture and movement of the whole body system [15]. Therefore, the findings of this study suggest that the visual feedback, through the use of mirror, in combination with rTMS may be of value in enhancing the balance function of patients with sub-acute hemiparesis, with the aim of improving their movement and functional ability. These results can be supported by previous studies that have demonstrated additional effects of mirror visual feedback in increasing the balance function and postural control [5, 11].

A study of functional brain images related to mirror therapy reported that the primary motor cortex, which is involved in the movements of the opposite side extremities, can excited by only observing the moving extremities on the mirrors [20]. This can indicate that the functional organization of motor systems, including the primary motor cortex, is achieved by not only the active movements of the ipsilateral extremities but also through passive observation of the movements of contralateral extremities [20].

Increasing evidence suggests that the use of mirror therapy is effective in facilitating recovery from sub-acute stroke hemiparesis. In addition, it is reasonable to assume that mirror therapy might be a useful additional choice to reinforce the efficacy of functional approaches in stroke rehabilitation.

This study has several limitations that can be improved by future studies. The small sample size may limit the generalization of the findings of this study, and the absence of a follow-up period hinders the understanding of the long-term effects for the current intervention. In addition, the subjects in this study were recruited from a self-selected group of patients, who are able to walk independently and are highly motivated. Thus, the findings of this study may not be generalized to the entire stroke population with a variety of functional levels. Therefore, further clinical controlled studies with larger sample sizes and longer interventions should be conducted to validate the clinical benefits of the mirror therapy.

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