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Stroke Recovery Can be Enhanced by using Repetitive Transcranial Magnetic Stimulation Combined with Mirror Therapy

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The aim of the present study was to examine whether mirror therapy, in conjunction with repetitive transcranial magnetic stimulation (rTMS), can improve the upper extremity function of stroke patient. This study was conducted with 35 subjects, who were diagnosed as a hemiparesis by stroke. The Mirror plus rTMS group was of 12 members who undertook mirror therapy in conjunction with rTMS, the Mirror group was of 11 members who undertook mirror therapy, and the control group was of 12 members who undertook sham therapy. A motor cortex excitability was performed by motor evoked potential, and upper limb function was evaluated by Fugl-Meyer Assessment, and Box and Block Test. Significant difference was shown after the experiment, in comparison of the groups in terms of latency, and as the result of *post hoc* test, significant difference was shown between the Mirror plus rTMS group and control group, and between the Mirror group and control group, respectively. Significant difference was shown after the experiment in comparison of the groups in amplitude, and as the result of *post hoc* test, significant difference was shown between the Mirror plus rTMS group and Mirror group, and between the Mirror plus rTMS group and control group. Significant difference was shown after the experiment, in comparison of the groups in FMA and BBT, and as the result of *post hoc* test, significant difference was shown between the Mirror plus rTMS group and Mirror group, and between the Mirror group and control group. The study showed that mirror therapy in conjunction with rTMS is more effective to improve upper extremity function, than mirror therapy and sham therapy.

Keywords : mirror therapy, transcranial magnetic stimulation, stroke

1. Introduction

Approximately 60-70% of persons post-stroke have symptoms of upper extremity paresis, and the treatment methods for upper extremity rehabilitation that have been emerging recently include constraint-induced movement theory, robot-arm training, training using virtual reality, task-oriented training, repetitive transcranial magnetic stimulation (rTMS), mirror therapy, and so on [1]. Mirror therapy was first used a decade ago, to aid in the recovery of upper limb hemiparesis following stroke. Mirror therapy involves the superimposition of reflections of unaffected limb movements on the affected limb, to make it appear as if the latter is moving [2]. There is evidence that both the motor and perceptual activity found in mirror therapy modulate the excitability of the primary motor cortex (M1). During mirror therapy, M1 excitability is modulated by both the ipsilateral limb movement, and the passive observation of movement of the contralateral limb, as reflected in the mirror [3]. A number of functional brain imaging studies have demonstrated the effects of mirror therapy on brain activity, and provided neurophysiological evidence for its application to treating stroke-induced hemiparesis [4]. rTMS was introduced by Barker *et al.* in 1985, and has since gained recognition as a safe, relatively painless, and noninvasive method for mapping cortical motor representation, in both normal and pathologic cases [5]. rTMS is a series of magnetic pulses that temporarily summate and change neural activities to a greater degree, than traditional single-pulse TMS. rTMS can modulate the excitability of the motor cortex beyond the period of stimulation [6]. According to recent rTMS research, the primary motor cortex can reorganize and modulate the interactions between the ipsilesional and contralesional motor cortex, following a stroke [7].

However, no study has investigated the effects of mirror

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therapy and rTMS conducted together, on stroke patients. The purpose of this study was to determine the effects of mirror therapy applied in conjunction with rTMS, in stroke patients.

2. Materials and Methods

This study was conducted with 35 subjects, who were diagnosed as a hemiparesis by stroke.

Sufficient explanation of the study's intent and the overall purpose was given, and voluntary consent to participate in the study was obtained from all of the subjects. All procedures were reviewed and approved by the Institutional Ethics Committee, Eulji University Hospital.

We used an assessor-blinded, randomized controlled design. The same investigator, who was blinded to the treatment assignment, performed all the assessments. After baseline measurements were obtained, the patients were randomly assigned to three groups, using computer-generated random numbers. Blocks were numbered, after which we used a random-number generator program to select numbers that established the sequence in which blocks were allocated to one or the other group.

Subjects were randomly divided into 3 groups. The Mirror plus rTMS group was of 12 members who undertook mirror therapy in conjunction with rTMS, the Mirror group was of 11 members who undertook mirror therapy, and the control group was of 12 members who undertook sham therapy. All subjects were conducted with traditional physical therapy for 30 minutes a day, 5 times a week, for 6 weeks. Traditional physical therapy consisted of neurodevelopment treatment.

A summary of the clinical and demographic features of the sample is shown in Table 1, which also shows that before training, there were no significant differences among groups.

Each group were instructed to sit on a table for therapeutic purposes, based on the mirror therapy program proposed by Sütbeyaz *et al.* [8], and to use a 35 cm × 35 cm mirror designed to control its angle. After placing the mirror between the non-affected and affected upper limbs in each patient, the affected upper limb was positioned behind the mirror. Each group performed repeated fingers flexion and extension on the unaffected side for 15 minutes. The Mirror plus rTMS group was instructed to take the therapy with applying rTMS, and the Mirror group was instructed to take the therapy without applying rTMS. The control group did not apply rTMS, and performed, after covering the mirror with a white cloth. For rTMS equipment, this study used a 70 mm coil, and a Magstim Rapid (Magstim, Wales, UK). 10 Hz rTMS was applied to the hotspot of the lesional hemisphere in 10 second trains, with 50 second intervals between trains, for 15 minutes. A motor evoked potentials (MEPs) was performed, using Magstim Rapid, and upper limb function was evaluated by Fugl-Meyer Assessment (FMA), and Box and Block Test (BBT). We then recorded MEPs, by adjusting the TMS intensity to achieve an MEP in the first dorsal interosseous muscle of about 1-mV peak-to-peak amplitude, and the intensity was maintained constantly, throughout the experiment. The MEPs gives a measure of global corticospinal excitability [9].

The mechanisms by which the motor cortex excitability appears are that the Ia afferent fiber is activated by the rTMS application, and it cause high excitation of the corticospinal tract. The latency and amplitude of MEPs means motor cortex excitability. Reduced latency and increased amplitude means high motor cortex excitability [10].

FMA uses the methods described by Brunnstrom, using a cumulative numerical scoring system for the measurement of motor recovery, balance, sensation, and joint range of motion in patients who have sustained stroke patients [11]. The Box and Block Test is used to measure unilateral gross manual dexterity. This test involves the patient moving as many blocks as possible, one by one, from one compartment of a box to another compartment of equal size, within 60 seconds [12].

Table 1. General and medical characteristics of subjects (N = 35).

	Mirror plus rTMS group (n = 12)	Mirror group (n = 11)	Control group (n = 12)
Age (year)	54.73 ± 7.88	50.53 ± 8.02	52.45 ± 8.08
Since onset (month)	9.20 ± 4.01	8.23 ± 3.09	9.23 ± 4.29
Weight (kg)	61.20 ± 9.97	60.30 ± 8.68	62.70 ± 8.27
Height (cm)	165.00 ± 8.37	164.50 ± 7.78	166.30 ± 8.24
Gender (male/female)	7/5	7/4	8/4
Affected side (left/right)	4/8	5/6	5/7
Causes (infarction/hemorrhage)	7/5	6/5	6/5

Values are expressed as mean ± SD

Table 2. Comparison of motor recovery pre and post, between each group (N=35).

		Mirror plus rTMS group[a] (n = 12)	Mirror group[b] (n = 11)	Control group[c] (n = 12)	Post hoc
Latency (ms)	Pre	27.13 ± 1.17	27.38 ± 0.91	27.90 ± 0.98	/
	Post	26.19 ± 0.97*	26.56 ± 0.67*	27.61 ± 0.64	a, b > c
Amplitude (mV)	Pre	0.55 ± 0.43	0.48 ± 0.49	0.45 ± 0.43	/
	Post	1.14 ± 0.54*	0.69 ± 0.48	0.53 ± 0.42	a > b, c
FMA (score)	Pre	39.20 ± 8.04	36.33 ± 6.61	40.23 ± 6.67	/
	Post	56.86 ± 6.17*	49.86 ± 7.21*	47.93 ± 8.45*	a > b > c
BBT (unit)	Pre	34.80 ± 12.21	33.73 ± 10.84	29.93 ± 9.89	/
	Post	49.73 ± 9.19*	40.80 ± 8.29*	35.46 ± 10.85	a > b > c

Values are expressed as mean ± SD, *$p < 0.05$, FMA: Fugl-Meyer Assessment, BBT: Box and Block Test

2.1. Statistical analysis

Paired t-tests were used to verify the statistical significance in each group, in performances before, and after, the experiment. To compare among the groups, a one-way ANOVA was conducted. In addition, a *post hoc* test was performed, using Fisher's Least Significance Difference (LSD) test. The statistical significance level was set at α =.05.

3. Results

The general characteristics and results of the homogeneity test of the subjects are shown in Table 1. The FMA of all groups were significantly improved, after the experiment ($p < 0.05$). The Latency and BBT of the Mirror plus rTMS group and the Mirror group were significantly improved, after the experiment ($p < 0.05$). The Amplitude of the Mirror plus rTMS group was significantly improved after the experiment ($p < 0.05$). Significant difference was shown after the experiment, in comparison with the groups in latency ($p < 0.05$), and as the result of *post hoc* test, significant difference was shown between the Mirror plus rTMS group and the control group, and between the Mirror group and the control group, respectively ($p < 0.05$). Significant difference was shown after the experiment, in comparison of the groups in amplitude ($p < 0.01$), and as the result of *post hoc* test, significant difference was shown between the Mirror plus rTMS group and Mirror group, and between the Mirror plus rTMS group and control group ($p < 0.05$). Significant difference was shown after the experiment, in comparison of the groups in FMA and BBT ($p < 0.05$), and as the result of *post hoc* test, significant difference was shown between the Mirror plus rTMS group and Mirror group, and between the Mirror group and control group ($p < 0.05$).

4. Discussion

According to the results of this study, the latency of the Mirror plus rTMS group and Mirror group were decreased, compared with the control group, after the experiment. The amplitude, BBT, and FMA of the Mirror plus rTMS group were improved after the experiment, compared with the Mirror group and control group. Mirror therapy in conjunction with rTMS was shown to be more effective in improving upper extremity function, than mirror therapy and sham therapy.

TMS was used to investigate possible mechanisms underlying both spontaneous and therapy-induced motor recovery, after stoke [13]. Transcranial magnetic stimulation is based on Faraday's principle of mutual induction: electrical energy can be converted into magnetic fields, and magnet fields can be converted into electric energy [14]. We thought that it could be possible, because of brain reorganization through mirror treatment and rTMS happening at the same time. In a randomized crossover study of 9 chronic stroke patients, Altschuler *et al.* [15] reported that range of motion (ROM), speed, and accuracy of arm movement were more improved after mirror therapy. Stevens and Stoykov [16] also reported that two stroke patients trained with mirror therapy for 3 to 4 weeks, and had an increase in Fugl-Meyer Assessment score, active ROM, movement speed, and hand dexterity, after mirror therapy.

Similarly, Sathian *et al.* [17] found that 2 weeks of intense mirror therapy in a chronic stroke patient resulted in a strong recovery of grip strength and hand movement in the paretic arm. Pennisi *et al.* [18] demonstrated that complete hand paralysis in association with the absence of early MEPs predicted poor neurological recovery at 1 year, in 15 subjects after stroke. Conversely, the preservation of motor potentials evoked by rTMS in the early period after stroke may cause good effect to recovery of function.

Fregni *et al.* [19] randomly assigned 15 patients with chronic stroke, to receive active or sham rTMS of the unaffected hemisphere. Compared with sham rTMS, active rTMS resulted in a significant improvement in motor function performance in the affected hand, which lasted for 2 weeks. This result was similar to that of the present study. We supposed that the upper extremity function was improved, due to synergistic effects of rTMS and mirror therapy.

Limitations of this study include the small sample size, and that it is difficult to be generalized. We didn't confirm the continuity of effect through follow-up. Future studies should employ larger sample sizes, and compare the effect between mirror therapy and other intervention.

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