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The Effect of Repetitive Transcranial Magnetic Stimulation on Upper Extremity Motor Function in Stroke Patients: A Meta-Analytical Review

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ABSTRACT

Repetitive magnetic stimulation (rTMS) is a non-invasive brain stimulation technique, which can alter excitability in the motor cortex and is a potential treatment for motor impairment in stroke patients. However, the effect of rTMS on upper extremity function in stroke patients remains controversial. This study systematically reviewed and meta-analyzed the current findings on the effectiveness of rTMS for restoring upper extremity motor function in stroke patients.

A comprehensive literature search up to March 2010 of PubMed, the Cochrane Library, Scirus and the Chinese Electronic Periodical Services (CEPS) was performed. The articles from these searches were used to obtain additional articles. The quality of each study was assessed by criteria suggested by Jadad and the American Academy of Neurology for grading therapeutic trials. Biostat meta-analysis software version 2.0 was used to perform meta-analysis.

Nine studies were included. The overall random effects model revealed a significant positive treatment effect of rTMS when applied to primary motor cortex (M1) (Hedges' g = 0.590, 95% CI = 0.133 - 1.048, p = 0.011). In subgroup analysis, positive treatment effects were seen in acute stroke (Hedges' g = 0.91, 95% CI = 0.339 - 1.481, p = 0.002) and on the nonlesional M1 cortex (Hedges' g = 0.807, 95% CI = 0.054 - 1.560, p = 0.036).

It is concluded that when applied to the nonlesional hemisphere, low frequency rTMS may improve the upper extremity motor function of patients with acute stroke.

Key words: stroke, repetitive transcranial magnetic stimulation (rTMS), upper extremity, motor function, meta-analysis

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INTRODUCTION

Cerebrovascular accidents (CVA) are the main cause of disability worldwide. According to the heart disease and stroke statistics for 2010 from the American Heart Association, 795,000 people in the U.S. experience a new or recurrent stroke each year. The majority of stroke survivors suffer from upper extremity motor impairment and the effect of traditional rehabilitation programs is not promising. On discharge from acute stroke units, only 5 - 20% of patients achieve nearly full motor recovery[(1)], 30 - 40% continue to have severe motor deficits 3 to 6 months after stroke[(1,2)], and 30 - 66% remain motor-impaired 6 months after stroke[(1-3)].

Recent evidence suggests that the brain undergoes plastic changes after damage[(4)]. After focal injury (e.g. focal stroke injury), uninjured brain areas compensate for injured ones, but the effect is controversial. Secondary motor areas such as the dorsolateral premotor cortex (PMd), supplementary motor area and cingulated motor areas are more frequently recruited in patients with marked impairment than in patients with no residual impairment[(5)]. An imbalance in interhemispheric inhibition has also been observed after stroke. Excessive inhibitory signals originating from intact areas of the brain result in excessive inhibition of the lesioned areas of the brain, rendering motor recovery more difficult[(6)].

Repetitive transcranial magnetic stimulation (rTMS) is used to modulate cortical excitability. In healthy subjects, low-frequency rTMS (1 Hz) can decrease cortical excitability and high-frequency rTMS can increase cortical

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excitability[7]. An increasing number of studies in recent years have shown that rTMS applied to the motor cortices of stroke patients can modulate interhemispheric inhibition and improve motor function[7,8]. The effect of rTMS on cortical excitability varies with frequency, duration and intensity[7], and the effect of rTMS on upper extremity function in stroke patients remains controversial. Therefore, the objective of this study is to evaluate the effect of rTMS (when applied to different cortical regions) on upper extremity motor function in stroke patients.

MATERIALS AND METHODS

A comprehensive literature search up to March 2010 of four computerized databases, namely PubMed, Scirus, Cochrane Library and Chinese Electronic Periodical Services, was carried out to identify references on the use of rTMS for patients with stroke. Three categories of search terms were employed: patient (stroke, cerebrovascular accident, cerebrovascular disease), intervention (transcranial magnetic stimulation, repetitive transcranial magnetic stimulation, brain stimulation) and outcome (upper limb function, upper extremity function, upper extremity motor function). The references in each identified article were examined thoroughly for additional relevant articles.

The articles identified by basic electronic searches were inspected by two medical doctors and excluded if they failed to meet the following criteria: (1) repetitive transcranial magnetic stimulation as an only intervention and comparison with a control intervention, (2) use of objective outcome measures previously to evaluate upper extremity motor function in evidence-based studies, and (3) not a case report.

A total of 510 articles were identified by basic electronic searches. After careful manual screening using the exclusion criteria, 9 articles were selected for final analysis. The characteristics of each study are listed in Table 1. In each of these articles, more than one outcome measure was used. The approach was to code effect sizes equally on all measures, in order to achieve a single global category of results[9]. Therefore, 15 outcome measures were used for analysis, including pinch force, Jebsen-Taylor hand function test, nine hole peg test, grip strength, Wolf motor function test, motor activity log, wrist velocity, movement time, Fugl-meyer assessment, finger tapping frequency and hand tapping frequency.

Hedges' g was calculated for individual effect sizes and 15 outcome measures. Funnel plots were generated and showed no publication bias. In addition, fail-safe analysis was also performed. Comprehensive meta-analysis version 2.0 software (Biostat, Englewood, NJ, USA) was used for all statistical analyses.

The quality of articles selected was assessed according to the Jadad scale and criteria of the American Academy of Neurology for grading therapeutic studies. The current evaluation revealed 5 studies with complete randomization.

RESULTS

The overall meta-analysis revealed a significant mean effect size of 0.59 (95% CI = 0.133 - 1.048, p = 0.011). Fail-safe analysis showed that 125 null effect studies were needed to overthrow this effect size, meaning that the evidence showing the effect of rTMS on upper extremity motor function in stroke patients was relatively strong. Table 3 shows the effect size, confidence interval and p value of each study.

Two separate meta-analyses were conducted for subgroups defined by two moderating variables: post-stroke period and rTMS frequency. Comparisons were made between patients with acute stroke (post-stroke period ≤ 6 months) and patients with chronic stroke, and between low frequency rTMS (≤ 1 Hz) applied to the non-lesional hemisphere and high frequency rTMS (> 1 Hz) applied to the lesional hemisphere[19,20]. Significant mean effect sizes were found for the acute stroke group (Hedges' g = 0.91, 95% CI = 0.339 - 1.481, p = 0.002) and low frequency rTMS applied to the nonlesional M1 group (Hedges' g = 0.807, 95% CI = 0.054 - 1.560, p = 0.036). Fail-safe analysis showed that 29 and 39 null effect studies were needed, respectively, to overthrow these sizes. The quality assessment of each study is presented in Table 2 and 4.

Table 1. Characteristics of each study

Study	Total N	Mean Age : Years	Lesion Type	Mean Time Post Stroke (Months)
Takeuchi *et al.* (2005)[10]	10	58.4	Ischemic, subcortical	25.2
Fregni *et al.* (2006)[11]	10	56	Ischemic, subcortical	44.94
Liepert *et al.* (2007)[12]	12	63	Ischemic, subcortical	0.24
Malcolm *et al.* (2007)[13]	9	67	Subcortical	45.6
Dafotakis *et al.* (2008)[14]	12	45	Ischemic, subcortical	1.875
Kirton *et al.* (2008)[15]	5	13.25	Ischemic, subcortical	75.96
Nowak *et al.* (2008)[16]	15	46	Ischemic, subcortical	1.93
Yozbatiran *et al.* (2008)[17]	12	67	Ischemic, subcortical	56.4
Ameli *et al.* (2009)[18]	29	56	Ischemic, subcortical and cortical	5.5

Table 2. Quality assessment of each study

Study	Jadad scale		AAN criteria*	
Reviewer†	Reviewer 1	Reviewer 2	Reviewer 1	Reviewer 2
Takeuchi *et al.* (2005)[10]	4/5	4/5	I	I
Fregni *et al.* (2006)[11]	5/5	5/5	I	I
Liepert *et al.* (2007)[12]	4/5	4/5	I	I
Malcolm *et al.* (2007)[13]	5/5	5/5	I	I
Dafotakis *et al.* (2008)[14]	2/5	2/5	III	III
Kirton *et al.* (2008)[15]	5/5	5/5	I	I
Nowak *et al.* (2008)[16]	2/5	2/5	III	III
Yozbatiran *et al.* (2008)[17]	1/5	1/5	III	III
Ameli *et al.* (2009)[18]	1/5	1/5	III	III

*Criteria of American Academy of Neurology for grading therapeutic studies.
†The inter-rater reliability was 100%.

Table 3. Summary statistics of each study

Study	Outcome measure	Frequency, episode (total number of stimuli), intensity (% of RMT)	Hedges'g
Takeuchi *et al.* (2005)*	Pinch force	1 Hz, 1 episode (1500), 90%	–1.600
Fregni *et al.* (2006)*	JTT	1 Hz, 5 episodes (6000), 100%	0.529
Liepert *et al.* (2007)†	NHPT	1 Hz, 1 episode (1200), 90%	1.271
	Grip strength		–0.004
Malcolm *et al.* (2007)*	WFMT	20 Hz, 10 episodes (2000), 90%	–0.010
	MAL		–0.634
Dafotakis *et al.* (2008)†	Grip strength	1 Hz, 1 episode (600), 100%	0.733
Kirton *et al.* (2008)*‡	Grip strength	1 Hz, 8 episodes (9600), 100%	4.235
Nowak *et al.* (2008)†	Wrist velocity	1 Hz, 1 episode (600), 100%	0.857
	Movement time		1.761
Yozbatiran *et al.* (2008)	FMA	20 Hz, 1 episode (1600), 90%	–0.537
	NHPT		0.591
	Grip strength		0.591
Ameli *et al.* (2009)	Finger tapping frequency	10 Hz, 1 episode (100), 80%	1.644
	Hand tapping frequency		0.987
Overall Hedges'g	P value	Confidence interval (95%)	Fail-safe, N
0.590	0.011	0.133 - 1.048	125

Abbreviations: JTT, Jebsen-Taylor Hand Function test; NHPT, Nine hole peg test; FMA, Fugl-Meyer assessment; WMFT, Wolf Motor Function test; MAL, Motor Activity Log; RMT, resting motor threshold.
*Chronic stroke patients.
†Acute stroke patients.
‡Pediatric stroke patients.

DISCUSSION

This meta-analysis revealed that low-frequency rTMS applied to the nonlesional M1 cortex is beneficial for recovering upper extremity motor function in patients with acute stroke. The study of Takeuchi *et al.*[21] in 2009, which allocated 30 patients to groups receiving a single-episode of either (1) low-frequency (1 Hz) rTMS on the nonlesional motor cortex, (2) high-frequency (10 Hz) rTMS on the lesional motor cortex, or (3) bilateral repetitive transcranial magnetic stimulation with both 1 Hz and 10 Hz rTMS, showed that both low-frequency and bilateral stimulation immediately improved the paretic hand and bilateral stimulation sustained the motor training effect on the paretic hand for 1 week. By contrast, high-frequency stimulation had no effect on motor function. The findings of Takeuchi's study

Table 4. Score details of Jadad scale for each study

	Jadad scale		
Study	Randomization	Double-blinding	Withdrawals and dropouts
Takeuchi *et al.* (2005)	2	2	0
Fregni *et al.* (2006)	2	2	1
Liepert *et al.* (2007)	2	2	0
Malcolm *et al.* (2007)	2	2	1
Dafotakis *et al.* (2008)*	1	0	1
Kirton *et al.* (2008)	2	2	1
Nowak *et al.* (2008)*	1	0	1
Yozbatiran *et al.* (2008)*	0	0	1
Ameli *et al.* (2009)*	0	0	1

*Papers scored less than 3 were included because they focused on the effects of rTMS on upper extremity motor function, which was the aim of this study.

and this study both indicate the greater effectiveness of low-frequency rTMS for upper extremity motor recovery. However, Takeuchi *et al.* proved that the combination of high-frequency and low-frequency rTMS has yet another effect, which is not examined by this study due to the lack of similar studies[21].

Previous studies concluded that the effect of rTMS, either low-frequency or high-frequency, on motor cortex excitability persists for 15 - 30 min[22-26]. In the current meta-analysis, only clinical effects right after rTMS were evaluated. However, the positive effect implied that cortical excitability changes could reflect clinical improvement. Further time-effect relationships need to be clarified.

In our meta-analysis, all patients received low-frequency rTMS over the nonlesional motor cortex. Therefore, the positive effect of rTMS could also be attributed to its low frequency. More studies are needed to identify the individual effects.

The quality of this meta-analysis is moderate, which was the major limitation of this study. Of the 9 studies selected, 5 were randomized-controlled trials, meeting Level I Oxford Centre for Evidence Based Medicine criteria; the other 4 articles met Level III criteria. As rTMS is a relatively novel stroke therapy, this situation was expected and more randomized controlled trials are needed to validate the therapeutic effect.

In summary, this meta-analysis of quantitative evidence demonstrated that a single episode of low-frequency rTMS improves upper extremity motor function in acute stroke patients. Immediate effects were observed in current studies, but the duration of the effects were still unknown and would need further investigation. Previous studies evaluated qualitative evidence; The usefulness of rTMS in stroke rehabilitation is suggested.

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