J Rehabil Med 2011; 43: 430–434

ORIGINAL REPORT

COMBINED STUDY OF TRANSCRANIAL MAGNETIC STIMULATION AND DIFFUSION TENSOR TRACTOGRAPHY FOR PREDICTION OF MOTOR OUTCOME IN PATIENTS WITH CORONA RADIATA INFARCT

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Objective: **This study compared the usefulness of transcranial magnetic stimulation (TMS), diffusion tensor tracto graphy (DTT), and the combined study of TMS and DTT for prediction of motor outcome in patients with corona radiata infarct.**

Methods: **Fifty-eight patients with complete motor weakness of the affected hand were recruited. TMS and DTT were performed in the early stage (7–28 days) of stroke. Patients were classified into 2 groups according to the presence of motor evoked potential in affected hand muscle, and according to the preservation of integrity of the affected corticospinal tract on DTT.**

Results: **The specificity of TMS (0.93) was higher than that of DTT (0.48), and the sensitivity of DTT (0.86) was higher than that of TMS (0.66). There was a good outcome in 89.5% of patients with TMS (+) and DTT (+), which was similar to the patients (90.5%) with single TMS (+). In contrast, there was a poor outcome in 87.5% of patients with TMS (–) and DTT (–), which was higher than those with single TMS (–) (73.0%) or DTT (–) (77.8%).**

Conclusion: **TMS showed higher positive predictability and DTT showed higher negative predictability. The combined study of TMS and DTT appeared to be more advantageous in prediction of negative motor outcome than did each single study. Single TMS appeared to be more advantageous in prediction of positive motor outcome.**

Key words: transcranial magnetic stimulation; diffusion tensor imaging; stroke; motor recovery; prognosis; cerebral infarct.

J Rehabil Med 2011; 43: 430–434

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Submitted October 18, 2010; accepted February 4, 2011

INTRODUCTION

Many studies of the clinical neuroscience of stroke have attempted to predict motor outcome for stroke patients over a long period of time. This is due to the fact that motor weakness is one of the most serious disabling sequelae of stroke, with over 50% of stroke patients experiencing a residual motor deficit (1). These studies could provide useful information for determination of specific management strategies for stroke patients.

With regard to motor control, the corticospinal tract (CST) is the most important neural tract, particularly for fine motor control of the hand in humans (2, 3). Many studies have attempted to predict the outcome of motor weakness following a stroke by elucidation of the CST status, using clinical findings (4), radiological methods (5), electrophysiological methods (6–10) and functional neuroimaging techniques (11, 9). However, transcranial magnetic stimulation (TMS) has been a very useful evaluation tool for the past 30 years (6–8, 10). During the 2000s, after the introduction of diffusion tensor imaging (DTI), around a dozen DTI studies reported on the prediction of motor outcome in stroke patients (12–22, 3, 23).

Because TMS and DTI estimate different aspects of the state of the CST, the combination of DTI with TMS would increase the predictability of motor outcome in stroke patients. TMS provides electrophysiological evaluation of the presence or the amount of the CST through the characteristics of motor evoked potentials (MEPs) (6–8, 24, 10), in contrast, DTI provides an evaluation of the integrity by visualization of the CST or the degree of injury to the CST by estimation of the diffusion anisotropy of the CST (12–14, 16, 17–23). To the best of our knowledge, there has been only 1 combined study of TMS and DTI for patients with intracerebral haemorrhage (15).

The current study compared TMS and DTI, and investigated the usefulness of the combined study of TMS and DTI in prediction of motor outcome in patients with corona radiata (CR) infarct.

PATIENTS AND METHODS

Patients

Fifty-eight consecutive patients (males: 33, mean age: 61.98 (standard deviation (SD) 12.22 years) were recruited according to the following inclusive criteria: (*i*) first-ever stroke due to cerebral infarct; (*ii*) complete weakness of the affected hand (finger flexor and extensor) at the time of stroke onset; (*iii*) an infarct at the level of the corona radiata, which explained the hand weakness (at least included the posterior half of the middle third and adjacent to the lateral wall of the lateral ventricle of

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the corona radiata) (25–27), as confirmed by a neuroradiologist; (*iv*) DTI scanning and TMS evaluation were performed simultaneously within 2 days of each other at an early stage (within 7–28 days after stroke onset); (*v*) absence of serious medical complications, such as pneumonia or cardiac problems, from onset to final evaluation; and (*vi*) no medications, such as sedatives, anticonvulsants, or muscle relaxants, which are known to influence the MEP at the time of TMS evaluation. Patients who showed apraxia, severe somatosensory problems (less than 12 points (full mark: 24) on the subscale for kinaesthetic sensation of the Nottingham Sensory Assessment (28), or severe cognitive problems (Mini-Mental State Examination <25) were excluded from the study. All of the patients provided written informed consent prior to the study, and the local ethics committee approved the study protocol.

Clinical evaluation

The motor function of each patient was evaluated twice: at onset (within 24 h of symptom onset) and at 6 months after onset, using the modified Brunnstrom classification (MBC) (29, 30). MBC was classified as the following: 1: unable to move fingers voluntarily; 2: able to move fingers voluntarily; 3: able to close hand voluntarily; unable to open hand; 4: able to grasp a card between the thumb and medial side of the index finger; able to extend fingers slightly; 5: able to pick up and hold a glass; able to extend fingers; 6: able to catch and throw a ball in a near-normal fashion; able to button and unbutton a shirt. The reliability and validity of the MBC are well established (28, 30). Evaluators of clinical data were blinded to the TMS and DTI data, and analysers of TMS and DTI were blinded to the clinical data.

Transcranial magnetic stimulation

TMS was performed with the patient seated comfortably in a 60 degree-reclined chair. A magnetic stimulator (Magstim Novametrix 200, Novametrix Inc., Wallingford, CT, USA) and circular coil (diameter 90 mm) were used. Cortical stimulation was performed at the vertex with the coil held tangentially. The left hemisphere was stimulated by a counterclockwise current, and the right hemisphere was stimulated by a clockwise current. MEPs were recorded from both abductor pollicis brevis muscles (APBs) while the patient was in a relaxed state. The excitatory threshold (ET) was defined as the minimum stimulus required for induction of MEPs with 50 μV peak-to-peak amplitude or greater in 2 of 4 attempts. Stimulation intensity was set at the ET plus 20% when the ET was below 80%, or 100% of the stimulator output when the ET was more than 80%. One hemisphere was stimulated 4 times with a minimum of 10 s intervals. The MEP with the shortest latency and the largest amplitude was adopted. Patients were classified into two groups according to the presence of MEP on the affected APB: the TMS (+) group, patients who showed MEP in the affected APB (21 patients), and the TMS (−) group, patients who did not show MEP in the affected APB (37 patients).

Diffusion tensor imaging

Diffusion tensor images were acquired using a 1.5 T Philips Gyroscan Intera (Philips Ltd, Best, The Netherlands) equipped with a 6-channel head coil with a single-shot spin echo planar imaging sequence. For each of the 32 non-collinear diffusion sensitizing gradients, we acquired 60 contiguous slices parallel to the anterior commissure–posterior commissure line. The following imaging parameters were used: matrix = 96 × 96, reconstructed to matrix = 128 × 128, field of view = 221 × 221 mm^2, echo time (TE) = 76 ms, repition time (TR) = 10,726 ms, parallel imaging reduction factor (SENSE factor) = 2, echo planar imaging factor = 49, b = 600 s/mm^2, NEX = 1, and a slice thickness = 2.3 mm (acquired isotropic voxel size 2.3 × 2.3 × 2.3mm^3). Each of the DTI replications was intra-registered to the baseline "b_0" images to correct for residual eddy-current image distortions and head motion effect, using a diffusion registration package (Philips Medical Systems). Fibre connectivity was also evaluated using fibre assignment by continuous tracking (FACT), a 3D fibre reconstruction algorithm contained within PRIDE software (Philips Medical Systems) (31). Termination criteria included fractional anisotropy (FA) < 0.2 and direction threshold = 750, as determined by a previous study of the optimal tractability threshold of FA (32). A seed region of interest (ROI) was drawn in the CST portion of the mid pons on 2D FA colour maps, and another ROI was drawn in the CST portion of the lower pons on a 2D FA colour map. Fibre tracts passing through both ROIs were designated as the final tracts of interest. Patients were classified into two groups according to the integrity of the CST in the affected hemisphere: the diffusion tensor tractography (DTT) (+) group, patients whose CST was preserved around the infarct (40 patients), and the DTT (−) group, patients whose CST was interrupted by the infarct (18 patients).

Statistical analysis

Statistic analysis was performed using SPSS 17.0 software (SPSS Inc, Chicago, USA). First, the significance of the parameter associated with outcome of motor function was assessed. Mann-Whitney test was used for difference in MBC at baseline in the (+) and (−) groups in the TMS and DTT groups, and changes in MBC score from baseline to 6-month follow-up evaluation were compared using a Wilcoxen signed-rank test. Secondly, patients were classified into two groups: the Good group and the Poor group, according to motor function, and whether or not they could perform grasp-release of the affected hand (33). Therefore, patients with an MBC score of 5 or 6 score were assigned to the Good group (MBC ≥ 5), and patients with an MBC score below 4 were assigned to the Poor group (MBC ≤ 4). Predictive values for TMS and DTT were compared using sensitivity and specificity according to statistical classification in the Good or Poor group and responses from TMS or DTT. Statistical significance was adopted at $\alpha < 0.05$.

RESULTS

Clinical evaluation

Table I shows the patient demographics and clinical data. Twenty-nine patients had infarction in the right hemisphere (50.0%), while the remaining 29 had infarction in the left hemisphere (50.0%). In distributions on the lesion side, no statistical difference was observed between the (+) group and (−) group in each of the two groups (TMS group $p = 0.585$, DTT group $p = 0.155$). During the duration from stroke attack to the two neural evaluations (i.e. TMS and DTT), no differences were observed between the (+) and (−) groups in either the TMS ($p = 0.288$) or the DTT group ($p = 0.407$). Forty patients (68.9%) had risk factors that included non-insulin-dependent diabetes mellitus (11 patients; 19.0%), hypertension (23 patients; 39.7%), atrial fibrillation (4 patients; 6.9%), hypercholesterolemia (8 patients; 13.8%), and cigarette smoking (21 patients; 36.2%). Distributions for all types of risk factors did not differ statistically between the (+) and (−) groups in the TMS and DTT group, respectively.

Initial MBC score was 1 for all patients. MBC scores showed significant improvement from the initial to the 6-month follow-up evaluation for all of the (+) and (−) groups in the TMS and DTT groups ($p < 0.001$) (Table II). Clinical classification was determined according to MBC score; 29 patients (50.0%) belonged to the Good group, while the remaining 29 patients (50.0%) were assigned to the Poor group (Table III).

Clinical motor function in the TMS group

Compared with changes in MBC score from the initial to the 6-month follow-up evaluation, better improvement was shown in the TMS (+) group (4.24 (SD 1.34)) than in the TMS (−)

Table I. *Demographic and clinical data for patients in the transcranial magnetic stimulation (TMS) group and the diffuse tensor tractography (DTT) group*

	TMS group				DTT group			
Variables	TMS (+)	TMS (−)	Total	*p*-value	DTT (+)	DTT (−)	Total	*p*-value
Patients, *n*	21	37	58		40	18	58	
Age, years, mean (SD)	62.14 (12.83)	61.89 (12.04)	61.98 (12.22)	0.942	63.75 (11.44)	58.06 (13.31)	61.98 (12.22)	0.101
Lesion side, *n* (%)								
Right	12 (57.1)	17 (45.9)	29 (50.0)	0.585	23 (57.5)	6 (33.3)	29 (50.0)	0.155
Left	9 (42.9)	20 (54.1)	29 (50.0)		17 (42.5)	12 (66.7)	29 (50.0)	
Days to TMS or DTT, mean (SD)	17.71 (3.21)	18.30 (3.34)	18.09 (3.28)	0.520	18.35 (3.02)	18.16 3.22)	18.29 (3.06)	0.835
Risk factor, *n* (%)								
NIDDM	5 (23.8)	6 (16.2)	11 (19.0)	0.478	8 (20.0)	3 (16.7)	11 (19.0)	0.764
HTN	10 (47.6)	13 (35.1)	23 (39.7)	0.350	17 (42.5)	6 (33.3)	23 (39.7)	0.509
Afib	3 (14.3)	1 (2.7)	4 (6.9)	0.130	4 (10.0)	0 (0.0)	4 (6.9)	0.164
Hchol	4 (19.0)	4 (10.8)	8 (13.8)	0.094	6 (28.6)	2 (11.1)	8 (13.8)	0.691
Cig	9 (42.9)	12 (32.4)	21 (36.2)	0.347	16 (40.0)	5 (27.8)	21 (36.2)	0.582

TMS (+) and TMS (−) indicate patients who showed motor evoked potential in the affected adductor pollicis brevis, or not, respectively. DTT (+) and DTT (−) indicate patients whose corticospinal tract was preserved around the infarct, or interrupted by the infarct.
NIDDM: non-insulin-dependent diabetes mellitus; HTN: hypertension; Afib: atrial fibrillation; Hchol: hypercholesterolemia; Cig: cigarette smoking; SD: standard deviation.

group (2.00 (SD 1.83)) ($p=0.000$). Table III shows the clinical classification into either the Good or the Poor group in terms of MBC score. In classification according to MBC score, 19 (90.5%) of 21 patients in the TMS (+) group belonged to the Good group, and the remaining 2 patients (9.5%) were assigned to the Poor group, while 10 (27.0%) of 37 patients in the TMS (−) group belonged to the Good group, and the remaining 27 patients (73.0%) were assigned to the Poor group.

Clinical motor function in the DTT group

In terms of changes in MBC score from the initial to the 6-month follow-up evaluation, motor function in the DTT (+) group (3.30 (SD 1.88)) was greatly improved compared with the DTT (−) group (1.72 (SD 1.78)) ($p=0.001$) (Table II). In classification according to MBC score (Table III), 25 (62.5%) patients out of 40 patients in the DTT (+) group belonged to the Good group, and the remaining 15 (37.5%) patients belonged to the Poor group, while 4 (22.2%) out of 18 patients in the DTT (−) group belonged to the Good group, and the remainder of the 14 patients (77.8%) were assigned to the Poor group (Table III).

Table II. *Changes in motor function between the initial and the 6-month follow-up evaluation in the transcranial magnetic stimulation (TMS) group and the diffuse tensor tractography (DTT) group*

	MBC			
	Initial	6 month	Difference	*p*-value
TMS (+)	1.00 (0.00)	5.24 (1.34)	4.24 (1.34)	0.000
TMS (−)	1.00 (0.00)	3.00 (1.83)	2.00 (1.83)	
DTT (+)	1.00 (0.00)	4.30 (1.88)	3.30 (1.88)	0.000
DTT (−)	1.00 (0.00)	2.72 (1.78)	1.72 (1.78)	

TMS (+) and TMS (−) indicate patients who showed motor evoked potential in the affected adductor pollicis brevis, or not, respectively. DTT (+) and DTT (−) indicate patients whose corticospinal tract was preserved around the infarct, or interrupted by the infarct.
MBC: modified Brunnstrom classification; TMS: transcranial magnetic stimulation.

Comparison of TMS and DTT

A higher specificity was observed in the TMS group (0.93) than in the DTT group (0.48) for prediction of motor outcome (Table III). On the other hand, DTT showed a higher sensitivity (0.86) than TMS (0.66). Among the patients included in the TMS (+) and DTT (+) groups, 17 out of 19 patients (89.5%) belonged to the Good group, and the remainder (10.5%) belonged to the Poor group. Among the patients included in the TMS (+) and DTT (−) groups, 8 out of 21 patients (38.1%) belonged to the Good group, and the remainder (61.9%) belonged to the Poor group. All patients who were included in the TMS (−)

Table III. *Proportion of the prevalence according to recovery conditions (good or poor) of modified Brunnstrom classification (MBC) in the transcranial magnetic stimulation (TMS) group and the diffuse tensor tractography (DTT) group*

		MBC	
Group	Number	Good *n* (%)	Poor *n* (%)
TMS group			
TMS (+)	21	19 (90.5)	2 (9.5)
TMS (−)	37	10 (27.0)	27 (73.0)
Sensitivity		0.66	
Specificity		0.93	
DTT group			
DTT (+)	40	25 (62.5)	15 (37.5)
DTT (−)	18	4 (22.2)	14 (77.8)
Sensitivity		0.86	
Specificity		0.48	
TMS and DTT groups			
TMS (+) DTT (+)	19	17 (89.5)	2 (10.5)
TMS (+) DTT (−)	21	8 (38.1)	13 (61.9)
TMS (−) DTT (+)	2	2 (100.0)	0 (0.0)
TMS (−) DTT (−)	16	2 (12.5)	14 (87.5)

TMS (+) and TMS (–) indicate patients who showed motor evoked potential in the affected adductor pollicis brevis, or not, respectively. DTT (+) and DTT (–) indicate patients whose corticospinal tract was preserved around the infarct, or interrupted by the infarct.

and DTT (+) groups belonged to the Good group. Among the patients included in the TMS (−) and DTT (−) group, 2 out of 16 patients (12.5%) belonged to the Good group, and the remainder (87.5%) belonged to the Poor group.

DISCUSSION

In the current study, we compared TMS and DTT, and investigated the usefulness of the combined study of TMS and DTT in prediction of motor outcome for patients with CR infarct. We found that TMS showed higher specificity (0.93) than DTT (0.48), while, in contrast, DTT had a higher specificity (0.86) than TMS (0.66). These findings suggest that the presence of MEP and disruption of the CST on DTT at the early stage of CR infarct are indicative of a high probability of good and poor motor outcome at the chronic stage, respectively. Predictability of TMS group was higher than that of DTT with regard to specificity/sensitivity (0.93/0.66) than DTT (0.48/0.86). Therefore, TMS appears to be superior to DTT for prediction of motor outcome in patients with CR infarct. On the other hand, when comparing motor outcome from combined study of TMS and DTT with that of each single study, a good outcome was revealed in 89.5% of patients with TMS (+) and DTT (+). This result was similar to that (90.5%) of TMS. However, in patients with TMS (–) and DTT (–), 87.5% of patients showed poor outcome, which was higher than with single TMS (73.0%) and single DTT (73.0%). Therefore, combined study of TMS and DTT would be more helpful than each single study in prediction of negative motor outcome.

The usefulness of TMS or DTI has been demonstrated by many studies (12, 13, 6, 14, 7, 8, 15–21, 10, 22, 23); however, only one study has reported on combined study of TMS and DTT (15, 9). The previous combined study of TMS and DTT compared the abilities of TMS and DTT, which were performed during the early stage (7–28 days) for prediction of motor outcome in 53 patients with intracerebral haemorrhage. Results revealed that TMS and DTT had different advantages in prediction of motor outcome; TMS showed higher positive predictive value than DTT, and DTT showed higher negative predictive value than TMS. Results of the current study were compatible with those of the previous study; however, classification criteria for motor outcome were different. The previous study was classified with the standard of the median value of motor outcome for all patients; in contrast, in the current study, we defined good recovery when a patient was able to move the affected hand against gravity.

In conclusion, TMS and DTT performed at an early stage of cerebral infarct have different advantages in prediction of motor outcome: TMS showed higher positive predictability than DTT, and DTT revealed higher negative predictability than TMS. In addition, the combined study of TMS and DTT seemed to be more advantageous in prediction of negative motor outcome than each single study. Similarly, single TMS seemed to be more advantageous in prediction of positive motor outcome. Our adoption of only one parameter with regard to the integrity of the CST among the various parameters of TMS and DTT is a limitation of this study. Further studies involving more parameters for TMS and DTT are warranted. In addition, further studies are needed to increase the predictability of DTI for motor outcome. DTI analysis according to the somatotopies of the hand and leg could provide more precise information about hand and gait function, respectively.

ACKNOWLEDGEMENT

This work was supported by National Research Foundation of Korea Grant funded by the Korean Government (KRF-2008-314-E00173).

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