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Comparison of TMS and DTT for predicting motor outcome in intracerebral hemorrhage

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ABSTRACT

Background: TMS (transcranial magnetic stimulation) and DTT (diffusion tensor tractography) have different advantages in evaluating stroke patients. TMS has good clinical accessibility and economical benefit. On the contrary, DTT has a unique advantage to visualize neural tracts three-dimensionally although it requires an expensive and large MRI machine. Many studies have demonstrated that TMS and DTT have predictive values for motor outcome in stroke patients. However, there has been no study on the comparison of these two evaluation tools. In the current study, we compared the abilities of TMS and DTT to predict upper motor outcome in patients with ICH (intracerebral hemorrhage).
Methods: Fifty-three consecutive patients with severe motor weakness were evaluated by TMS and DTT at the early stage (7–28 days) of ICH. Modified Brunnstrom classification (MBC) and the motricity index of upper extremity (UMI) were evaluated at onset and 6 months after onset.
Results: Patients with the presence of a motor evoked potential (MEP) in TMS or a preserved corticospinal tract (CST) in DTT showed better motor outcomes than those without ($p = 0.000$). TMS showed higher positive predictive value than DTT. In contrast, DTT showed higher negative predictive value than TMS.
Conclusions: TMS and DTT had different advantages in predicting motor outcome, and this result could be a reference to predict final neurological deficit at the early stage of ICH.

1. Introduction

Stroke is a leading cause of major adult disability. Motor weakness is one of the most serious disabling sequelae of stroke, with over 50% of stroke patients experiencing a residual motor deficit. Predicting an accurate prognosis for motor function in stroke patients is important, as it could provide useful information for specific rehabilitation strategies and final motor outcomes. Therefore, many previous studies have attempted to predict motor outcomes in stroke patients using various methods, including clinical findings [1,2], radiologic measurements [3,4], electrophysiological methods [5,6], and functional neuroimaging [7,8].

In stroke patients, transcranial magnetic stimulation (TMS) has been most commonly used to predict motor outcome by evaluating the status of the corticospinal tract (CST) through the motor evoked potential (MEP) [5,6,9,10]. In contrast, diffusion tensor tractography (DTT), which is derived from diffusion tensor imaging (DTI), allows the visualization of three-dimensional images of the CST by virtue of its ability to capture water diffusion characteristics [11]. Several recent studies have reported on the predictive value of DTT for motor outcome in stroke patients [12–17]. Therefore, TMS and DTT might have different advantages in predicting motor outcome in stroke patients. However, no study has yet applied these two evaluation tools simultaneously and compared their capacities for prediction.

In the current study, we compared TMS and DTT and investigated whether TMS and DTT have different predictive values for motor outcomes in patients with ICH.

2. Methods

2.1. Subjects

Fifty-three consecutive patients (31 males; average age, 54.0 (range: 41–79)) were recruited according to the following inclusion

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criteria: (1) first ever hemorrhagic stroke, (2) severe weakness of the affected extremities to the extent of an inability to move without gravity and complete weakness of the affected hand (finger flexor and extensor) and ankle (ankle dorsiflexor and plantarflexor) within 24 h of onset, (3) a hematoma involving the CST at the corona radiata (CR) or posterior limb of internal capsule level (PLIC) on brain MRI, and confirmed by a neuroradiologist (Byun WM) [18–20], (4) DTT scanning and TMS evaluation were performed simultaneously within 2 days of each other at an early stage (within 7–28 days after ICH onset), (5) absence of serious medical complications such as pneumonia or cardiac problems from onset to final evaluation, and (6) no medication that could influence the motor evoked potential (MEP) [21], inhalation anesthetics [22], anticonvulsants, or muscle relaxants, at the time of TMS. Patients who showed apraxia, somatosensory problems, or severe cognitive problems (Mini-Mental State Examination <25) were excluded from the study. All patients provided written informed consent prior to the study, and the ethics committee of Yeungnam university hospital approved the study protocol.

2.2. 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. The function of the affected hand was categorized according to the modified Brunnstrom classification (MBC) [23,24]: 0 (unable to move fingers voluntarily), 1 (able to move fingers voluntarily), 2 (able to close hand voluntarily; unable to open hand), 3 (able to grasp a card between the thumb and medial side of the index finger; able to extend fingers slightly), 4 (able to pick up and hold a glass; able to extend fingers), 5 (able to catch and throw a ball in a near-normal fashion; able to button and unbutton a shirt). The motricity index of upper extremity (UMI) [25] was used to measure motor function, with a maximum score of 100. The reliability and validity of the MI and MBC are well-established [23–25]. The clinical evaluators were blinded to the TMS and DTT data, and the TMS and DTT analyzers were blinded to the clinical data.

2.3. Transcranial magnetic stimulation

TMS was performed using a Magstim Novametrix 200 magnetic stimulator (Novametrix Inc., Wallingford, CT, USA) with a 9 cm mean diameter circular coil. Cortical stimulation was performed with the coil held tangentially over the vertex. The left hemisphere was stimulated by a counterclockwise current, and the right hemisphere was stimulated by a clockwise current. MEPs were obtained from both abductor pollicis brevis muscles (APBs) in a relaxed state. The excitatory threshold (ET) was defined as the minimum stimulus required to elicit an MEP with a peak to peak amplitude of 50 μV, or greater in two of four attempts. Stimulation intensity was set at the ET plus 20% of the maximum stimulator output. One hemisphere was stimulated four times at a minimum of 10 second intervals. The MEP with the shortest latency and the largest amplitude was adopted. The patients were classified into two groups according to the presence of MEP on the affected APB: TMS (+) group — the patients who showed MEP in the affected APB (23 patients), and TMS (−) group — the patients who did not show MEP in the affected APB (30 patients) (Fig. 1).

2.4. Diffusion tensor imaging

Diffusion tensor images were acquired using a 1.5 T Philips Gyroscan Intera (Hoffman-LaRoche, Ltd, Best, the Netherlands) equipped with a Synergy-L Sensitivity Encoding (SENSE) head coil with a single shot spin echo planar imaging sequence. For each of the

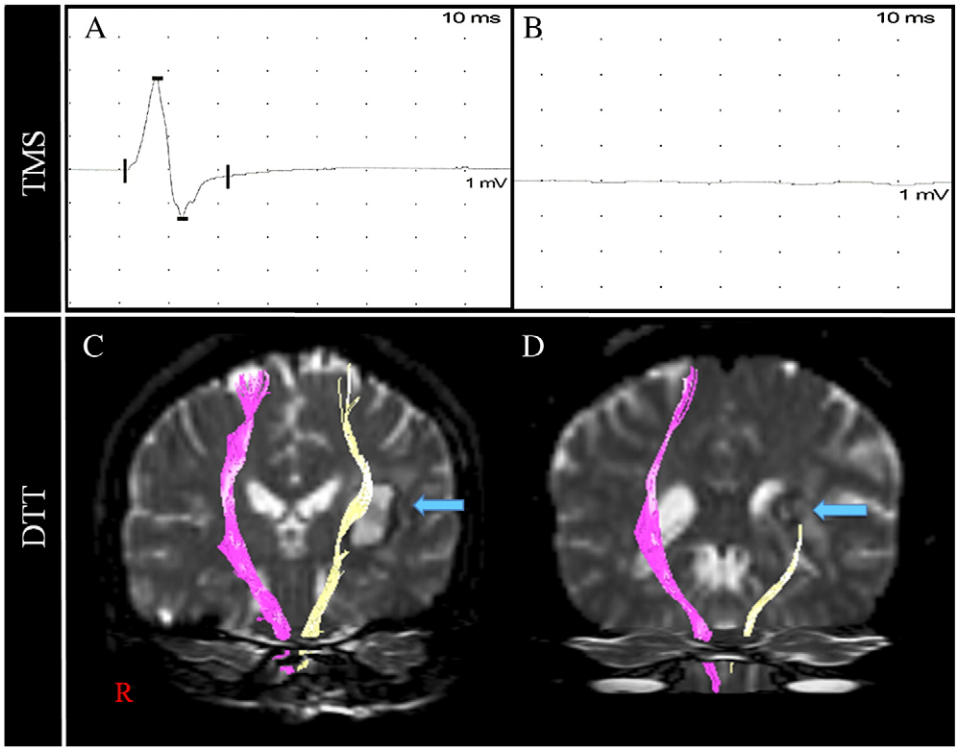

Fig. 1. Grouping according to the results of transcranial magnetic stimulation and diffusion tensor tractography. The results of TMS (upper low) were classified into A: TMS (+) group (presence of motor evoked potential) and B: TMS (−) group (absence of motor evoked potential). The results of DTT (lower low) were classified into C: DTT (+) group (preservation of corticospinal tract) and D: DTT (−) group (disruption of corticospinal tract). TMS: transcranial magnetic stimulation and DTT: diffusion tensor tractography.

32 non-collinear and non-coplanar diffusion sensitizing gradients, we acquired 60 contiguous slices parallel to the anterior commissure–posterior commissure line. The imaging parameters used were: matrix = 128 × 128, field of view = 221 × 221 mm^2, TE = 76 ms, TR = 10,726 ms, SENSE factor = 2, echo planar imaging factor = 67, b = 600 mm^2 s^{-1}, and slice thickness = 2.3 mm. Fiber connectivity was also evaluated using FACT (fiber assignment by continuous tracking), a 3D fiber reconstruction algorithm contained within PRIDE software (Philips Medical Systems) [26]. The termination criteria used were fractional anisotropy (FA) < 0.2 and direction threshold = 750, as determined by a previous study on the optimal tractability threshold of FA [27]. A seed region of interest (ROI) was drawn in the CST portion of the mid pons on 2D FA color maps, and another ROI was drawn in the CST portion of the lower pons on a 2D FA color map. Fiber tracts passing through both ROIs were designated as the final tracts of interest. The patients were classified into two groups according to the integrity of the CST in the affected hemisphere: DTT (+) group — the patients whose CST was preserved around the hematoma (32 patients), and DTT (−) group — the patients whose CST was interrupted by the hematoma (21 patients) (Fig. 1).

2.5. Statistical analysis

In the current study, statistical analysis was performed in two steps. In the first step, the significance of the parameters influencing motor outcomes was assessed. Motor and functional scores at onset in the (+) and (−) groups on TMS and DTT were compared using an independent *t*-test, and the changes of motor and functional scores from onset to 6 months after onset were compared using a paired *t*-test. The differences in the improvement between the TMS and DTT groups were analyzed using one way ANCOVA, controlling for the motor dysfunction at the onset of ICH. In the second step, the patients were classified into two groups, the Good group and Poor group using two step cluster analysis, according to the results of MBC and UMI. Median value of MBC was 2.45 and patients with above 3 score of MBC were classified to the Good group and patients with below 2 of MBC were to the Poor group. For UMI, median value was 62, patients with above 62 of UMI belonged to the Good group and patients with below 62 of UMI were to the Poor group. The predictive values of TMS and DTT were compared using positive predictive values and negative predictive values according to the statistical classification in the Good or Poor group and responses of TMS and DTT. The adopted level of significance was $\alpha < 0.05$. Statistical analyses were conducted using SPSS 12.0 software (SPSS Inc, Chicago, USA).

3. Results

3.1. Clinical evaluation

Twenty-eight of 53 patients had a hematoma in the right hemisphere, and the other 25 patients had a hematoma in the left hemisphere (Table 1). The duration (days) from onset of ICH to TMS (17.16 ± 3.15) and to DTT scanning (17.04 ± 3.84) did not differ between groups (TMS: $p = 0.515$; DTT: $p = 0.525$). Forty-seven (88.7%) of 53 patients had risk factors; 29 (54.7%) had hypertension, 16 (30.2%) had noninsulin dependent diabetes mellitus, 8 (15.1%) had atrial fibrillation, 20 (37.7%) had hypercholesterolemia, 27 (50.9%) were cigarette smokers, and 36 (67.9%) patients had more than one risk factor. The distributions of risk factors did not differ between the TMS and DTT groups (+/−) (TMS: $p = 0.217$; DTT: $p = 0.200$). The MBC scores measured at onset were 0 in all patients. There were no differences in the UMI scores at onset between the (+) and (−) groups of TMS and DTT (TMS: $p = 0.146$, DTT: $p = 0.110$).

There was also significant changes in the MBC score from onset (0) to the 6 month evaluation (3.45 ± 2.11) ($p = 0.000$) (Table 2). The UMI score was significantly improved between the onset (3.94 ± 8.16) and 6 month evaluations (62.00 ± 30.25) ($p = 0.000$).

In clinical classification according to MBC scores, 25 patients (47.2%) belonged to the Good group, the other 28 patients (52.8%) to the Poor group. In classification according to UMI scores, 31 patients (58.5%) belonged to the Good group and 22 patients (41.5%) to the Poor group (Table 3).

3.2. Transcranial magnetic stimulation

When the changes in the MBC scores from onset to the 6 month evaluation were compared, the TMS (+) group (5.52 ± 0.79) showed better recovery than the TMS (−) group (1.87 ± 1.22) ($p = 0.000$). As for UMI scores, the TMS (+) group (84.30 ± 12.88) also showed greater improvement than the TMS (−) group (40.63 ± 21.02) ($p = 0.000$) (Table 2).

In classification by MBC, 22 (95.7%) of 23 patients in the TMS (+) group belonged to the Good group, while only 3 (10.0%) of 30 patients in the TMS (−) group belonged to the Good group. Twenty-seven (90.0%) of 30 patients in the TMS (−) group belonged to the Poor group, but only 1 (4.3%) of 23 patients in the TMS (+) group were classified in the Poor group. In classification by UMI, all of 23 patients in the TMS (+) group belonged to the Good group, while 8 (26.7%) of 30 patients in the TMS (−) group belonged to the Good group. Twenty-two (73.3%) of 30 patients were categorized in the Poor

Table 1
Demographic and clinical data of patients.

Variables		TMS group		Total	*p* value	DTT group		Total	*p* value
		TMS (+)	TMS (−)			DTT (+)	DTT (−)		
Number (%)		23(100.0)	30(100.0)	53(100.0)	0.414	32(100.0)	21(100.0)	53(100.0)	0.121
Age (years)		55.30 ± 12.2	53.30 ± 8.34	54.00 ± 10.00	0.473	55.10 ± 11.60	52.80 ± 7.62	54.00 ± 10.00	0.413
Lesion side	Right (%)	13 (46.4)	15(53.6)	28(52.8)	0.637	17(60.7)	11(39.3)	28(52.8)	0.958
	Left (%)	10(40)	15(60)	25(47.2)		15(60)	10(40)	25(89.3)	
Days to TMS or DTT		17.43 ± 3.69	16.73 ± 3.98	17.16 ± 3.15	0.515	17.31 ± 3.50	16.62 ± 4.36	17.04 ± 3.84	0.525
MBC		0[a]	0[a]	0[a]		0[a]	0[a]	0[a]	
UMI		4.70 ± 7.96	2.60 ± 7.07	3.94 ± 8.16	0.146	4.72 ± 8.89	2.76 ± 6.93	3.94 ± 8.16	0.110
Risk factor (%)		22(95.7)	25(83.3)	47(88.7)	0.217	30(93.8)	17(81.0)	47(88.7)	0.200
NIDDM (%)		7(30.4)	9(30)	16(30.2)	0.729	9(28.1)	7(33.3)	16(30.2)	0.185
HTN (%)		12(52.2)	17(56.7)	29(54.7)	0.745	16(50)	13(61.9)	29(54.7)	0.394
Afib (%)		3(13.0)	5(16.7)	8(15.1)	0.302	4(12.5)	4(19.0)	8 (15.1)	0.365
Hchol (%)		11(47.8)	9(30)	20(37.7)	0.185	13(40.6)	7(33.3)	20(37.7)	0.592
Cig (%)		14(60.9)	13(43.3)	27(50.9)	0.206	19(59.4)	8(38.1)	27(50.9)	0.130

Values: mean ± standard deviation.
TMS: transcranial magnetic stimulation, DTT: diffusion tensor tractography, UMI: motricity index of upper extremity, NIDDM: noninsulin-dependent diabetes mellitus, HTN: hypertension, Afib: atrial fibrillation, Hchol: hypercholesterolemia, and Cig: cigarette smoking.
[a] All patients showed scores of 0.

Table 2
The changes of motor function according to the group of transcranial magnetic stimulation and diffusion tensor tractography.

Variables	Group	Initial[a]	6 month	Difference	*p* value
Total					
MBC		0[b]	3.45 ± 2.11	3.45 ± 2.11	0.000
UMI		3.94 ± 8.16	62.00 ± 30.25	59.15 ± 27.86	0.000
TMS					
MBC	TMS (+)	0[b]	5.52 ± 0.79	5.52 ± 0.79	0.000
	TMS (−)	0[b]	1.87 ± 1.22	1.87 ± 1.22	
UMI	TMS (+)	4.70 ± 7.96	89.00 ± 14.02	84.30 ± 12.88	0.000
	TMS (−)	2.60 ± 7.07	41.30 ± 21.70	40.63 ± 21.02	
DTT					
MBC	DTT (+)	0[b]	4.69 ± 1.73	4.75 ± 1.70	0.000
	DTT (−)	0[b]	1.57 ± 0.87	1.57 ± 0.87	
UMI	DTT (+)	4.72 ± 8.89	78.81 ± 22.89	74.09 ± 21.10	0.000
	DTT (−)	2.76 ± 6.93	36.38 ± 20.64	33.62 ± 21.27	

Values: mean ± standard deviation.
TMS: transcranial magnetic stimulation, DTT: diffusion tensor tractography, MBC: modified Brunnstrom classification, and UMI: motricity index of upper extremity.
[a] Assessment within 24 h of onset.
[b] All patients showed scores of 0.

group, while no patient in the TMS (+) group belonged to the Poor group (Table 3).

3.3. Diffusion tensor tractography

In terms of the changes of MBC scores from onset to 6 month evaluation, the DTT (+) group (4.75 ± 1.70) showed greater improvement than the DTT (−) group (1.57 ± 0.87) ($p = 0.000$). The changes of UMI scores from onset to 6 month evaluation differed according to the DTT group ($p = 0.000$), with the DTT (+) group (74.09 ± 21.10) showing better recovery than the DTT (−) group (33.62 ± 21.27) (Table 2).

In classification by MBC scores, 20 (95.2%) patients in the DTT (−) group belonged to the Poor group, and 8 (25.0%) out of 32 patients in the DTT (+) group belonged to the Poor group. As for the Good group, only 1 patient in the DTT (−) group and 24 (75.0%) of 32 patients in the DTT (+) group were included. In terms of UMI classification, 18 (85.7%) of 21 patients in the DTT (−) group and 4 (12.5%) of 32 patients in the DTT (+) group belonged to the Poor group. Twenty-eight (87.5%) of 32 patients in the DTT (+) group were included in the Good group, while three patients in the DTT (−) group was in the Good group (Table 3).

3.4. Comparison of transcranial magnetic stimulation and diffusion tensor imaging

Under conditions in which 40% patients of all patients showed a favorable prognosis, TMS showed a relatively higher positive predictive value (MBC; 0.96, UMI: 1.00) than DTT (MBC; 0.75; UMI; 0.88) in predicting motor outcome (Table 4). By contrast, DTT revealed a higher negative predictive value (MBC; 0.95, UMI; 0.86) than TMS (MBC; 0.90, UMI; 0.73).

Table 3
Classification according to the results of transcranial magnetic stimulation and diffusion tensor tractography.

Classification		MBC		UMI	
		Good	Poor	Good	Poor
TMS					
TMS (+)	23	22(95.7)	1(4.3)	23(100.0)	0(0.00)
TMS (−)	30	3(10.0)	27(90.0)	8(26.7)	22(73.3)
DTT					
DTT (+)	32	24(75.0)	8(25.0)	28(87.5)	4(12.5)
DTT (−)	21	1(4.8)	20(95.2)	3(14.3)	18(85.7)

TMS: transcranial magnetic stimulation, DTT: diffusion tensor tractography, MBC: modified Brunnstrom classification, and UMI: motricity index of upper extremity.

4. Discussion

In the current study, we compared the predictive values of TMS and DTT for motor outcomes in patients at the early stage of ICH. Our results indicated that the patients who showed any MEP in TMS and a preserved CST in DTT had better motor outcomes than those without these characteristics. Comparing the two evaluation techniques, TMS revealed higher positive predictive value than DTT. In other words, MEP at the early stage of ICH was well correlated with good motor recovery, and there was a good probability of the presence of MEP in a patient who eventually showed a good motor outcome. By contrast, DTT had a better negative predictive value than TMS. That is, patients with disruption of the CST on DTT at the early stage of ICH could be expected to have poor motor outcomes.

In the current study, we focused on whether the integrity of the CST could affect the motor outcome by evaluating the presence of MEP on TMS and of a preserved CST on DTT. Many studies have reported that TMS had predictive value for motor outcome in stroke patients [28–34], and have indicated that stroke patients who showed the presence of MEP at the day of stroke onset [29,32], within 1 week [30,31,33] and within 1 month after onset [10,28] had better motor outcomes than those without MEP. Since the development of DTI [25], several researchers have reported on the predictive value of DTI for motor outcome in stroke patients [12–17]. These studies have been classified into two groups according to what DTI parameters were used for predicting motor outcome: one group used DTI parameters in or around the lesion [12,16,17], and the other used the integrity of the CST obtained by DTT [4,13–15]. There have been four studies that used the integrity of the CST as we have in this study. In 2005, Konishi et al. [4] reported that the degree of CST involvement measured by DTT performed within 3 days of symptom onset was highly correlated with a motor deficit and the clinical outcome at 3 months in patients with an acute lenticulostriate infarct. Three subsequent studies demonstrated that information on the integrity of the CST obtained in the early stage (7–30 days) of stroke was useful for predicting motor outcome in ICH [13], corona radiata infarct [14], and pontine infarct [15]. Recently, Nelles et al. [35] reported that the degree of CST disruption on DTI performed within 3 days after onset of anterior choroidal artery infarct was negatively associated with motor outcome at 3 months after onset. The results of single evaluation of TMS or DTT in this study are generally in agreement with the previous TMS and DTT studies. To the best of our knowledge, there has been no study on comparison of TMS and DTT for predicting motor outcome at the early stage of stroke.

In conclusion, TMS and DTT performed at an early stage of ICH have different advantages in predicting motor outcome. More specifically, TMS had higher positive predictive value than DTT, while DTT had higher negative predictive value than TMS. These results could provide invaluable clinical information for the prediction of motor outcomes in stroke patients, and have important implications in terms of motor

Table 4
Comparison of transcranial magnetic stimulation and diffusion tensor tractography in predicting motor outcome.

Variables	Positive predictive value	Negative predictive value
MBC		
TMS	0.91	0.93
DTT	0.72	1.00
UMI		
TMS	0.78	0.93
DTT	0.59	0.95

TMS: transcranial magnetic stimulation, DTT: diffusion tensor tractography, MBC: modified Brunnstrom classification, and UMI: motricity index of upper extremity.

recovery following stroke. TMS and DTT have unique advantages. TMS has better clinical and economical accessibility than DTT. On the other hand, DTT has distinguished strength of visualizing neural tracts. We think that the small number of patients examined is a limitation of this study. Another limitation is that we adopted only one parameter about the presence of the CST among the various parameters of TMS and DTT. Further complementary studies involving larger case numbers and more parameters for TMS and DTT are warranted. In addition, we think that studies on the acute stage of ICH, infarct, or other lesions are needed in the near future.

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