

Evaluation of the motor cortical excitability changes after ischemic stroke

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Abstract

Background: We evaluated progressive changes in excitability of motor cortex following ischemic stroke using Transcranial Magnetic Stimulation (TMS). **Materials and Methods:** Thirty-one patients (24 men, 7 women; age 37.3 ± 8.2 years) were recruited and TMS was performed using Magstim 200 stimulator and a figure-of-eight coil. Resting motor threshold (RMT) was recorded from affected and unaffected hemispheres and motor evoked potential (MEP) was recorded from contralateral FDI muscle. Central motor conduction time (CMCT) was calculated using F wave method. All measurements were done at baseline (2nd), 4th, and 6th week of stroke. **Results: Affected hemisphere:** MEP was recordable in 3 patients at baseline (all had prolonged CMCT). At 4 weeks, MEP was recordable in one additional patient and CMCT remained prolonged. At 6 weeks, CMCT normalized in one patient. RMT was recordable (increased) in 3 patients at baseline, in one additional patient at 4 weeks, and reduced marginally in these patients at 6 weeks. **Unaffected hemisphere:** MEP was recordable in all patients at baseline, and reduced significantly over time (2nd week 43.52 ± 9.60 , 4th week 38.84 ± 7.83 , and 6th week 36.85 ± 7.27 ; $P < 0.001$). The CMCT was normal and remained unchanged over time. **Conclusion:** The increase in excitability of the unaffected motor cortex suggests plasticity in the post-stroke phase.

Key Words

Central motor conduction time, cortical excitability, ischemic stroke, plasticity, resting motor threshold, transcranial magnetic stimulation

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Introduction

Ischemic stroke is associated with diffuse changes in the cortical excitability of the affected and unaffected hemispheres. Transcranial magnetic stimulation (TMS) serves as an excellent non-invasive tool to map these electrophysiologic changes. TMS can be used to dissect the physiological mechanisms underlying motor deficits, spontaneous motor recovery, and the beneficial effects of therapeutic interventions in ischemic stroke.^[1] The most frequently measured TMS parameters in ischemic stroke include cortical thresholds (both resting and active), motor evoked potential (MEP) amplitudes, cortical silent period, central motor conduction time (CMCT), etc.^[2]

The changes in the cortical excitability following stroke are best observed in the initial hours following the ictus and

can modify over time. These can range from failure to elicit MEPs^[3,4] to recordable MEPs that suggest good prognosis.^[5,6] The resting motor thresholds (RMTs) also are raised in the acute and sub-acute phase of stroke.^[4,7-14] The CMCT, wherever obtained, is usually marginally prolonged.^[15,16] During the early post-stroke phase, the changes are attributable to pathophysiologic changes like reversal of diaschisis, resolution of edema, etc. while in the chronic phases, it is due to functional reorganization.^[17] TMS, therefore, can provide a basis for eliciting the functional reorganization in the post-stroke phase.

In the current study, we investigated progressive changes in the cortical excitability of the affected and unaffected hemispheres and the integrity of the corticospinal tract in sub-acute ischemic stroke patients.

Materials and Methods

Subjects

The study was conducted in the Department of Neurology, National Institute of Mental Health and Neuro Sciences (NIMHANS), Bangalore. It was approved by the Institute Ethics Committee. Patients and/or relatives were explained about the nature and design of the study and informed consent was obtained. Thirty-one patients (24 men and 7 women; mean age

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37.3 ± 8.2 years) were recruited for the study. Patients received standard medical care and rehabilitation during the period. Patients were included if aged between 20 and 60 years, of either gender; with ischemic stroke in middle cerebral artery (MCA) territory diagnosed by history, clinical examination, and CT scan/MRI of brain, with stable neurological status and motor weakness of at least one limb of Medical Research Council (MRC) Grade 0–3. Patients were excluded if sensorium was altered or severely aphasic to comprehend simple instructions.

Assessments

Clinical

All patients were evaluated at baseline (at 2 weeks) and again at the end of 4th and 6th weeks of the ictus using the National Institute of Health Stroke Scale (NIHSS), Barthel Index (BI), modified Rankin Score (mRS) and the MRC scale for grading power of the first dorsal interosseous (FDI) of the affected hand.

Cortical excitability and corticospinal integrity

A Magstim 200 stimulator and a figure-of-eight coil with an inner diameter of 70 mm were used for TMS. Patients were made to sit comfortably on a chair with eyes open. The coil was held in antero-medial direction at an angle of 45° with respect to Cz and the direction of flow of the induced electric field was from posterior to anterior. Surface EMG recordings were done from the first dorsal interossei (FDI) muscle of both hands. The area of motor cortex, which when stimulated gave optimal MEP, was marked over the scalp and subsequently the coil was positioned on the same area for evaluation of resting motor threshold (RMT) and central motor conduction time (CMCT).

RMT was defined as the minimal stimulator output eliciting MEP of at least 50 µV in amplitude in 5 out of 10 trials from FDI muscle at rest. Thirty trials were performed at intensities of 110%, 130%, and 150% of the RMT and the shortest latency from all the 30 trials was taken for measuring the CMCT. CMCT was calculated using the F wave method. The F wave was obtained after stimulating the ulnar nerve at the wrist with supramaximal strength. A total of 20 F wave recordings were taken and the shortest F wave latency was taken for the measurement of CMCT. The following formula was used to calculate CMCT: $CMCT = MEP - (F + M - 1) / 2$, where MEP-shortest MEP latency, F-shortest F wave latency, M-latency of the direct M response and 1 ms is the turnaround time across anterior horn cell.

Control data

Control data was obtained from 50 clinically healthy subjects (32 men and 18 women; mean age of 33.9 ± 7.7 years) without any neurological deficit, after taking written informed consent. No one had any history of medical or surgical illness in the past and did not have any contraindications for TMS. RMT and CMCT were determined using the same methodology and protocol as for the patients to the right FDI muscle. RMT was calculated at three different points of time in control subjects to look for any variability in the excitability of the motor cortex.

Statistical analysis

Descriptive statistical analysis was carried out in the present study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements

are presented in Number (%). Significance was assessed at 5% level of significance. Student 't' test (two-tailed, independent) was used to find the significance of study parameters on continuous scale between the 2 groups. Repeated Measures Analysis of Variance (RMANOVA) has been used to find the significance of parameters on continuous scale. Chi-square/Fisher Exact test has been used to find the significance of study parameters on categorical scale between the groups.

Results

Of the 31 patients, 12 had right MCA territory infarction and 19 had left MCA territory infarction. All the patients had cortical and sub-cortical involvement on the side of infarct on CT scan. Five patients were unavailable for assessment at second follow-up due to various reasons.

Clinical variables in ischemic stroke patients

There was a statistically significant improvement in the NIHSS, BI, and mRS at first and second follow-up ($P < 0.001$). The power of the FDI in the affected hand was grade 0 in all patients at baseline. At first follow-up, the power of FDI of the affected hand improved in four patients (grade 2-two patients; grade 4-one patient). At second follow-up, it improved in seven patients (grade 1-three patients; grade 3-two patients; grade 4 and 5-one patient each) [Table 1].

TMS parameters in control subjects

The RMT from 3 consecutive trials was 41.8 ± 6.3 (%), 41.84 ± 6.75 (%) and 41.84 ± 6.52 (%) of the maximum stimulator

Table 1: Clinical variables in ischemic stroke patients

Variable	Baseline	I follow-up	II follow-up	Significance
Barthel index	37.42±19.32	57.58±18.43	72.58±15.32	<0.001
NIHSS	11.84±3.24	9.32±3.27	7.65±3.12	<0.001
mRS	3.87±0.34	3.61±0.62	3.23±0.59	<0.001
MRC [§]	0 [†]	2.67±1.15 [‡]	2.57±1.62 [*]	-

The data represent Mean±SD; NIHSS-National Institute of Health Stroke Scale; mRS-modified Rankin Score; MRC-Medical Research Council; Repeated Measures of ANOVA; [†]n=31, [‡]n=3, ^{*}n=7; [§] MRC of first digital interosseus (FDI) of affected limb, statistical analysis not performed.

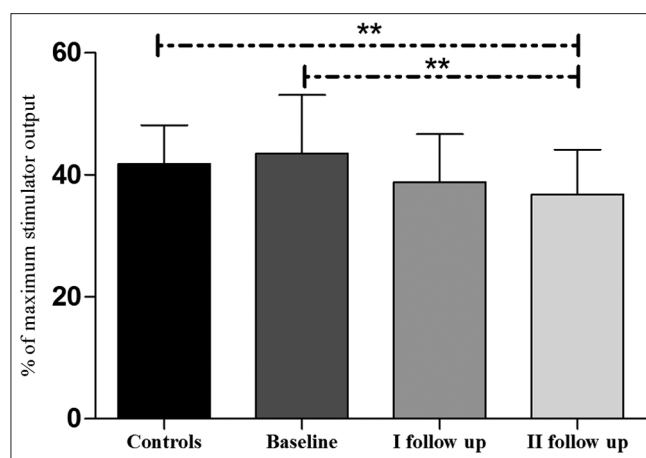


Figure 1: Comparison of the resting motor threshold of the unaffected hemisphere between healthy controls and ischemic stroke patients over time. Values represented as Mean±SD

output and the difference was statistically insignificant. Hence, the RMT from the first trial was used for further analyses. The mean CMCT to the FDI was 4.69 ± 0.6 ms.

TMS parameters in ischemic stroke patients

Affected hemisphere

In the affected hemisphere, MEP was elicited in only 3 patients at baseline and the CMCT was prolonged in them (7.5, 9 and 10 ms). Two of them had a RMT of 55% and the other had RMT of 37% of the maximum stimulator output. Comparison of the clinical scores of the patients with ($n = 3$) and without ($n = 28$) MEPs revealed that the former had better scores on the BI (51.3 vs 38.2) and NIHSS (9.6 vs 11.96). At 4 weeks, the MEP was elicited in four patients (three previous patients and one additional patient) and CMCT remained prolonged in all. The RMTs in these four patients was 34, 35, 37, and 73% of the maximum stimulator output. At 6 weeks, MEP was still elicited in the same four patients while CMCT normalized in one of the patients. The RMTs had reduced in the patients (range 25 to 58). The FDI power of all the three patients who demonstrated recordable MEPs improved; in the patients without recordable MEPs ($n = 28$), the FDI power improved in only four patients. Statistical analysis could not be performed due to the small sample of patients with recordable parameters.

Unaffected hemisphere

In the unaffected hemisphere, MEP was elicited in all patients at baseline; RMT reduced significantly over time (baseline- 43.52 ± 9.60 , first follow-up- 38.84 ± 7.83 , second follow-up- 36.85 ± 7.27 ; $P < 0.001$) [Figure 1]. Comparison of the RMT of the unaffected hemisphere with that of healthy controls showed no difference at baseline ($P = 0.340$); at first follow-up, there was a trend towards reduction ($P = 0.071$) and at second follow-up there was a significant difference ($P < 0.003$). The mean CMCT to FDI was normal and remained unchanged over time (5.13 ± 1.19 ms, 5.04 ± 0.86 ms, and 4.44 ± 1.02 ms, respectively).

Discussion

We measured the RMT and the CMCT in the unaffected and affected hemispheres at progressive time points following an ischemic stroke. To our knowledge, there are no studies eliciting such organizational changes in the post-stroke phase, performed in an Indian population. The results of the current study confirm previous findings of the prognostic value of MEPs on stimulation of affected hemisphere, better clinical scores in patients with recordable MEPs in the affected hemisphere, and enhanced RMT in the unaffected hemisphere.

The presence or absence of MEPs on stimulation of the affected hemisphere in the acute phase of ischemic stroke has been linked with better or poor outcome in most studies^[6,18] while a few others do not regard this criterion as a good prognostic indicator.^[19] In the current study too, the power of FDI in all the 3 patients who demonstrated recordable MEPs at baseline improved considerably over time (100%) while among the patients whose MEPs were not elicited at baseline, the power improved in only 4 patients (14.3%). Therefore, our study reaffirms that presence of MEP is a good prognostic indicator of motor recovery.

Evaluation of the unaffected hemisphere following stroke gives valuable information on the reorganization and plasticity changes that may occur in the post-stroke phase. The unaffected hemisphere is also known to be affected in stroke.^[20,21] In the current study too, the RMT in the unaffected hemisphere progressively reduced over time in the patients and also when compared with healthy controls. This suggests a progressive increase in the cortical excitability of the unaffected hemisphere. The proposed mechanisms for such changes may include damage to the transcallosal fibers arising from the affected hemisphere causing loss of inhibition over the unaffected hemisphere, and also the enhanced use of the unaffected hand resulting in cortical excitability.^[22,23] Transcallosal inhibition and intracortical inhibition is also known to be disrupted in early stroke and can contribute to the increased excitation of the unaffected hemisphere due to plastic reorganization.^[21] Therefore, the findings of our study also reiterate the reported changes of excitability of the unaffected hemisphere.

The current study had its limitations in that it was performed in a small cohort of patients with ischemic stroke. However, our findings were along the lines of earlier studies. Further studies in a larger population with longer follow-up and using paired pulse paradigms may better reflect the organizational changes in the cerebral hemispheres and provide better insight for the development of rehabilitative techniques.

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