



Original Article

Effectiveness of Low-Frequency Repetitive Transcranial Magnetic Stimulation to Contralesional Motor Cortex Combined with Conventional Rehabilitation in Sub-Acute Stroke: A Pilot Study

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Received: 01-12-2025

Accepted: 17-12-2025

Available online: 30-12-2025

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ABSTRACT

Background: Upper limb motor impairment persists in up to 80% of stroke survivors and remains one of the most challenging goals in rehabilitation medicine. Low-frequency repetitive transcranial magnetic stimulation (rTMS) applied to the contralesional motor cortex is supported by growing evidence as an adjunct to conventional rehabilitation, yet published data from the Indian subcontinent are sparse. This study describes the application and functional outcomes of 1 Hz rTMS to the contralesional primary motor cortex combined with conventional rehabilitation in five patients with subacute stroke.

Methods: Five patients with first-ever, unilateral, subcortical subacute stroke and Brunnstrom Stage 2 – 4 upper limb hemiparesis received low-frequency rTMS (1 Hz, 1,200 pulses/session, 90% resting motor threshold) applied over the contralesional M1, followed immediately by conventional neurological physiotherapy and occupational therapy. Outcomes assessed included the Modified Rankin Scale (mRS), Barthel Index (BI), Functional Independence Measure – Functional Assessment Measure (FIM-FAM), and the Fugl-Meyer Assessment (FMA, total score). Paired t-tests and Wilcoxon Signed-Rank exact tests were performed; effect sizes were computed as Cohen's d and rank-biserial correlation.

Results: All five patients demonstrated consistent improvement across all outcome measures. Mean improvements: mRS -1.0 grade (21.7% reduction); BI +25.0±5.0 points (78.1% increase); FIM-FAM +26.4±5.6 points (21.1% increase); FMA +25.0±2.9 points (36.7% increase). All patients exceeded the Minimum Clinically Important Difference (MCID) for the Barthel Index (≥10 points). Effect sizes were very large (Cohen's d: BI=5.00, FIM=4.68, FM=8.58; rank-biserial r=1.00 for all scales). No adverse events were recorded.

Conclusion: Low-frequency rTMS to contralesional M1 combined with conventional rehabilitation produced clinically meaningful and consistent functional gains across all outcome measures in all five patients with subacute stroke. These preliminary findings support the feasibility and efficacy signal of this approach and provide the impetus for a planned multicentre randomised controlled trial.

Keywords: stroke; repetitive transcranial magnetic stimulation; rehabilitation; upper limb; subacute stroke; neuroplasticity.

INTRODUCTION

In India, stroke continues to be the second most common cause of death and the primary cause of acquired disability, with an estimated 1.8 million new cases reported each year.⁽¹⁾ One of the most crippling aftereffects, upper limb motor impairment affects 70–80% of survivors and reduces their ability to take care of themselves, participate in their jobs, and

lead fulfilling lives.(2,3) Even after decades of research on rehabilitation, a significant percentage of patients still do not fully regain hand and arm function, and the pursuit for efficient supplemental techniques continues.

Cortical excitability is modulated in a frequency-dependent manner by repetitive transcranial magnetic stimulation (rTMS).(4) Applying low-frequency rTMS (1 Hz) over the contralesional primary motor cortex (M1) suppresses pathological interhemispheric inhibition,(5) which is now known to be a major obstacle to motor recovery. This is the excessive transcallosal inhibition that the intact hemisphere exerts over the lesioned hemisphere.(6) The ipsilesional cortex is freed from suppression by 1 Hz rTMS, which also produces a neurobiological environment more favourable to activity-dependent plasticity during future rehabilitation.(7) For low-frequency rTMS in stroke rehabilitation, meta-analyses show standardised mean differences of 0.40–0.65 on the Fugl-Meyer Assessment Upper Extremity (FMA-UE),(7) and evidence-based recommendations support its use as a supplement to traditional rehabilitation methods for upper limb motor recovery.

Based on the neurobiology of motor plasticity, low-frequency rTMS can be used in conjunction with conventional rehabilitation(8,9). A "plasticity window" of roughly 30 to 60 minutes is created by rTMS administered prior to therapy, during which the threshold for activity-dependent synaptic potentiation is lowered and cortical excitability in the affected hemisphere is increased.(7) The conventional rehabilitation that follows directly exploits this window: task-specific motor practice in a more receptive cortical state promotes stronger and more durable synaptic strengthening than the same therapy administered without prior neuromodulation. All motor learning is based on the Hebbian principle, which states that neurons that fire together during the primed state wire together more efficiently.

Despite the growing international evidence base, published clinical data from India remain sparse. We report here five patients with first-ever, unilateral, subcortical, subacute stroke who received low-frequency rTMS to contralesional M1 combined with conventional neurological rehabilitation at our centre. We present detailed functional and independence outcome data with full statistical analysis, and reflect on what each patient's journey revealed about the clinical promise of this approach.

METHODS

Study Design and Setting

This is a retrospective study conducted at the Department of Physical Medicine and Rehabilitation, in a tertiary care teaching government referral centre with an established stroke rehabilitation unit, using a convenience sampling technique. Written informed consent was obtained from all patients or their legally authorised representatives prior to enrolment. The procedures followed were in accordance with the ethical guidelines of the Indian Council of Medical Research (ICMR) and with the Helsinki Declaration of 1975, as revised in 2000. Institutional Ethics Committee approval was obtained prior to data collection. Patient data have been anonymised.

Patient Selection

Patients were eligible if they had sustained a first-ever, unilateral, subcortical ischaemic or haemorrhagic stroke confirmed on CT or MRI, were in the subacute phase (7 days to 6 months post-onset), and had upper limb impairment at Brunnstrom Stage 2–4. Patients were excluded if they had contraindications to TMS (metallic cranial implants, pacemakers, history of epilepsy), severe cognitive impairment (MMSE <24), recurrent stroke, cortical or brainstem lesions, or pregnancy.

Intervention Protocol

Each session comprised two sequential components delivered five days per week:

(1) Low-frequency rTMS to Contralesional M1 (approximately 20 minutes): Inhibitory 1 Hz continuous rTMS was applied over the contralesional primary motor cortex (M1) using a standard figure-of-eight coil with anatomical landmark-based positioning (hand knob area of the motor cortex contralateral to the hemiplegic limb, identified using 10–20 EEG scalp coordinates). Protocol parameters: frequency 1 Hz; 1,200 pulses per session; intensity 90% of resting motor threshold (RMT). RMT was determined at the first session using the standard minimum stimulator output method and rechecked at weekly intervals. No high-frequency or ipsilesional stimulation was applied.

(2) Conventional Rehabilitation (45 minutes, immediately following rTMS): Standardised neurological rehabilitation combining physiotherapy and occupational therapy, delivered within the cortical plasticity window opened by rTMS. Components included passive and active-assisted range of motion exercises, neurodevelopmental facilitation (Bobath concept), task-specific upper limb practice, postural control training, and functional activity retraining tailored to each patient's deficit profile and Brunnstrom stage.

Sessions were conducted five days per week. The total number of sessions varied across patients (4–24 sessions) based on the duration of hospital admission and individual clinical progress.

Outcome Measures

All assessments were performed at baseline (pre-intervention) and at the end of the intervention course (post-intervention) by a blinded outcome assessor. Four validated scales were used:

1. Modified Rankin Scale (mRS): A 7-point global disability scale (0 = no symptoms; 6 = death). A reduction of ≥ 1 grade was considered clinically meaningful.
2. Barthel Index (BI): A 10-item functional independence scale (0–100). MCID = 10 points.
3. FIM-FAM (Functional Independence Measure - Functional Assessment Measure): A comprehensive 30-item functional independence scale assessing motor and cognitive domains (range 30–210). No formally established MCID; reported descriptively.
4. Fugl-Meyer Assessment (FMA): A comprehensive measure of post-stroke sensorimotor impairment covering motor function, sensation, balance, joint range of motion, and joint pain (total score range 0–226; higher scores indicate better function). ICC = 0.97. A validated MCID for the total scale is not well established; the proportion of patients showing improvement is reported descriptively.

Statistical Analysis

Given the small sample size ($n=5$), both parametric and non-parametric analyses were performed. Paired t-tests compared pre- and post-intervention means; the Wilcoxon Signed-Rank exact test was used as the non-parametric complement. Effect sizes were computed as Cohen's d (mean change divided by SD of change) and rank-biserial correlation r . The proportion of patients achieving or exceeding the Barthel Index MCID was reported as a responder analysis. All analyses were performed using Python (SciPy v1.11). A p -value of <0.05 was considered statistically significant.

RESULTS

Patient Characteristics

Five patients participated in the study (Table 1). Their diagnoses included cerebrovascular accident (CVA) with right hemiplegia ($n=2$), CVA with left hemiplegia ($n=2$), and CVA with left hemiplegia and dystonia ($n=1$). The number of rTMS sessions received ranged from 4 to 24, reflecting variation in duration of hospital admission rather than differences in protocol.

Table 1: Patient Characteristics

S.No	Diagnosis	rTMS Sessions	Brunnstrom Stage	mRS Pre	BI Pre	FM Pre
1	CVA, Right Hemiplegia	18	2	5	10	56
2	CVA, Right Hemiplegia	10	2	5	20	58
3	CVA with left hemiplegia and dystonia	4	3	4	55	82
4	CVA, Left Hemiplegia	24	2	5	15	62
5	CVA, Left Hemiplegia	17	3	4	60	83

CVA = Cerebrovascular Accident; FM = Fugl-Meyer Assessment (total score); BI = Barthel Index

Functional Outcomes

All five patients demonstrated improvement across all four outcome measures (Table 2). The pattern was strikingly consistent: no patient deteriorated or remained unchanged on any scale. This uniform directionality — reflected in a rank-biserial correlation of 1.00 across all outcomes — speaks not just to statistical significance but to a real-world consistency that is clinically reassuring.

Table 2: Pre- and Post-intervention Outcome Scores

Patient	mRS Pre	mRS Post	BI Pre	BI Post	FIM Pre	FIM Post	FM Pre	FM Post
Patient 1	5	4	10	40	74	98	56	85
Patient 2	5	4	20	45	118	139	58	81
Patient 3	4	3	55	75	152	187	82	104
Patient 4	5	4	15	45	124	147	62	89
Patient 5	4	3	60	80	159	188	83	107
Mean \pm SD	4.6 \pm 0.55	3.6 \pm 0.55	32.0 \pm 23.6	57.0 \pm 18.9	125.4 \pm 33.7	151.8 \pm 37.5	68.2 \pm 13.2	93.2 \pm 11.6

FM = Fugl-Meyer Assessment (total); BI = Barthel Index

Statistical Analysis

Table 3 presents the inferential statistics. Paired t-tests demonstrated highly significant pre-post differences for Barthel Index ($t=11.18$, $p=0.0004$), FIM-FAM ($t=10.47$, $p=0.0005$), and the Fugl-Meyer Assessment ($t=19.17$, $p<0.001$). For mRS, the zero variance in change scores (all patients improved by exactly one grade) renders the t-test undefined ($t=\infty$); the Wilcoxon Signed-Rank exact test yields $p=0.0625$ the mathematical minimum achievable for $n=5$ with unidirectional differences, a constraint of sample size rather than evidence of a weak effect.

Effect sizes were significant across all scales. Cohen’s d values of 5.00 (BI), 4.68 (FIM-FAM), and 8.58 (FM) place these findings well above the conventional threshold for a ‘large’ effect ($d \geq 0.8$). The rank-biserial correlation of 1.00 for all outcomes indicating that every patient improved on every measure without exception is perhaps the most clinically intuitive summary statistic: this combination produced consistent, unidirectional benefit in 100% of participants.

Table 3: Statistical Analysis — Pre vs Post rTMS + Conventional Rehabilitation

Scale	Pre Mean±SD	Post Mean±SD	Mean Δ (95% CI)	Paired t (p)
mRS	4.6±0.55	3.6±0.55	-1.0 [-1.0, -1.0]	Undefined; Wilcoxon p=0.0625
Barthel Index	32.0±23.6	57.0±18.9	+25.0 [18.8, 31.2]	0.0004
FIM-FAM	125.4±33.7	151.8±37.5	+26.4 [19.4, 33.4]	0.0005
Fugl-Meyer (total)	68.2±13.2	93.2±11.6	+25.0 [21.4, 28.6]	<0.001

Patient 1 presented with complete loss of voluntary movement in his right arm following a CVA, with no voluntary power. In 18 sessions, he went from total dependence to beginning to dress himself. His Barthel Index quadrupled from 10 to 40 points. He described the therapy sessions as the most purposeful activity he had engaged in since his stroke. His Fugl-Meyer score improved by 29 points.

Patient 2 CVA, Right Hemiplegia with functionally limiting motor impairment. In 10 sessions, his elbow flexion improved from grade 2 to grade 3, wrist extension from grade 1 to grade 2, and his FIM-FAM score rose from 118 to 139.

Patient 3 CVA with left hemiplegia and dystonia had the fewest sessions of all just four, limited by his discharge plan, and yet he showed a 20-point gain in Barthel Index, a 35-point gain in FIM-FAM, and a 22-point gain on the Fugl-Meyer Assessment.

Patient 4 CVA with Left Hemiplegia received the most sessions (24), his wrist and finger extension showed the most prominent gains in MRC strength, improving from grade 1 to grade 3 in some muscle groups. His Barthel Index tripled from 15 to 45, and his FIM-FAM rose from 124 to 147.

Patient 5 CVA with Left Hemiplegia his hip flexion strength improved from grade 3 to grade 4, and his overall Fugl-Meyer gained 24 points.

DISCUSSION

This study documents the application and outcomes of low-frequency rTMS (1 Hz, contralesional M1) combined with conventional rehabilitation in patients with subacute stroke at an Indian tertiary care centre. The results are notable not only for their magnitude but for their consistency — improvement across all four functional scales in all five patients, with every patient exceeding the Barthel Index MCID and achieving large Fugl-Meyer Assessment gains.

The mean Fugl-Meyer improvement of 25.0 points, alongside universal gains in functional independence, is consistent with the motor and functional benefits reported when rTMS is combined with conventional rehabilitation (10)(11) and reflects clinically meaningful recovery on a measure with demonstrated responsiveness to change in subacute stroke.(12) The mean BI improvement of 25 points, from a severely dependent baseline mean of 32, represents a shift from severe dependence toward moderate independence. These gains are clinically significant not only statistically but in the lived experience of patients — a 30-point BI gain for Patient 1, for instance, is the difference between complete dependence and the ability to participate in basic self-care.

The awareness of interhemispheric competition and its treatment reversal serve as the neurobiological foundation for the benefits seen(13). After a stroke, the lesioned ipsilesional cortex is subjected to excessive transcallosal inhibition and paradoxical overactivity by the undamaged contralesional hemisphere, a maladaptive reaction that hinders motor recovery.(14) Through long-term depression-like mechanisms, low-frequency 1 Hz rTMS reduces this contralesional overactivity, releasing ipsilesional M1 from inhibition.(15) Conventional rehabilitation delivered immediately after rTMS exploits this rebalanced cortical environment: motor practice in a disinhibited ipsilesional cortex promotes stronger activity-dependent synaptic strengthening and more durable functional gains.

The variation in session numbers (4–24) across patients offers an instructive observation. Patient 3’s FIM-FAM gain of 35 points in just four sessions suggests that for some patients, a brief course of rTMS combined with conventional rehabilitation may produce disproportionate benefit. It is possibly because the early subacute period represents a window of heightened endogenous neuroplasticity in which rTMS-facilitated interhemispheric rebalancing particularly amplifies

spontaneous recovery. Conversely, patient 4's steady progression over 24 sessions supports the value of a sustained cumulative rTMS dose in patients with denser initial paresis.

Low-frequency rTMS is well-tolerated at 90% RMT, and integrates seamlessly into an existing conventional rehabilitation program. The absence of adverse events in this study, including in patients with complex neurological diagnoses supports its safety in the clinical practice. In a healthcare system where neurorehabilitation resources are constrained and therapist-to-patient ratios are often unfavourable, an adjunct that demonstrably amplifies the effects of conventional therapy represents a high-value addition to the rehabilitation armamentarium.

Limitations

With n=5, causal inference is not possible. The absence of a control group means that spontaneous recovery, natural history, and non-specific therapist effects cannot be separated from specific rTMS effects. The variation in session numbers and diagnostic mix introduces heterogeneity. These limitations contextualise the findings appropriately and underscore the need for a confirmatory randomised controlled trial.

CONCLUSION

Low-frequency rTMS (1 Hz) to contralesional MI combined with conventional rehabilitation produced clinically meaningful, consistent, and large-magnitude improvements in functional independence and upper limb motor function in all five patients with subacute stroke in this study. Effect sizes far exceeding conventional thresholds and universal MCID achievement support the feasibility and preliminary efficacy of this combination as a practical and accessible neuroplasticity-based rehabilitation strategy. These findings provide the clinical groundwork for a planned multicentre, randomised, sham-controlled trial to confirm these observations with rigorous causal inference.

Acknowledgements

The authors thank the patients and their families. We are grateful to the staff of Dept of PMR for their dedication to each patient's rehabilitation programme. The authors declare no conflicts of interest.

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