

Low-Frequency Repetitive Transcranial Magnetic Stimulation as an Adjunct to Conventional Rehabilitation for Hand Recovery in Subacute Stroke: A Randomized Pilot Clinical Study

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ABSTRACT:

Background: Upper-limb weakness and impaired hand function are frequent sequelae of stroke and may substantially limit functional independence. Low-frequency repetitive transcranial magnetic stimulation (LF-rTMS) has been proposed as a non-invasive neuromodulatory adjunct to conventional rehabilitation by reducing maladaptive interhemispheric inhibition and facilitating motor recovery.

Objective: This study aimed to evaluate the feasibility and exploratory clinical effect of contralesional LF-rTMS combined with conventional rehabilitation on hand grip strength and hand function in patients with subacute stroke.

Methods: In this randomized pretest–posttest controlled study, 14 of 55 screened patients with first-ever subacute stroke were assigned to LF-rTMS plus conventional rehabilitation ($n = 7$) or conventional rehabilitation alone ($n = 7$). LF-rTMS was delivered over the contralesional primary motor cortex at 1 Hz, 90% resting motor threshold, and 1,200 pulses per 20-minute session, five days weekly for two weeks. We assessed grip strength and manual dexterity in both hands before and after treatment using a hand dynamometer and the Box and Block Test, respectively.

Results: Both groups demonstrated improvement trends in paretic-hand outcomes after the intervention period. Paretic-hand grip strength increased by 1.08 ± 1.26 kg in the control group and 2.27 ± 3.74 kg in the LF-rTMS group. Paretic-hand BBT scores increased by 4.14 ± 7.88 blocks/min in the control group and 5.00 ± 8.33 blocks/min in the LF-rTMS group. However, between-group comparisons of change scores did not

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show statistically significant differences for either grip strength or BBT.

Conclusion: Contralesional LF-rTMS combined with conventional rehabilitation was feasible and associated with within-group improvement trends in paretic-hand grip strength and manual dexterity among patients with subacute stroke. However, this pilot study did not demonstrate superiority over conventional rehabilitation alone. Larger adequately powered studies with longer follow-up are needed to clarify the clinical benefit and durability of LF-rTMS in post-stroke upper-limb rehabilitation.

Keywords: stroke rehabilitation, low-frequency rTMS, grip strength, hand function, Box and Block Test.

1. Introduction

Stroke remains a major global health problem and major cause of disability, accounting for 160 million disability-adjusted life-years. As survival after stroke improves, the number of individuals requiring long-term rehabilitation is expected to steadily increase.¹ Motor impairment is among the most disabling consequences of stroke, occurring in approximately 80% of patients and contributing to permanent disability or dependence in at least 30%. Upper-limb and hand dysfunction are particularly important because reaching, grasping, releasing, and manipulating objects are required for essential activities of daily living. Recovery of hand function is often slower and less complete than recovery of basic mobility. Consequently, persistent weakness and loss of manual dexterity substantially increase dependence on caregivers and reduce quality of life.²

Conventional stroke rehabilitation such as physical and occupational therapy remains the foundation of motor recovery. Repetitive, task-specific, goal-directed, and progressively challenging practice promotes motor relearning and improves functional independence. Nevertheless, the response to conventional therapy remains heterogeneous, and many patients continue to experience clinically important hand impairment despite receiving appropriate rehabilitation. This lasting disability supports the need of adjunctive interventions

that may increase the capacity of the nervous system to respond to motor training.

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive neuromodulatory technique investigated as an adjunctive intervention for post-stroke rehabilitation.⁵ Low-frequency rTMS (LF-rTMS), typically delivered at 1 Hz, is commonly applied over the contralesional primary motor cortex to reduce excessive contralesional excitability after stroke. This approach is based on the interhemispheric imbalance model, in which the unaffected hemisphere may exert excessive inhibitory influence on the affected hemisphere and thereby limit motor recovery.⁶

Systematic reviews suggest that rTMS may support upper-limb motor recovery after stroke; however, treatment effects may vary, and the optimal stimulation protocol and patient selection remain under investigation.⁵ A randomized sham-controlled trial of contralesional 1-Hz rTMS combined with occupational therapy found no significant overall advantage for Box and Block Test performance, although exploratory benefits were observed in patients without cortical involvement.⁶

Despite growing evidence, further clinical studies are still needed to clarify the effect of LF-rTMS on practical hand-specific outcomes such as grip strength and manual dexterity in subacute stroke patients.⁵ The present study therefore evaluated the feasibility and exploratory clinical effect of

contralesional LF-rTMS combined with conventional rehabilitation on hand grip strength and hand function in patients with subacute stroke. We assessed hand grip strength with a hand dynamometer and hand function with the Box and Block Test as a measure of gross manual dexterity. This study hypothesized that LF-rTMS combined with conventional rehabilitation would produce greater improvement in paretic-hand grip strength and hand function than conventional rehabilitation alone.

2. Methodology

This randomized pretest–posttest controlled clinical study evaluated the effect of low-frequency repetitive transcranial magnetic stimulation (LF-rTMS) as an adjunct to conventional rehabilitation in patients with subacute stroke. The study was conducted at the outpatient rehabilitation clinic of Dr. Soetomo General Hospital, Surabaya, Indonesia. Participants were allocated into two groups: an intervention group receiving LF-rTMS combined with conventional rehabilitation and a control group receiving conventional rehabilitation alone.

We recruited patients consecutively from the outpatient clinics. Eligible participants were men or women aged 30-70 years with a first-ever ischemic or hemorrhagic stroke, confirmed by clinical examination and/or neuroimaging, who were in the late subacute phase, defined as 3-6 months after stroke onset. Participants were required to be hemodynamically stable, able to understand and follow rehabilitation instructions, and to have upper-limb muscle strength of Medical Research Council grade 1-4 and a Modified Ashworth Scale score of ≤ 2 .

Exclusion criteria were severe impairment of communication, memory, or comprehension; a personal history of seizures; a first-degree relative with idiopathic epilepsy; use of medications known to substantially alter seizure threshold or cortical excitability; a cardiac pacemaker, intracranial metallic implant, or calvarial defect; pregnancy; or a recent severe musculoskeletal injury that prevented participation in rehabilitation. Participants were withdrawn if

they requested discontinuation, missed more than two consecutive sessions or more than 20% of the intervention, or developed a medical condition that precluded continued participation.

The Health Research Ethics Committee of RSUD Dr. Soetomo, Surabaya, Indonesia, approved the study (1301/KEPK/V/2025). All participants received information about the study procedures and provided informed consent before participation. The study team monitored safety during the intervention period and recorded adverse events according to the study protocol. Participants were randomly allocated in a 1:1 ratio to the LF-rTMS plus conventional rehabilitation group or the conventional rehabilitation-only group. We used a lottery to allocate participants, with each participant drawing one of the prepared group assignments. Because the control group did not receive sham stimulation, participants and treating clinicians were not blinded to group allocation.

The intervention group received LF-rTMS followed by conventional rehabilitation. LF-rTMS was delivered over the contralesional primary motor cortex using a Neuro-MS/D stimulator with a figure-of-eight coil. The stimulation protocol consisted of 1 Hz frequency, 90% motor threshold, and 1,200 pulses per day for five consecutive days per week over two weeks. After LF-rTMS, participants continued conventional rehabilitation consisting of physical therapy and/or occupational therapy according to each participant's impairment. The control group received conventional rehabilitation only, consisting of physical therapy and/or occupational therapy according to each participant's impairment. Both groups received conventional rehabilitation five consecutive days per week for four weeks.

We evaluated hand grip strength and hand function. We measured hand grip strength in kilograms using a CAMRY EH101 hand dynamometer. We assessed hand function using the Box and Block Test (BBT). After a 15-second familiarization trial, participants transferred one block at a time across the central partition for 60 seconds. We assessed each hand separately and

recorded the score as the number of blocks successfully transferred per minute. We assessed grip strength and BBT in both paretic and non-paretic hands before the first intervention session and after the final intervention session at week 4. We monitored adverse events during and after each rTMS session. Participants were instructed to report headache, local pain, neck discomfort, sensory symptoms, or other complaints immediately. Treatment was discontinued when clinically indicated, and predefined emergency procedures were available for serious adverse events, including seizures.

We assessed data distribution using the Shapiro–Wilk test and evaluated homogeneity of variance using Levene’s test. We present continuous data as mean $\pm$ standard deviation or median [interquartile range], as appropriate. We analyzed within-group pre–post differences using paired-samples *t* tests for normally distributed data and Wilcoxon signed-rank tests for non-normally distributed data. We assessed between-group differences in change scores using Welch’s independent-samples *t* test or the Mann–Whitney *U* test, as appropriate. We calculated change scores as the post-intervention value minus the pre-intervention value. We reported between-group effect sizes as standardized mean differences for continuous outcomes and rank-

based effect sizes for nonparametric comparisons. We compared categorical baseline characteristics using Fisher’s exact test. All tests were two-sided, and *we considered* $p < 0.05$ statistically significant.

3. Results

A total of 55 patients with subacute stroke were screened for eligibility. We excluded 41 patients because they did not meet the inclusion and exclusion criteria. We included 14 participants in the final analysis and randomized them to the control group ($n = 7$) and the LF-rTMS group ($n = 7$). Baseline characteristics were generally comparable between groups. The mean age was 50.71 ± 8.04 years in the control group and 57.86 ± 9.82 years in the LF-rTMS group. The control group included 1 male participant (14.29%) and 6 female participants (85.71%), whereas the LF-rTMS group included 3 male participants (42.86%) and 4 female participants (57.14%). Ischemic stroke was the most common stroke type in both groups, occurring in 6 participants (85.71%) in the control group and 5 participants (71.43%) in the LF-rTMS group. All participants were right-hand dominant. There were no statistically significant differences between groups in baseline grip strength or baseline BBT scores.

Table 1. Baseline characteristics of participants

Characteristic	Control ($n = 7$)	LF-rTMS ($n = 7$)	p-value
Age, years	50.71 ± 8.04	57.86 ± 9.82	0.163
Male sex	1 (14.3)	3 (42.9)	0.559
Time since stroke onset, months	3.43 ± 1.51	4.14 ± 1.57	0.250*
Right-sided paresis	5 (71.4)	3 (42.9)	0.592
Diabetes mellitus	5 (71.4)	2 (28.6)	0.286
Hypertension	7 (100.0)	7 (100.0)	1.000
Paretic-hand grip strength, kg	8.76 ± 6.24	7.21 ± 6.52	0.658

Characteristic	Control (n = 7)	LF-rTMS (n = 7)	p-value
Non-paretic hand grip strength, kg	18.08 ± 4.35	19.74 ± 8.11	0.644
Paretic-hand BBT, blocks/min	39.86 ± 16.41	24.29 ± 19.07	0.128
Non-paretic hand BBT, blocks/min	48.86 ± 11.04	45.57 ± 8.39	0.543

Values: mean ± SD or n (%). P-values compare control with LF-rTMS and are exploratory: Welch independent-samples t tests were used for age and baseline motor outcomes, the Wilcoxon rank-sum test for time since stroke onset, and Fisher exact tests for categorical variables.

At baseline, mean paretic-hand grip strength was 8.76 ± 6.24 kg in the control group and 7.21 ± 6.52 kg in the LF-rTMS group. Baseline non-paretic hand grip strength was 18.08 ± 4.35 kg in the control group and 19.74 ± 8.11 kg in the LF-rTMS group. Baseline grip strength did not differ significantly between groups in either the paretic or non-paretic hand. After the intervention period, paretic-hand grip strength in the control group increased from 8.76 ± 6.24 kg to 9.84 ± 6.67 kg, with a mean change of 1.08 ± 1.26 kg. This within-group change was not statistically significant. In the LF-rTMS group, paretic-hand grip strength increased from 7.21 ± 6.52 kg to 9.48 ± 9.77 kg, with a mean change of 2.27 ± 3.74 kg. This within-group change was also not statistically significant.

For the non-paretic hand, grip strength changed from 18.08 ± 4.35 kg to 17.60 ± 9.70 kg in the control group, with a mean change of -0.48 ± 6.94 kg. In the LF-rTMS group, non-paretic hand grip strength increased from 19.74 ± 8.11 kg to 20.39 ± 8.52 kg (mean change, 0.65 ± 1.89 kg). These changes were not statistically significant. Between-group analysis of change scores showed

no statistically significant difference in paretic-hand grip strength improvement between the control group and LF-rTMS group. However, the direction of change favored the LF-rTMS group, with a small-to-moderate effect size for paretic-hand grip strength.

Mean paretic-hand BBT score was 39.86 ± 16.41 blocks/min in the control group and 24.29 ± 19.07 blocks/min in the LF-rTMS group. Mean non-paretic hand BBT score was 48.86 ± 11.04 blocks/min in the control group and 45.57 ± 8.39 blocks/min in the LF-rTMS group. There were no statistically significant baseline differences between groups in paretic-hand or non-paretic hand BBT scores. Paretic-hand BBT score in the control group increased from 39.86 ± 16.41 to 44.00 ± 14.75 blocks/min, with a mean change of 4.14 ± 7.88 blocks/min. In the LF-rTMS group, paretic-hand BBT score increased from 24.29 ± 19.07 to 29.29 ± 19.20 blocks/min, with a mean change of 5.00 ± 8.33 blocks/min. These within-group improvements were not statistically significant. For the non-paretic hand, BBT score increased from 48.86 ± 11.04 to 54.43 ± 8.34 blocks/min in the control group, with a mean change of 5.57 ± 6.70 blocks/min. In the LF-rTMS group, non-paretic hand BBT score increased from 45.57 ± 8.36 to 50.14 ± 11.65 blocks/min, with a mean change of 4.57 ± 9.40 blocks/min. These changes were not statistically significant.

Table 2. Pre-post changes and between-group comparison of grip strength and Box and Block Test

Outcome	Control baseline	Control week 4	Control change	LF-rTMS baseline	LF-rTMS week 4	LF-rTMS change	Between-group comparison of change
Paretic-hand grip strength, kg	8.76 ± 6.24	9.84 ± 6.67	1.08 ± 1.26	7.21 ± 6.52	9.48 ± 9.77	2.27 ± 3.74	Mann-Whitney U = 22.0; p = 0.798
Non-paretic hand grip strength, kg	18.08 ± 4.35	17.60 ± 9.70	-0.48 ± 6.94	19.74 ± 8.11	20.39 ± 8.52	0.65 ± 1.89	Mann-Whitney U = 31.0; p = 0.443
Paretic-hand BBT, blocks/min	39.86 ± 16.41	44.00 ± 14.75	4.14 ± 7.88	24.29 ± 19.07	29.29 ± 19.20	5.00 ± 8.33	MD 0.86 (95% CI -8.59 to 10.30); p = 0.847
Non-paretic hand BBT, blocks/min	48.86 ± 11.04	54.43 ± 8.34	5.57 ± 6.70	45.57 ± 8.36	50.14 ± 11.65	4.57 ± 9.40	MD -1.00 (95% CI -10.62 to 8.62); p = 0.823

Between-group comparison of BBT change scores showed no statistically significant difference between the control and LF-rTMS groups for either paretic or non-paretic hands. The effect size for paretic-hand BBT change was very small. The modest BBT improvement observed in both groups should also be interpreted in relation to measurement variability. Chen et al. reported satisfactory test-retest reproducibility for common hand function tests in patients with stroke but also noted higher measurement error when tests were performed with the more affected hand and in patients with hand hypertonicity. In the present study, mean paretic-hand BBT improved by approximately 4–5 blocks/min, suggesting that some individual improvements may be clinically relevant, but the average group-level change should be interpreted cautiously.⁸

The mean change in paretic-hand grip strength was 1.08 ± 1.26 kg in the control group and 2.27 ± 3.74 kg in the LF-rTMS group. The between-group effect size for paretic-hand grip strength was Cohen's $d = 0.43$, indicating a small-to-

moderate effect favoring the LF-rTMS group. The mean change in non-paretic hand grip strength was -0.48 ± 6.94 kg in the control group and 0.65 ± 1.89 kg in the LF-rTMS group. The between-group effect size was Cohen's $d = 0.22$, indicating a small effect. The mean change in paretic-hand BBT score was 4.14 ± 7.88 blocks/min in the control group and 5.00 ± 8.33 blocks/min in the LF-rTMS group. The between-group effect size was Cohen's $d = 0.11$, indicating a negligible effect. The mean change in non-paretic hand BBT score was 5.57 ± 6.70 blocks/min in the control group and 4.57 ± 9.40 blocks/min in the LF-rTMS group. The between-group effect size was Cohen's $d = 0.12$, indicating a negligible effect. Overall, both groups showed improvement trends in paretic-hand grip strength and BBT performance, but LF-rTMS combined with conventional rehabilitation did not show statistically significant superiority over conventional rehabilitation alone.

4. Discussion

Contralesional LF-rTMS combined with conventional rehabilitation was feasible and well

tolerated, but did not improve grip strength or manual dexterity significantly more than conventional rehabilitation alone. Both groups improved numerically in paretic-hand grip strength and Box and Block Test (BBT) performance. The largest between-group effect was observed for paretic-hand grip strength, but its magnitude and precision were insufficient to establish efficacy. The principal finding is therefore one of feasibility with an inconclusive treatment effect, rather than evidence that LF-rTMS enhances conventional rehabilitation.

Grip strength and BBT capture related but distinct components of hand recovery. Grip strength measures force generation, whereas BBT performance additionally depends on movement speed, coordination, object manipulation, and sensorimotor integration.⁹⁻¹¹ Recovery in these domains may therefore diverge. Pennati et al. demonstrated that precision-grip recovery is influenced by initial sensorimotor impairment and corticospinal tract lesion load, indicating that improved force production does not necessarily translate into proportional gains in dexterity.¹² This distinction may explain why the numerical advantage of LF-rTMS was greater for grip strength than for BBT. The mechanistic rationale for contralesional LF-rTMS derives from the interhemispheric imbalance model. Following stroke, excessive contralesional excitability may increase inhibitory influence on the ipsilesional motor cortex. Low-frequency stimulation of contralesional M1 is intended to reduce this influence and facilitate activity within the affected motor network.^{3,13} When followed by task-oriented rehabilitation, rTMS may prime the motor system for activity-dependent plasticity rather than produce functional recovery independently.^{14,15} However, interhemispheric imbalance is not universal after stroke. Its contribution varies with stroke phase, lesion location, corticospinal tract integrity, and residual structural reserve. The absence of a clear treatment effect in our cohort may therefore reflect biological heterogeneity that was not captured by the clinical eligibility criteria.

The numerically greater improvement in paretic-hand grip strength with LF-rTMS is directionally

consistent with previous studies of contralesional stimulation. Luk et al. reported increased ipsilesional cortical excitability and improved upper-limb function after LF-rTMS combined with motor practice, while Lv et al. suggested that response may depend on stimulation dose and treatment duration.^{6,13} Meta-analytic evidence also indicates a possible benefit of low-frequency stimulation over the unaffected hemisphere, although estimates vary substantially across protocols and patient populations.¹⁶ In the present study, improvement in both groups could reflect conventional rehabilitation, ongoing recovery during the subacute phase, or their combination. The data do not allow these effects to be separated from a specific rTMS effect.

Interpretation is constrained by the small sample and baseline heterogeneity. With seven participants per group, the study had limited power to detect small or moderate effects and produced unstable estimates sensitive to individual responses. Paretic-hand BBT performance was also lower at baseline in the LF-rTMS group. Although this difference was not statistically significant, statistical non-significance does not establish baseline equivalence in a small trial. Because the analysis compared unadjusted change scores, it may not have fully accounted for baseline motor severity or regression to the mean. A definitive trial should use outcome-specific, baseline-adjusted models, such as analysis of covariance, and consider stratified randomization by baseline impairment and lesion characteristics.

The lack of sham stimulation and blinding adds uncertainty. Participants and treating clinicians knew group assignment, and the authors did not report assessor blinding. Expectation, treatment intensity, and therapist behavior may therefore have influenced performance-based outcomes. The single-center design limits generalizability, while the absence of longer-term follow-up prevents assessment of whether any gains were sustained. Furthermore, the study did not obtain neurophysiological measures such as motor-evoked potentials, cortical excitability, or interhemispheric inhibition. The proposed mechanism of cortical modulation therefore remains inferential.

No serious adverse events or treatment discontinuations occurred, supporting the feasibility of this protocol in a supervised outpatient setting. This finding is consistent with safety recommendations emphasizing careful screening for seizure risk, relevant medication use, intracranial metal, and other contraindications.¹⁷ Nevertheless, the absence of serious events in 14 participants should not be interpreted as a comprehensive assessment of safety.

Response to rTMS after stroke is unlikely to be uniform. Differential effects have been reported according to stimulation target, baseline motor impairment, lesion location, and neurophysiological status.¹⁸ Future trials should therefore move beyond treating post-stroke upper-limb impairment as a homogeneous

condition. Larger sham-controlled studies should incorporate concealed allocation, blinded outcome assessment, baseline-adjusted analysis, longer follow-up, and measures of corticospinal integrity and cortical excitability. These features may help determine not only whether LF-rTMS is effective, but also which patients are most likely to benefit.

5. Conclusion

Overall, contralesional LF-rTMS was feasible and well tolerated but did not demonstrate superiority over conventional rehabilitation for hand recovery after subacute stroke. The possible signal in paretic-hand grip strength is hypothesis-generating and requires confirmation in an adequately powered, mechanistically informed trial

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