Effects of Repetitive Transcranial Magnetic Stimulation on Upper Extremity Function in Acute Stroke: A Meta-analysis and Systematic Review

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Abstract [**Objectives**] To conduct a comprehensive examination of the evidence-based impact of repetitive transcranial magnetic stimulation (rTMS) on upper extremity functionality in patients with acute stroke. [**Methods**] A rigorous and systematic electronic search was conducted across the Medline, PubMed, and Web of Science databases, encompassing literature up to July 1, 2024. To ensure the reliability of the included studies, an assessment of their risk of bias was conducted using RevMan 5.4 software, in accordance with the rigorous standards outlined in the *Cochrane Handbook for Systematic Reviews*. Subsequently, we employed either the random-effects model or the fixed-effects model, depending on the heterogeneity of the data, to estimate the standardized mean difference (SMD) in outcomes, utilizing Stata 18.0 software for statistical analysis. [**Results**] Our review encompassed a total of five studies, involving 252 patients with acute stroke. The pooled analysis of these studies revealed a statistically significant improvement in Fugl - Meyer Assessment of the Upper Extremity (FMA-UE) scores among patients who received rTMS therapy ($SMD = 2.71$, 95% CI: 0.85 to 4.56; $P < 0.000\ 1$), albeit with considerable heterogeneity ($I^2 = 97.65\%$) across the trials. [**Conclusions**] The results of this systematic review and meta-analysis underscore the promising potential of rTMS in enhancing upper extremity function in patients who have experienced an acute stroke. These findings provide compelling evidence for the therapeutic benefits of rTMS in this patient population.

Key words Acute stroke, rTMS, Upper extremity function, Meta-analysis

1 Introduction

Stroke, a prevalent cerebrovascular disease, is characterized by high rates of incidence, mortality, and disability. Globally, over 10 million stroke cases occur annually, with more than 5 million resulting in mortality, and another 5 million plus patients suffering from various functional impairments, encompassing cognitive and motor dysfunction, language disorders, pain, and emotional disturbances[1]. Clinically, the exploration of effective therapeutic strategies for stroke has become a focus. Recombinant tissue plasminogen activator (rt-PA) is currently the only treatment for acute ischemic stroke that has been proven effective, yet its application is limited due to the narrow window of time during which it can be administered[2]. Currently, there is no established treatment that can effectively reverse the damage to brain tissue and thereby restore patients' functions. Modern rehabilitation theories and evidence-based medicine have confirmed that post-stroke rehabilitation is the most effective strategy for reducing disability rates and constitutes an essential component of stroke management[3]. Recently, non-invasive brain stimulation (NIBS) has been extensively applied in clinical stroke rehabilitation, encompassing repetitive transcranial magnetic stimulation (rTMS)[4], transcranial direct current stimulation (tDCS)[5], and transcranial focused ultrasound stimulation (tFUS)[6]. rTMS is a physical neuromodulation technique that employs pulsed magnetic fields to interact with the central nervous system, particularly the brain. Depending on the stimulation frequency, rTMS can either excite or inhibit cortical neurons in the stimulated brain region[7]. Typically, high-frequency stimulation ($\geqslant$5 Hz) and intermittent theta-burst stimulation (iTBS) have the effect of enhancing neuronal excitability, whereas low-frequency stimulation ($\leqslant$1 Hz) and continuous theta-burst stimulation (cTBS) have the effect of inhibiting neuronal excitability[8]. This literature review aims to examine the efficacy of rTMS in the rehabilitation of acute ischemic stroke.

2 Methods

2.1 Literature search A comprehensive literature search was conducted across multiple databases, including PubMed and Web of Science, up to July 1, 2024. The search terms used were "acute stroke", "acute ischemic stroke", "repetitive transcranial magnetic stimulation", and "rTMS". The search strategy for article types encompassed the following terms: ("clinical study" OR "RCT" OR "human" OR "patients"). The search was limited to articles published in the English language.

2.2 Inclusion and exclusion criteria

2.2.1 Inclusion criteria. (i) Study design. Studies were included exclusively if they adhered to the rigorous standards of either randomized controlled trials (RCTs) or clinical controlled trials (CCTs), ensuring a high level of methodological rigor and validity. (ii) Patient population. The study population consisted of adults aged 18 years and older who were undergoing the acute phase of stroke recovery. This focus ensured the homogeneity of the sample population and relevance to the clinical context. (iii) Intervention. A comprehensive and detailed account of repetitive transcranial magnetic stimulation (rTMS) intervention was mandatory for inclusion. This criterion was designed to guarantee a clear

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understanding of the therapeutic approach and its potential effects. (iv) Control group. The control group consisted of two subgroups: those who received sham rTMS and those who did not receive any intervention. This design facilitated the isolation and evaluation of the specific effects of rTMS. (v) Outcome measures. Studies were required to employ the Fugl – Meyer Motor Assessment for Upper Extremity (FMA-UE) as an outcome measure. This quantitative instrument is known for its sensitivity in detecting changes in upper limb motor recovery post-stroke, thereby providing a reliable and validated metric for assessing therapeutic efficacy[9].

2.2.2 Exclusion criteria. Any study that failed to meet the aforementioned stringent inclusion criteria was systematically excluded from our analysis, ensuring that only those of the highest scientific quality and relevance to our research objectives were considered.

2.3 Data extraction The primary reviewer crafted a data extraction sheet, which was subsequently scrutinized by the secondary reviewer, adhering strictly to the guidelines outlined in the *Cochrane Handbook for Systematic Reviews*. Whenever the numerical values of the outcomes were not explicitly disclosed in the text or tables of the published paper, a diligent attempt was made to contact the corresponding author via email in order to request clarification. The outcomes were subjected to an independent evaluation by two authors, utilizing the WebPlotDigitizer software (version 4.3), with the objective of extracting data from the graphical representations presented in the published literature[10]. The extracted data were considered suitable for further analysis only if the discrepancy between the readings of the two authors did not exceed a threshold of 20%, thereby ensuring scientific rigor and accuracy in the data acquisition process. In scenarios where a study presented multiple follow-up endpoints, we prioritized the endpoint that exhibited the most significant difference. Furthermore, if the median, standard error, and interquartile range were reported, these values underwent careful conversion to mean and standard deviation (SD) to ensure consistency and comparability across the studies.

2.4 Quality assessment The methodological rigor of each randomized controlled trial (RCT) was independently evaluated by two authors, adhering to the stringent guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta – Analyses (PRISMA) statement, which advocates the utilization of the Cochrane Collaboration's risk of bias tool. This comprehensive instrument is comprised of two distinct sections. The first meticulously assesses seven core domains pertinent to trial validity, including sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, completeness of outcome data, selective outcome reporting, and any other potential sources of bias.

The second section of the tool assigns a categorical judgment to each domain, categorizing them as exhibiting either a "low risk of bias", a "high risk of bias", or an "unclear risk of bias". In cases where initial evaluations diverged, a consensus-building approach was employed to reconcile disagreements regarding the quality ratings. If consensus remained elusive, a third, impartial reviewer was consulted to provide an additional perspective and facilitate a resolution.

2.5 Statistical methods The analysis was conducted utilizing Stata 18.0 software (College Station, Texas, USA). For continuous outcome variables, standard mean differences (SMD) were employed as the primary measure of effect, accompanied by 95% confidence intervals (CIs) as summary statistics. Given the considerable variability in outcomes across studies, a fixed-effects model was initially employed, with the option of switching to a random-effects model based on the assessment of heterogeneity using the I^2 statistic. Once the outcome measures were determined to be comparable, the datasets were aggregated in accordance with the meta-analysis framework. The extent of heterogeneity between studies was rigorously evaluated using the I^2 statistic. Depending on the I^2 result, either a fixed-effects model or a random-effects model was selected for the analysis. In instances where I^2 exceeded 50%, indicating significant heterogeneity, a random-effects model was adopted to calculate the parameters. Conversely, in the absence of substantial heterogeneity ($I^2 \leqslant 50\%$), a fixed-effects model was deemed to be the most appropriate approach. To investigate the presence of publication bias, particularly when the analysis encompassed at least three studies, a funnel plot was employed. A two-tailed P-value threshold of less than 0.05 was established as the criterion for statistical significance.

3 Results and analysis

3.1 Characterization of included studies Table 1 provides a comprehensive and concise synopsis of the key characteristics of the five studies encompassed within our rigorous analysis. These studies, collectively representing a sample size of 252 stroke patients, offer valuable insights into the field. Across the five articles considered, a consistent methodology was observed, with all utilizing Sham rTMS as the control arm for comparative purposes.

Within the intervention groups, a deeper exploration was undertaken in two studies, which directly compared the influence of distinct stimulation frequencies—specifically, high-frequency versus low-frequency—on the FMA-UE scores, a widely recognized and validated measure of upper limb functionality. Furthermore, a single article ventured into the realm of differing stimulation patterns, examining their unique effects on the same outcome measure.

Consistently, all articles adopted the FMA-UE as the primary instrument for assessing upper limb function, reinforcing the reliability and robustness of our findings. Additionally, one study extended beyond the conventional approach to scoring by incorporating score improvement as an analytical parameter, thereby offering a nuanced understanding of the therapeutic gains attained.

Table 1 Characterization of included studies

Study	Group	Age // years	Stroke onset time // d
Chen *et al.* [11]	Group 1: 1 Hz – 10 Hz (n = 25)	Group 1: 58.00 (44.50, 65.50)	Group 1: 7 (5.00, 10.00)
	Group 2: sham – 10 Hz (n = 25)	Group 2: 62.00 (49.00, 67.00)	Group 2: 5 (4.00, 9.00)
	Group 3: 1 Hz-sham (n = 25)	Group 3: 63.00 (43.00, 67.00)	Group 3: 7 (4.50, 11.50)
	Group 4: sham-sham (n = 25)	Group 4: 65.00 (52.00, 73.00)	Group 4: 5 (4.00, 9.50)
Guan *et al.* [12]	Group 1: real rTMS (n = 21)	Group 1: 59.7 ± 6.8	Group 1: 3.8 ± 3.4
	Group 2: sham rTMS (n = 21)	Group 2: 57.4 ± 14.0	Group 2: 4.8 ± 4.1
Du *et al.* [13]	Group 1: 3-Hz rTMS (n = 23)	Group 1: 56.78 ± 8.47	Group 1: 7 (4 – 16)
	Group 2: 1-Hz rTMS (n = 23)	Group 2: 56.78 ± 12.4	Group 2: 6 (5 – 12)
	Group 3: control (n = 23)	Group 3: 53.61 ± 13.55	Group 3: 8 (3 – 24)
Matsuura *et al.* [14]	Group 1: real rTMS (n = 10)	Group 1: 72.2 ± 6.0	Group 1: 9.4 ± 5.3
	Group 2: sham rTMS (n = 10)	Group 2: 74.7 ± 12.7	Group 2: 9.8 ± 2.8
Watanabe *et al.* [15]	Group 1: iTBS (n = 8)	Group 1: 72.5 (6.5)	within 7 d
	Group 2: 1-Hz rTMS (n = 7)	Group 2: 67.6 (6.4)	
	Group 3: sham rTMS (n = 6)	Group 3: 75.2 (5.5)	

3.2 Risk of bias The risk of bias in the efficacy analysis for each included RCT is clearly demonstrated in Fig. 1. No study was identified as having a high risk of bias. All the documents adopted the method of random grouping, except for one article[14]. The other four articles mentioned the concealment of random grouping. Two articles[12-13] mentioned that all patients were blinded to their treatment allocation. In all articles, the evaluators were unaware of the experimental grouping information. All articles presented all results without any evidence of selective reporting.

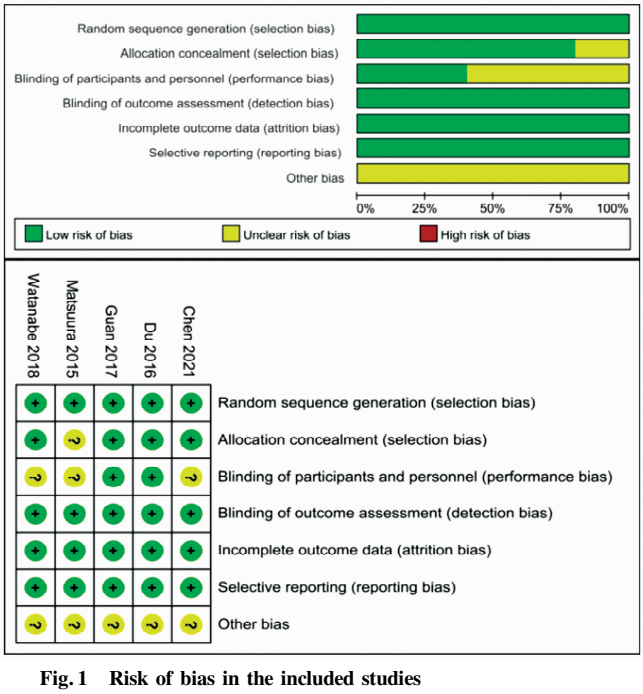

Fig. 1 Risk of bias in the included studies

3.3 rTMS improved the upper extremity function within the acute cerebral ischemic stroke A meticulous and exhaustive meta-analysis was conducted, adhering rigorously to a random-effects model to ensure the highest standards of scientific rigor and precision. By integrating data from five meticulously selected studies, we observed a statistically significant enhancement in Functional Motor Assessment – Upper Extremity (FMA-UE) scores, with a SMD of 2.71 ([95% confidence interval: 0.85 to 4.56]; P < 0.000 1), accompanied by substantial heterogeneity (I^2 = 97.65%). This improvement underscores the promising outcomes of real rTMS over sham rTMS, offering valuable insights into the potential therapeutic benefits of rTMS in upper extremity rehabilitation for patients with acute stroke (Fig. 2).

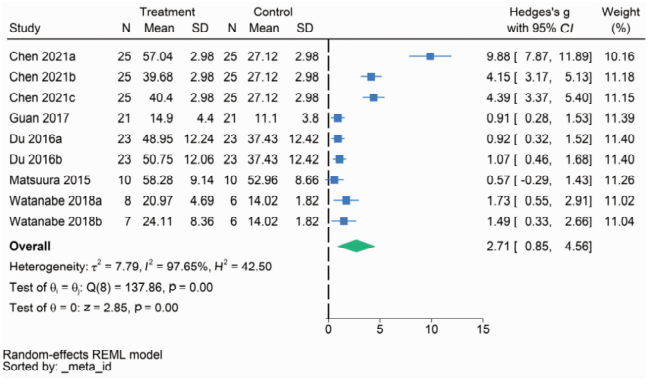

Fig. 2 The forest plot illustrating the overall impact of rTMS on FMA-UE in the acute stroke

4 Discussion

A comprehensive systematic review and meticulous meta-analysis were undertaken to assess the effects of rTMS on the upper extremity in individuals with acute cerebral ischemic stroke. The primary findings of this rigorous meta-analysis indicate that rTMS is remarkably effective in improving Fugl – Meyer Motor Assessment for Upper Extremity (FMA-UE).

Currently, the latest evidence-based guidelines on rTMS for motor dysfunction after stroke indicate: Grade A (definite efficacy) recommends low-frequency rTMS targeting the unaffected hemisphere to improve motor dysfunction during the subacute phase of stroke, with one Class I and four Class II studies confirming the definitive efficacy of low-frequency stimulation to the M1 area of the unaffected hemisphere in rehabilitating and improving hand motor function during the subacute phase of stroke; Grade B

(probable efficacy) recommends high-frequency rTMS targeting the affected hemisphere for the same purpose, supported by four Class II studies suggesting the potential effectiveness of high-frequency stimulation to the M1 area of the affected hemisphere in motor function rehabilitation and improvement during the subacute phase of stroke[8]. Although the clinical guidelines do not explicitly recommend rTMS treatment protocols for acute stroke, numerous studies have demonstrated promising effects of rTMS during this period. Khedr *et al.*[16] found that, compared to a sham stimulation group, 3 Hz rTMS to the affected hemisphere significantly improved stroke disability scores in a study involving 52 stroke patients (5 – 10 d post-stroke). Similarly, Khedr *et al.*[17] demonstrated more pronounced motor recovery in the hemiplegic side among patients treated with 3 or 10 Hz rTMS to the affected hemisphere, compared to the sham group, in a study of 48 stroke patients (5 – 15 d post-stroke). Conforto *et al.*[18] showed, in a study of 30 stroke patients (5 – 45 d post-stroke), that 1 Hz rTMS to the unaffected hemisphere produced more significant improvements in Jebsen – Taylor Hand Function Test and grip strength compared to sham stimulation. Khedr *et al.*[19], in a study of 36 stroke patients (7 – 20 d post-stroke), found that both 1 Hz rTMS to the unaffected hemisphere and 3 Hz rTMS to the affected hemisphere significantly outperformed sham stimulation in improving grip strength, keyboard typing, and pegboard tasks; furthermore, patients receiving 1 Hz rTMS showed better outcomes than those receiving 3 Hz rTMS. However, Sasaki *et al.*[20], in a study of 29 stroke patients (6 – 29 d post-stroke), observed significant improvements in grip strength and tapping frequency only with 10 Hz rTMS to the affected hemisphere compared to sham, while no significant improvement was seen with 1 Hz rTMS to the unaffected hemisphere. Although much research has focused on the effects of rTMS on motor function during the chronic phase of stroke, the most significant changes in functional recovery and neuroplasticity occur within days to weeks post-stroke.

5 Conclusions

A thorough systematic review and meticulous meta-analysis have been conducted to evaluate the impact of rTMS on upper extremity function in acute cerebral ischemic stroke patients. The key findings reveal that this therapy significantly enhances FMA-UE, suggesting a potential advantage of rTMS in upper extremity rehabilitation.

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