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Network meta-analysis of transcranial magnetic stimulation in improving upper limb dyskinesia after stroke: a protocol for systematic review and meta-analysis

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Review question / Objective: **Stroke has become the main cause of lifelong disability in humans, bringing a heavy economic burden to patients, families and society. Upper limb movement disorder is a common complication after stroke and one of the causes of disability after stroke. Although the rehabilitation system is relatively complete, there are still many patients who are unable to independently perform daily activities such as eating, dressing, and grooming due to upper limb problems, and more or less need the help of others. Transcranial magnetic stimulation(TMS) modulates the excitability of the cerebral cortex by increasing or decreasing synaptic activity. There can also be broader effects on distal brain regions that are functionally closely linked to the stimulated region. Therefore, it is widely used in the recovery of upper limb function after stroke. Repetitive transcranial magnetic stimulation(rTMS) is one of the most commonly used treatment modality. However, with the improvement of the technical level of physical factors, several new transcranial magnetic modes, such as theta burst stimulation(TBS), have emerged. The new modality has a shorter treatment time and longer duration of post-stimulation effects than rTMS. Different stimulation protocols produce different results, but there is no consensus on which TMS modality is better for improving upper extremity dyskinesia. Therefore, this study uses network meta-analysis to conduct quantitative comprehensive statistical analysis and sequencing of the existing clinically relevant evidence to determine the best TMS model, which provides reference value and evidence-based theoretical basis for the selection of TMS regimens in clinical practice.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 17 March 2022 and was last updated on 17 March 2022 (registration number INPLASY202230081).

INTRODUCTION

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of the causes of disability after stroke. Although the rehabilitation system is relatively complete, there are still many patients who are unable to independently perform daily activities such as eating, dressing, and grooming due to upper limb problems, and more or less need the help of others. Transcranial magnetic stimulation(TMS) modulates the excitability of the cerebral cortex by increasing or decreasing synaptic activity. There can also be broader effects on distal brain regions that are functionally closely linked to the stimulated region. Therefore, it is widely used in the recovery of upper limb function after stroke. Repetitive transcranial magnetic stimulation(rTMS) is one of the most commonly used treatment modality. However, with the improvement of the technical level of physical factors, several new transcranial magnetic modes, such as theta burst stimulation(TBS), have emerged. The new modality has a shorter treatment time and longer duration of post-stimulation effects than rTMS. Different stimulation protocols produce different results, but there is no consensus on which TMS modality is better for improving upper extremity dyskinesia. Therefore, this study uses network meta-analysis to conduct quantitative comprehensive statistical analysis and sequencing of the existing clinically relevant evidence to determine the best TMS model, which provides reference value and evidence-based theoretical basis for the selection of TMS regimens in clinical practice.

Condition being studied: Since TMS has many different protocols in terms of duration, stimulation mode and so on, it brings a major problem for TMS in the treatment of upper extremity dyskinesia after stroke. There is no consensus on the optimal treatment regimen and assessment of cortical excitability changes. Current research mostly focuses on the pairwise comparison of low-frequency rTMS and high-frequency rTMS. There is no study using NMA method to evaluate and compare the effectiveness of several TMS modes in improving upper limb hemiplegia, and to provide the best TMS mode for clinical improvement of upper limb function.

METHODS

Participant or population: Stroke patients with upper extremity motor dysfunction.

Intervention: The experimental group received TMS on the basis of rehabilitation training.

Comparator: The control group only received rehabilitation training or sham TMS stimulation on this basis.

Study designs to be included: Randomized controlled trials(RCTs).

Eligibility criteria: Type of participant. Stroke was diagnosed by CT or MRI, and the age, sex and type of stroke were not limited. Type of interventions and comparators.The experimental group received TMS on the basis of rehabilitation training; and the control group only received rehabilitation training or sham TMS stimulation on this basis. Type of outcomes.The predetermined primary indicators are Fugl-Meyer upper limb motor function scale (Fugl-Meyer upper extremity assessment, UE-FMA). And the secondary indicators are Barthel Index/Modified Barthel Index (BI/MBI) and motor evoked potential (MEP),etc. Type of study. RCTs in Chinese and English.

Information sources: The studies of TMS in the improvement of upper limb function after stroke are searched in Chinese databases, such as CNKI, VIP, CBM, WANFANG and foreign databases, such as PubMed, Web of science, Embase and Cochrane Library.

Main outcome(s): The predetermined primary indicators are Fugl-Meyer upper limb motor function scale (Fugl-Meyer upper extremity assessment, UE-FMA).

Additional outcome(s): And the secondary indicators are Barthel Index/Modified Barthel Index (BI/MBI) and motor evoked potential (MEP),etc.

Quality assessment / Risk of bias analysis: Refer to the Cochrane system evaluation manual to evaluate the quality and bias risk of the included literature. And two evaluators independently evaluate each of the items as "high risk", "low risk" and "unclear".

Strategy of data synthesis: We first used Revman5.3 software to conduct a traditional meta-analysis of the included outcome indicators. All the included outcome indexes are continuous variables, so the weighted mean difference(WMD) and standardized mean difference(SMD) are used as the effect size. The estimated value and confidence interval (CI) of effect size are provided. The significance threshold was set to $p < 0.05$. Secondly, we used R language programming software for Network-meta analysis. In order to provide an indirect comparison of several different TMS modes, we used R4.0.5 software to draw the network diagram.The R programming language starts the NETMETA program, calls the data results of the random effect model based on the Bayesian MCMC (Markov chain Monte Carlo) algorithm, and evaluates and processes it. We will analyze the results of all direct or indirect comparisons and estimate the rank probability of each group according to the MCMC method to evaluate which TMS modality has the best effect on the treatment of upper extremity spasticity after stroke.

Subgroup analysis: When there is a high heterogeneity in the results of Meta analysis, a subgroup analysis is conducted according to the patient's age, sex, course of disease, treatment cycle and research quality to analyze the possible sources of heterogeneity.

Sensitivity analysis: When the meta-analysis results are positive and more than 3 articles are included, a sensitivity analysis is performed using R language.

Country(ies) involved: China.

Keywords: Transcranial magnetic stimulation; TMS; stroke; upper limb dyskinesia; network meta-analysis.

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