International Platform of Registered Systematic Review and Meta-analysis Protocols

INPLASY PROTOCOL

To cite: Xu et al. Effects of high-frequency transcranial magnetic stimulation over the contralesional hemisphere on motor recovery in severe hemiplegic stroke: A systematic review and meta-analysis. Inplasy protocol 202180044. doi: 10.37766/inplasy2021.8.0044

Received: 11 August 2021

Published: 11 August 2021

Corresponding author:
Pan Xu

xp2052428564@163.com

Author Affiliation:
The second Affiliated Hospital of Kunming Medical University.

Support: **National Program of China.**

Review Stage at time of this submission: **Preliminary searches.**

Conflicts of interest:
None declared.

Effects of high-frequency transcranial magnetic stimulation over the contralesional hemisphere on motor recovery in severe hemiplegic stroke: A systematic review and meta-analysis

Xu, P[1]; Yao, LQ[2]; Wang, WL[3]; Zhang, CJ[4].

Review question / Objective: **A few studies have shown that contralateral high-frequency transcranial magnetic stimulation can more improve the recovery of motor function in stroke patients with moderate hemiplegia compared with contralateral low-frequency or ipsilateral high-frequency stimulation, but the evidence is insufficient. Therefore, the research purpose of this paper is to investigate the effect of high-frequency transcranial magnetic stimulation over the contralesional hemisphere on motor recovery in stroke patients with severe hemiplegia compared with contralateral low-frequency or ipsilateral high-frequency stimulation.**
Eligibility criteria: **(1) all the participants were adult (≥18 years); (2) patients were diagnosed with a stroke; (3) focused on rTMS effects on motor function in post-stroke patients; (4) the design of the studies was randomized controlled; (5) ≥ 5 patients were included; (6) the outcome measures included continuous scales that assessed the motor function of the affected limb.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 11 August 2021 and was last updated on 11 August 2021 (registration number INPLASY202180044).

INTRODUCTION

Review question / Objective: **A few studies have shown that contralateral high-frequency transcranial magnetic stimulation can more improve the recovery of motor function in stroke patients with moderate hemiplegia compared with contralateral low-frequency or ipsilateral high-frequency stimulation, but the evidence is insufficient. Therefore, the research purpose of this paper is to**

investigate the effect of high-frequency transcranial magnetic stimulation over the contralesional hemisphere on motor recovery in stroke patients with severe hemiplegia compared with contralateral low-frequency or ipsilateral high-frequency stimulation.

Rationale: Stroke, also known as cerebrovascular accident, is characterized by high morbidity, high disability rate and high mortality, and patients with stroke may have varying degrees of motor dysfunction.Transcranial magnetic stimulation (TMS) is a non-invasive brain stimulation technique that uses a pulsed magnetic field to induce electrical currents in functional areas of the cerebral cortex, resulting in long-term depression,LTD) or long-term potentiation (LTP) effects, which induced changes in cortical excitability and synaptic connections, and promote the recovery of motor function. Currently, TMS is mostly based on the interhemispheric competition model, using high-frequency stimulation of ipsilesional primary motor cortex（iM1） and/or low-frequency stimulation of contralesional primary motor cortex（cM1, with the aim of rebalancing the interhemispheric inhibition (IHI).However, this type of stimulus has produced contradictory results. Although this type of stimulation improved function in patients with mild upper limb hemiplegia, it did not improve function in patients with severe upper limb hemiplegia. Recent evidence suggests that in patients with severe upper limb hemiplegia, the contralateral motor cortex compensates to support the movement of the affected limb because the ipsilateral motor cortex is so damaged. The role of activation of the contralateral hemisphere in recovery depends on the extent of injury to the corticospinal tract (CST). The more severe injury, the greater activation of the contralateral cortex supports recovery of the affected upper limb. Liu and Rouiller proposed a cerebral cortical plasticity gradient based on stroke severity, which varied with stroke severity. When the damage was minor and the pathway of corticospinal tract remained, the M1 area around the lesion and the iplateral higher motor area, such as the premotor cortex (PMC) and supplementary motor area (SMA), were supported by functional restructuring. However, when the damage is large, the ipsilateral M1 and higher motor areas are damaged, and the plasticity of the intact, contralateral cortex is relied on to promote functional recovery. Therefore, the TMS approach based on the "hemispheric competition model" is not suitable for all patients. Instead, a multidimensional model should take into account the dependence on the healthy side motion network, as well as the degree of structural damage and the availability of residual motion pathways. Studies have shown that all surviving neurons in the ipsilateral and contralateral hemispheres can participate in remodeling and recombination, and functional recombination in the contralateral hemisphere replaces lost function in the damaged area, contributing to functional recovery after stroke. The corticospinal tract is also involved in the compensatory process. A small portion of the corticospinal tract, which insures the contralateral trunk muscles, does not cross over the medullary vertebrae. Structural and functional connections in the ipsilateral corticospinal pathway are increased in stroke patients and are higher in patients with severe motor dysfunction. In 2014,Di Pino G et al. proposed the "bimodal balance-recovery model".This model indicates that when motor functional structure reserve is high in the ipsilateral cerebral hemisphere (i.e., M1 area and corticospinal tract are less damaged), increased excitability in the contralateral hemisphere is considered to inhibit motor recovery, while when motor functional structure reserve is low in the ipsilateral cerebral hemisphere (i.e., M1 area and corticospinal tract are more severely damaged),increased contralateral hemisphere excitability is thought to support recovery of limb motor function. To account for the opposite effect of stimulation based on the interhemispheric competition model, stroke patients should be assigned to at least two groups (mild and severe injury). The theoretical focus of the bimodal balance recovery model is to stratify the severity of stroke patients according to their iplateral structural reserve to develop personalized treatment plans. High-frequency transcranial magnetic stimulation over contralesional hemisphere based on bimodal balance recovery model may be more suitable for stroke patients with severe motor function impairment.

Condition being studied: There are obstacles in rehabilitation training for stroke patients with severe motor dysfunction. Different from routine rehabilitation training, TMS is a "central intervention" treatment method that directly stimulates the functional areas of cerebral cortex and can enhance the neuroplasticity of the affected upper limb. According to the 2020 European TMS evidence-based guidelines, rTMS has a good effect on upper limb functional rehabilitation after stroke, but there are still few clinical studies on severe motor dysfunction. Due to the heterogeneity of patients, the stimulation based on the interhemispheric competition model produced different therapeutic effects. The heterogeneity of the lesion and the extent of injury to the ipsilateral M1 and corticospinal pathways impair the effectiveness of stimulation. These results challenge the classical model of interhemispheric competition, and the stimulation based on the model alone is not suitable for all patients. A non-invasive brain stimulation in patients with cerebral apoplexy of Meta analysis, points out that stimulation method based on hemisphere competition model between yield greater in patients with mild stroke, which is based on "bimodal balance model" of the contralateral hemisphere high frequency rTMS is likely to be severe upper limb hemiplegia the effective treatment of upper limb function rehabilitation in patients with cerebral apoplexy. This study was supported by National Key R&D Program of China and supervised by Professor Yao Liqing from the Second Affiliated Hospital of Kunming Medical University and teachers of literature Retrieval and Medical Statistics from Kunming Medical University. I had enough time to complete this meta-analysis.

METHODS

Search strategy: Query: ((TMS) OR ((((((((("Transcranial Magnetic Stimulation"[Mesh]) OR (Transcranial Magnetic Stimulation)) OR (Magnetic Stimulation, Transcranial)) OR (Magnetic Stimulations, Transcranial)) OR (Stimulation, Transcranial Magnetic)) OR (Stimulations, Transcranial Magnetic)) OR (Transcranial Magnetic Stimulations)) OR (Transcranial Magnetic Stimulation, Single Pulse)) OR (Transcranial Magnetic Stimulation, Paired Pulse)) OR (Transcranial Magnetic Stimulation, Repetitive))) AND ((((((((((((((((((((((((((((((((Cerebrovascular Accidents, Acute) OR (Acute Cerebrovascular Accidents)) OR (Acute Cerebrovascular Accident)) OR (Cerebrovascular Accident, Acute)) OR (Strokes, Acute)) OR (Acute Strokes)) OR (Acute Stroke)) OR (Stroke, Acute)) OR (Strokes, Cerebral)) OR (Stroke, Cerebral)) OR (Cerebral Strokes)) OR (Cerebral Stroke)) OR (Apoplexy)) OR (Strokes, Cerebrovascular)) OR (Stroke, Cerebrovascular)) OR (Cerebrovascular Strokes)) OR (Cerebrovascular Stroke)) OR (Vascular Accidents, Brain)) OR (Brain Vascular Accidents)) OR (Brain Vascular Accident)) OR (Vascular Accident, Brain)) OR (Apoplexy, Cerebrovascular)) OR (Cerebrovascular Apoplexy)) OR (CVAs)) OR (CVA)) OR (Cerebrovascular Accidents)) OR (Cerebrovascular Accident)) OR (Strokes)) OR (Stroke)) OR (“Stroke"[Mesh]))) Filters: Humans, from 2016/1/1 - 3000/12/12.

Participant or population: Severe hemiplegic stroke patients worldwide.

Intervention: High-frequency transcranial magnetic stimulation over the contralesional hemisphere.

Comparator: Low-frequency transcranial magnetic stimulation over the contralesional hemisphere,or high-frequency transcranial magnetic stimulation over the ipsilateral hemisphere.

Study designs to be included: Randomized controlled trial.

Eligibility criteria: (1) all the participants were adult (⩾18 years); (2) patients were diagnosed with a stroke; (3) focused on rTMS effects on motor function in post-stroke patients; (4) the design of the studies was randomized controlled; (5) ⩾ 5 patients were included; (6) the outcome measures included continuous scales that assessed the motor function of the affected limb.

Information sources: Pubmed, EMBASE, Cochrane Library, Web of Science, CNKI, VIP, WANFANG, CBM

Main outcome(s): Contralateral high-frequency transcranial magnetic stimulation can more improve the recovery of motor function in stroke patients with moderate hemiplegia compared with contralateral low-frequency or ipsilateral high-frequency stimulation.

Data management: EndNote.

Quality assessment / Risk of bias analysis: The Cochrane Collaboration's tool for assessing risk of bias.

Strategy of data synthesis: The included literatures were analyzed using the Review Manager software of the Cochrane collaboration. Relative risk (RR) was calculated when the final variable was binary data, and mean difference (MD) or standardized mean difference (SMD) was calculated when the continuous variable was continuous. 95% confidence intervals of the statistical results were reported.The heterogeneity of the included studies was calculated by chi-square test, and I^2 statistics were used to reflect the proportion of the heterogeneous part of the effect size in the total variation of the effect size.I^2 values divided heterogeneity into four degrees: none, light, medium and high : $I^2<25\%$, no heterogeneity;$25\% < I^2 < 50\%$, mild heterogeneity; $50\% < I^2 < 75\%$, moderate heterogeneity;$I^2 \geq 75\%$, high heterogeneity.When the $I^2 < 50\%$, fixed effects model was used for meta-analysis; When $I^2 \geq 50\%$, random effects model was used for meta-analysis.If the number of included tests is sufficient (n ≥ 10), an inverted funnel plot is used for bias analysis.

Subgroup analysis: No.

Sensitivity analysis: No.

Language: No restriction.

Country(ies) involved: China.

Keywords: stroke, transcranial magnetic stimulation, motor function.

Contributions of each author:

Author 1 - Pan Xu - Complete literature retrieval, analysis and paper writing.
Email: xp2052428564@163.com
Author 2 - Liqing Yao - Determine topic topics, develop retrieval strategies, guide and modify thesis writing.
Email: yaoliqing98731@163.com
Author 3 - Wenli Wang - Complete the chart.
Email: wangwenli0871@kmmu.edu.cn
Author 4 - Chunjun Zhang - Assist in literature screening and data analysis.
Email: 342529711@qq.com