Review article

Repetitive transcranial magnetic stimulation for the treatment of post-stroke depression: A systematic review and meta-analysis of randomized controlled clinical trials

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ABSTRACT

Background: Every year, more than fifteen million people worldwide experience a stroke, nearly 30% of stroke survivors are likely to experience post-stroke depression (PSD). Repetitive transcranial magnetic stimulation (rTMS) is one of the emerging techniques which assist in targeting rehabilitation after stroke. Although deterioration of PSD greatly affects the recovery and quality of life of stroke sufferers, the effect of rTMS therapy has not been systematically studied.

Objective: A systematic review and meta-analysis was conducted to determine the effect of rTMS on PSD.

Methods: We carried out a systematic review and meta-analysis of randomized controlled trials (RCTs) of rTMS for the treatment of PSD. Primary outcome was severity of depression measured by the Hamilton Depression Rating Scale (HAMD). Secondary outcomes were response rates, remission rates, stroke severity and ability to perform daily activities.

Results: 22 RCTs studies (n=1764 patients) were included. The results demonstrated that rTMS was beneficial on PSD using three scales: HAMD (MD=−6.09, 95% CI: −7.74, −4.45, $P < 0.001$); response rates (OR=3.46, 95% CI: 2.52, 4.76, $P < 0.00001$); remission rates (OR 0.99, 95% CI: 0.56, 1.75, $P < 0.00001$); National Institutes of Health Stroke Scale (NIHSS) (MD=−2.74, 95% CI: −3.33, −2.15, $P < 0.001$); Activities of daily living (ADL) (SMD=−1.20, 95% CI: 0.68, 1.72, $P < 0.001$); Montgomery-Asberg Depression Scale (MARDE) (MD=−6.21; 95% CI: −9.34, −3.08; P=0.0001);

Conclusion: In present meta-analysis, the positive findings suggest rTMS has beneficial effects on PSD. However, those findings should be treated with caution because of heterogeneity and potential biases.

1. Introduction

PSD may develop immediately following the stroke lasts for more than 5 years. It could be viewed as depression resulting first from damage caused by the initial ischemia and reperfusion injury symptoms (Barra et al., 2016). PSD patients often display both anxiety and depressive symptoms, ending to decrease quality of life, increased mortality and heightened risk of recurrent stroke or suicide (Vahid-Ansari et al., 2016). Consequently highlight the need for patient care that extends beyond that of physical and cognitive rehabilitation (Nguyen et al., 2016).

When diagnosed, patients with PSD are treated with antidepressants, such as serotonin selective reuptake inhibitors (SSRI) (Campbell Burton et al., 2011; Mead et al., 2012). However, these drugs take at least 3–4 weeks to elicit a clinical response and the efficiency is just approximately 50%, with only 30% of patients achieving remission (Trivedi et al., 2006). What's more, using of tricyclic antidepressant (TCAs), SSRIs or multiple types users had increased risk of stroke recurrence (Juang et al., 2015). Thus, there is clearly a need to develop additional safe and effective treatments for PSD. In recent years, more and more researchers have focused on the rTMS therapy (Jorge et al., 2004). RTMS appears to target distributed brain networks that are

central to the pathophysiology of depression and is not followed by epileptic seizure activity (Ren et al., 2014). Equipment for rTMS includes a comfortable chair with a computerized electromechanical head support system that allows reliable positioning of the stimulating coil placed directly on the scalp (Ontario, 2016) to produce and deliver non-invasive, magnetic stimulation using brief duration, rapidly alternating, or pulsed, magnetic fields to induce electrical currents directed at spatially discrete regions of the cerebral cortex (Perera et al., 2016). RTMS can be applied relatively painlessly to conscious patients and can be used for outpatients or for inpatients (Ontario, 2016). And rTMS does not require anesthesia and does not cause seizure in general if used properly and in compliance with the safety guidelines (Ontario, 2016). Therefore, numerous RCT studies have explored the effect of rTMS on PSD (Fan, 2014; Jorge et al., 2004; Li et al., 2013; Liu, 2010b; Liu and Xu, 2015; Narushima et al., 2010). However, the results remained inconsistent. In the present study, we performed a meta-analysis to validate the association between the rTMS and PSD by including data from studies that were published from 2005 until November 2016.

2. Methods

2.1. Study design and registration

Our meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (Liberati et al., 2009) and is registered with PROSPERO (registration number CRD42016045624).

2.2. Search strategy

Our research question for this review was "Whether rTMS has effect on PSD?" a systematic review and meta-analysis. This meta-analysis is based on the methodology recommended by the Cochrane Collaboration (Furlan et al., 2009). A comprehensive literature search was performed to find studies published up to August 20, 2016. Electronic searches were done with Pubmed medline, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), Chinese National Knowledge Infrastructure (CNKI), Chongqing VIP Database (VIP), Wan Fang Database and Chinese Biomedical Literature Database. The search strategies combined free-text searching with keywords probing. Our key search terms included English and Chinese versions of depression, TMS, rTMS, transcranial magnetic stimulation, Repetitive transcranial magnetic stimulation, stroke, Cerebrovascular Accident, Apoplexy, Brain Vascular Accident. And reference lists from the resulting publications and reviews were used to identify further relevant publications. Subsequently, we checked each article according to our inclusion criteria.

2.3. Inclusion criteria and exclusion criteria

Selected studies had to meet the subsequent inclusion criteria:

1) Design: double-blinded RCTs or randomized controlled trials. The manuscript had a minimum sample size of more than three participants in order to calculate the effect size.
2) Participants: a. the patients were diagnosed with stroke of clinically relevant examinations (computed tomography, magnetic resonance imaging) with a Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) diagnosis of depression due to stroke (Jorge et al., 2004), or Classification and Diagnostic Criteria of Mental Disorders in China-Second-Revised Edition (CCMD-3). b. Multimodal Approach to Diagnosis of PSD (MMADD).
3) Intervention and control group: rTMS alone or in combination with other treatments (antidepressant, acupuncture, and regular treatment.) compared with sham-rTMS, placebo, antidepressant treat-

ments, acupuncture treatments or regular treatment. Regular treatments include general treatment, etiological treatment, regular rehabilitation treatment and drug treatment.
4) Efficacy evaluation and outcome reporting: efficacy should be rated by HAMD (17- or 21-items), and only trials that reported in a continuous (means and standard deviations (SDs) of pro- and post-treatment HAMD scores) form able to be synthesized in this meta-analysis. This scale has been used in virtually every study of PSD. Previous work has demonstrated that it is sensitive to changes produced by treatment and has reliability and validity in this patient population (Jorge et al., 2004; Robinson and Benson, 1981).
5) Outcome measures were used of the HAMD for assessing the degree of depression of patients.

The number of studies and reasons for exclusion was as follows:

1) Valid data were unavailable or data not completed so that the study could not be analyzed.
2) Relevant outcome indexes were not reported.
3) Case reports, abstracts, comments, reviews, editorials, and thesis.
4) Studies with primary diagnosis of epilepsy, anxiety, or cognitive disorder.
5) Duplicate publications.
6) Patients with metal installed, intracranial hypertension or a history of depression.

2.4. Data extraction

1) Sample characteristics: mean age, gender.
2) RTMS parameters: frequency, intensity, location, number of treatment sessions and total pulses.
3) The primary outcomes: a. depression: continuous scores assessed by the HAMD.
4) The secondary outcomes: a. Response: Clinically important response was defined as a 50% or more reduction in the baseline HAMD score at the end of treatment. b. Remission: Pre-defined HAMD based remission criteria from each individual trial. c. ADL: measured by Barthel Index (BI) or Modified Barthel Index (MBI). d. stroke severity: measured by NIHSS. e. depression measured by other scales such as, the MARDE, Beck Depression Inventory II(BDI-II), Patient Health Questionnaire-9, and so on.

2.5. Statistical analysis

All statistic work was performed by Review Manager 5.3 and Excel 2013. Two reviewers (Liu, M.Y., Shen, X.Y.) worked independently to identify RCTs that met the inclusion criteria, and extracted data independently, analyzing date with Zhang, L.S. They discussed any disagreements with other authors, Cheng, Y., Pan, X.Y. and Gou, Q.Y. Cheng, Y., Jia, C. and Cao, H. contributed material and analysis tools.

We expressed dichotomous outcomes as odds ratio (OR) and calculated 95% confidence intervals (CIs). We expressed continuous variables as a mean difference (MD) if reported on the same scale as a standardized mean difference (SMD) if reported using different continuous scales and calculated 95% CIs. We employed the approach recommended by the Cochrane Handbook for Systematic Reviews of Interventions (Cochrane Collaboration, Oxford, UK; http://handbook.cochrane.org/), for assessing risk of bias, addressing the domains of sequence generation, allocation concealment, masking, incomplete outcome data, selective reporting and other issues.

Heterogeneity between the studies in effect measures will be assessed using both the χ^2 test and the I^2 statistic. We performed a fixed-effect meta-analysis when no heterogeneity was present. We considered possible explanations where substantial heterogeneity (I^2 statistic above 50%) was detected and where applicable. We used a