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Review article

Bilateral vs. unilateral repetitive transcranial magnetic stimulation in treating major depression: A meta-analysis of randomized controlled trials

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ABSTRACT

Previous studies have demonstrated inconsistent findings regarding the efficacy of bilateral vs. unilateral repetitive transcranial magnetic stimulation (rTMS) in treating major depressive disorder (MDD). Therefore, this meta-analysis was conducted to compare the efficacy of these two rTMS modalities. Data were obtained from seven randomized controlled trials (RCTs) consisting of 509 subjects. Bilateral and unilateral rTMS displayed comparable efficacy in treating MDD with a pooled odds ratios of 1.06 (95% confidence interval (CI)=0.58–1.91) for response rates and 1.05 (95% CI=0.52–2.11) for remission rates. Subgroup analysis found that bilateral rTMS was equally effective in comparison with both left and right unilateral rTMS. No significant differences in drop-out rates were found. No publication bias was detected. In conclusion, the pooled examination demonstrated that bilateral rTMS displays comparable anti-depressant efficacy and acceptability to unilateral rTMS in treating MDD. These findings suggest that simultaneous rTMS of the right and left dorsolateral prefrontal cortices in MDD patients does not provide marginal benefits in terms of efficacy or acceptability. As the number of RCTs included here was limited, further large-scale multi-center RCTs are required to validate our conclusions.

Contents

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1. Introduction

Major depression (major depressive disorder, MDD) is a highly prevalent psychiatric disorder, resulting in substantial personal suffering, disability, and societal costs (Simon, 2003). Despite a vast number of established antidepressant medication options for MDD, a significant percentage of patients (usually estimated to be 30%) fail to respond to first-line treatments (Fava, 2003). These patients are usually referred to as having treatment-resistant depression (TRD). In addition, owing to relapses and recurrences, MDD tends to be a persistent illness (Kennedy et al., 2003). Therefore, there is an urgent need to investigate alternative treatments to reduce the burden of MDD on patients, families, and society at large.

Repetitive transcranial magnetic stimulation (rTMS), as a non-invasive brain-stimulation technique, is being intensively explored as a potential alternative treatment for major neuropsychiatric disorders (Rosa and Lisanby, 2012). RTMS applies rapidly changing electromagnetic fields to induce electrical currents and depolarize neurons, thereby affecting brain activity (George and Post, 2011). When applied repetitively, TMS can increase or decrease cortical excitability depending on the stimulation frequency (Fregni and Pascual-Leone, 2007). Previous studies have found high-frequency rTMS (~5–10 Hz) to be typically excitatory and low-frequency rTMS (< 1 Hz) to be typically inhibitory (Leyman et al., 2011). To date, the primary rTMS treatment approach is to apply high-frequency rTMS over the left dorsolateral prefrontal cortex (DLPFC). Most clinical trials in addition to a number of substantive positive meta-analyses support the anti-depressant effect of this type of rTMS (George et al., 2010; Slotema et al., 2010). More recently, investigators have searched for alternative types of rTMS that may increase response rates and/or decrease side effects such as headaches and seizures. A number of randomized controlled trials have reported that low-frequency rTMS over the right DLPFC displays comparable efficacy to high-frequency rTMS over the left DLPFC (Isenberg et al., 2005; Fitzgerald et al., 2009). Our recently published meta-analysis also showed that left and right rTMS methods were equally effective therapies for MDD (Chen et al., 2013). Moreover, two recent meta-analyses support the efficacy of this type of rTMS compared with sham stimulation (Berlim et al., 2012a; Schutter, 2010). Another novel rTMS treatment protocol for MDD termed bilateral rTMS, the sequential or simultaneous application of low-frequency rTMS over the right DLPFC and high-frequency rTMS over the left DLPFC (Daskalakis et al., 2008), has been reported to be superior to sham stimulation in a recent systematic review (Berlim et al., 2012b).

The efficacy of rTMS is tied to its stimulus parameters (Shi et al., 2014; Xie et al., 2013), and one of the important parameters is the stimulus site. Considerable evidence from neuropsychological, lesion, and imaging studies has shown that the right and left hemispheres have contrasting roles in mood regulation (Silberman and Weingartner, 1987; Mitchell and Loo, 2006; Malhi et al., 2007). It is unclear, however, whether simultaneous stimulation of the right and left hemispheres produces superior antidepressant effects, as studies that have explored the relative efficacy of unilateral (left and right) vs. bilateral rTMS have shown inconsistent results. For example, some studies have reported that bilateral rTMS displays greater antidepressant effects than unilateral rTMS (Blumberger et al., 2012), while other studies have reported that there is no difference in efficacy between unilateral and bilateral rTMS (Pallanti et al., 2010; Fitzgerald et al., 2011). These discrepant findings may be due to a lack of statistical power among some of the individual randomized controlled trials (RCTs) (Maxwell et al., 2008). Therefore, this meta-analysis seeks to examine the efficacy of unilateral and bilateral rTMS in treating MDD. This approach should obtain more accurate results by integrating the findings from multiple studies (Huf et al., 2011).

2. Methods

2.1. Study selection

A selective article search dating up to October 2013 was conducted using scientific and medical databases – including international databases (PubMed, CCTR, Web of Science, Embase), two Chinese databases (CBM-disc, CNKI), and relevant websites – to find RCTs on rTMS in the treatment of MDD. The search terms used were “depression,” “TMS,” “unilateral,” “bilateral,” and “transcranial magnetic stimulation.” No language or year limitation was imposed. To avoid omitting relevant RCTs, conference summaries and reference documents listed in the articles were also researched.

Among the articles identified in the initial search, only those meeting the following criteria were selected for subsequent analysis: (1) RCTs comparing unilateral and bilateral rTMS; (2) MDD patients over 18 years of age without metallic implants or foreign bodies, epileptic seizures, severe suicidal risk, substance abuse, alcohol or drug dependence; (3) informed consent provided; and (4) mood assessed by the Hamilton Depression Rating Scale (HDRS), the Montgomery–Åsberg Depression Rating Scale (MADRS), or the Clinical Global Impression (CGI).

Potential articles meeting any one of the following criteria were excluded: (1) reviews and case reports; (2) subjects with ‘narrow’ or secondary depression diagnoses; (3) non-random allocation; or (4) comparing rTMS with sham or other treatment modalities.

2.2. Data extraction

Two primary authors of this study served as reviewers to independently verify all potentially suitable RCTs by the aforementioned inclusion and exclusion criteria in addition to the completeness of data abstraction. Any disagreement was resolved by consensus and, if needed, a third reviewer was consulted. Data retrieved from the included RCTs were recorded in a structured fashion as follows: (1) sample characteristics (i.e., mean age, gender, mean depression score, treatment strategy used, and presence of treatment-resistant depression); (2) rTMS parameters (i.e., stimulation location, frequency, motor threshold, and duration); and (3) primary outcome measures (i.e., response rate and remission rate). The response rate was chosen as a primary outcome measure, since it was the most consistently reported estimate of acute treatment efficacy (Cipriani et al., 2009). The remission rate was also chosen as a primary outcome measure, being arguably more clinically relevant than response rate (Keller, 2004; Rush et al., 2006). Response was defined as at least a 50% reduction in the absolute HDRS or MADRS score from baseline, or significant improvement in the CGI, at the conclusion of therapy (Hamilton, 1960; Montgomery and Åsberg, 1979); if all three rating scales were used to evaluate the outcome, the HDRS was preferentially selected; (4) Remission was defined according to the definition of remission in each included study. The overall drop-out rate at the conclusion of each study was used as a secondary outcome measure. For data that could not be directly retrieved, good faith efforts were applied to obtain the data by dispatching e-mails to the author, researching other studies citing the RCT in question, and researching associated conference summaries.

2.3. Bias risk in individual studies

Two primary authors of this study (Jianjun Chen and Dan Zhu, Chongqing Medical University) served as reviewers to independently assess the quality of each