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Preliminary communication

Effectiveness and acceptability of accelerated repetitive transcranial magnetic stimulation (rTMS) for treatment-resistant major depressive disorder: An open label trial

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ABSTRACT

Background: Major depressive disorder (MDD) is a significant cause of worldwide disability and treatment resistance is common. High-frequency repetitive transcranial magnetic stimulation (HF-rTMS) has emerged as a treatment for MDD, and while efficacious, the daily commitment for typical 4–6 weeks of treatment poses a significant challenge. We aimed to determine the effectiveness and acceptability of an accelerated rTMS protocol for MDD.

Methods: In this naturalistic trial, 27 patients with moderate to severe chronic and treatment-resistant MDD were treated with twice-daily HF-rTMS (10 Hz) applied over the left dorsolateral prefrontal cortex for 2 consecutive weeks (60,000 pulses). The primary outcomes were rates of clinical remission and response (16-item Quick Inventory of Depressive Symptomatology post-treatment score ≤ 6, and $\geq 50\%$ reduction, respectively). Secondary outcomes were self-reported anxious symptoms, depressive symptoms and quality of life, and dropout rates as a proxy for acceptability.

Results: Ten (37.0%) patients met criteria for clinical remission and 15 (55.6%) were classified as responders, with comparable outcomes for both moderate and severe MDD. Clinician-rated improvements in depressive symptoms were paralleled in self-reported depressive and anxious symptoms, as well as quality of life. No patient discontinued treatment.

Limitations: This study is limited by short treatment duration that might be lengthened with corresponding improvements in effectiveness, limited duration of follow-up, small sample size, and an open-label design requiring randomized controlled replication.

Conclusion: An accelerated protocol involving twice-daily sessions of HF-rTMS over the left DLPFC for 2 weeks was effective in treatment-resistant MDD, and had excellent acceptability. Additional research is required to optimize accelerated rTMS treatment protocols and determine efficacy using sham-controlled trials.

1. Background

Major depressive disorder (MDD) is a significant cause of global disability (WHO, 2008). It typically manifests as a chronic condition, characterized by a relapsing/remitting course and by severe impairment that persists even during periods of remission (Conradi et al., 2011). Treatment-resistance is relatively common in MDD, with up to 20–30% of patients continuing to experience pervasive depressive symptoms despite receiving several adequate trials of medications and/or psychotherapy (Rush et al., 2006).

Once pharmacological and psychotherapeutic approaches have been exhausted, the psychiatric armamentarium includes interventions such as electroconvulsive therapy or psychosurgery that are of limited palatability to the majority of patients. Recently, a novel neuromodulation technique, called repetitive transcranial magnetic stimulation (rTMS), has provided a non-invasive and safe method of stimulating brain parenchyma (George and Aston-Jones, 2010). Due to its overall acceptability to patients, rTMS applied to the dorsolateral prefrontal cortex (DLPFC) has emerged as a viable treatment option for resistant cases of MDD. Indeed, rTMS has demonstrated antidepressive efficacy in numerous double-blind sham-controlled trials, with meta-analyses suggesting that unilateral protocols

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involving high frequency stimulation (HF-rTMS) are associated with a number needed to treat (NNT) of 8 to achieve clinical remission and 6 for clinical response (Berlim et al., 2014).

In recent years there has been growing interest in accelerating the clinical response that is achieved with rTMS, as conventional treatment protocols for MDD usually involve once daily sessions typically administered for 4–6 weeks (Daskalakis et al., 2008). This has spurred interest in condensing the time requirement of such protocols in order to improve accessibility by reducing role disruptions and commuting requirements. There is some evidence that clinical improvement with rTMS may be related to the total number of magnetic pulses delivered, and that offering a temporally accelerated protocol could result in comparable rates of response, without affecting overall acceptability (Holtzheimer et al., 2010). For example, in an open-label study, Holtzheimer et al. (2010) demonstrated a 47% response rate among 14 treatment-resistant depressed patients using an accelerated 2-day HF-rTMS protocol involving 15,000 pulses delivered over 15 sessions. This is somewhat superior to what is typically observed in 4–6 weeks rTMS trials in treatment-resistant MDD (Lam et al., 2008), and this protocol occurred without serious adverse events. Similarly, in another open-label trial, Hadley et al. (2011) provided a 2-week accelerated HF-rTMS protocol (involving a higher number of pulses delivered in once daily sessions [i.e., 6800 pulses/day]) to 19 patients with treatment-resistant MDD. In this study, 33% of patients met criteria for clinical remission at the conclusion of the study.

To date, two randomized, double-blind, sham-controlled trials (RCT) have tested accelerated rTMS protocols in MDD (George et al., 2014; Loo et al., 2007). More specifically, Loo et al. (2007) have shown, in a sample of 40 patients with moderately treatment-resistant MDD, that twice daily active HF-rTMS (involving 1500 pulses per session) was associated with response and remission rates of 31% and 15.7%, respectively (compared with 15% and 9.5% following sham rTMS). Furthermore, this protocol was shown to be highly acceptable to patients, with a dropout rate of only 5% at study end. The second RCT tested the efficacy of accelerated rTMS protocols in acute suicidality in a unique subpopulation, namely 41 depressed patients with concomitant post-traumatic stress disorder, traumatic brain injury or both (George et al., 2014). Though unable to demonstrate efficacy, this RCT clearly demonstrated the safe and well tolerated application (80% retention) of 54,000 pulses delivered over 9 sessions spread over 3–4 days in a severely ill population.

In the current study, we sought to characterize the clinical utility of an accelerated rTMS protocol modeled after Loo et al. (2007), however aimed at improving effectiveness by increasing the total number of magnetic pulses delivered (i.e., from 3000 to 6000/day). Here we report on rates of clinical response and remission, pre-post changes in depressive and anxious symptoms and in quality of life scores in a sample of patients with treatment-resistant MDD who received twice daily sessions of HF-rTMS applied over the left DLPFC for 2 consecutive weeks.

2. Methods

2.1. Patients

Our open-label clinical study was registered at http://www.clinicaltrials.gov (#NCT02125799) and was approved by the Douglas Mental Health University Institute's (DMHUI) Research Ethics Board. Written informed consent was obtained from all participants. Patients were recruited between September 2012 and November 2013 from the Depressive Disorders Program at the DMHUI—a tertiary care outpatient clinic providing specialized follow up for individuals with moderate to severe MDD.

Participants were aged between 18 and 60 years and had a primary diagnosis of a unipolar major depressive episode (MDE) as assessed by the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998). In order to be considered for the study, they had to also have a MDE of at least moderate intensity as determined by the clinician administered 16-item Quick Inventory of Depressive Symptomatology (QIDS-C-16; i.e., a score ≥ 13) (Rush et al., 2003). Moreover, they had to have failed to respond to at least 2 adequate courses of antidepressants (in terms of dose, duration and adherence) in the current MDE as assessed by the Antidepressant Treatment History Form (Sackeim, 2001). A total convenience sample of 28 depressed subjects was recruited. Of these, 27 received rTMS (one participant withdrew prior to beginning treatment).

Patients were not withdrawn from psychotropics, but their doses were required to remain stable in the 4 weeks preceding this trial and for its entire duration. The only exceptions were benzodiazepines (e.g., lorazepam ≤ 3 mg/day) or equivalent, which could be initiated or titrated as required for the management of insomnia.

Exclusion criteria included uncontrolled medical illnesses, the presence of current psychotic features, lifetime history of any non-mood psychotic disorder, lifetime history of bipolar disorder types I or II, current substance or alcohol dependence (within the past 6 months), lifetime neurological disease (e.g., Parkinson's, stroke), pregnancy and/or presence of any contraindication for rTMS (e.g., personal history of epilepsy and metallic head implants).

In order to exclude medical causes of secondary MDD, laboratory investigations were performed (e.g., CBC, electrolytes, urea, creatinine, and hepatic enzymes).

2.2. Instruments evaluation

A psychiatrist (M.T.B.) performed medical and psychiatric assessments as well as safety screenings.

Our primary outcome measure of depressive symptoms was the QIDS-C-16 (Rush et al., 2003). Clinical response was defined as $\geq 50\%$ reduction in QIDS-C-16 scores from baseline to week 3 and clinical remission was defined as a score ≤ 6 at week 3. We also employed the self-report version of the QIDS-16 (QIDS-SR-16 (Rush et al., 2003)).

Anxiety symptoms were assessed using the Beck Anxiety Inventory, a 21-item self-report measure with very good internal consistency in this sample (baseline $\alpha = .93$, after rTMS $\alpha = .92$).

Quality of life was measured using the WHOQOL-BREF (Skevington et al., 2004), a 26 item instrument with good internal consistency in this sample (baseline $\alpha = .87$, after rTMS $\alpha = .86$).

Self-reported side effects were rated using the Frequency, Intensity, and Burden of Side Effects Ratings (FIBSER) scale, a three item scale developed for the STAR*D trial (Wisniewski et al., 2006).

2.3. rTMS treatment

A Magstim Rapid$^{2®}$ magnetic stimulator (Magstim Company Ltd., U.K.) was used with a standard figure-of-eight coil placed over the left DLPFC as determined using the 10/20 EEG system. The resting motor threshold was determined weekly using the visualization method. Patients received two daily sessions of HF-rTMS for 2 weeks (i.e., 20 sessions and 60,000 pulses in total). Stimulation was delivered at 10 Hz in 75 trains with a 26 s inter-train interval at 120% of the resting motor threshold. Every day, the patients received two sessions separated by an hour.