Review Article

Repetitive Transcranial Magnetic Stimulation for Depression Due to Cerebrovascular Disease: A Systematic Review

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Objective: This study aims to perform a systematic review evaluating the effectiveness of repetitive transcranial magnetic stimulation (rTMS) in improving depression resulting from cerebrovascular disease including vascular depression (VD) and poststroke depression (PSD). *Methods:* A literature search of multiple scientific databases was conducted for English studies published from January 1980 to June 2016. Studies were included if the sample consisted of 50% or more adult humans with VD or PSD and had 3 or more subjects, the intervention applied was rTMS, and depression was assessed pre- and post intervention using a formal outcome measure. Randomized controlled trials (RCTs) were assessed for methodological quality using the Physiotherapy Evidence Database (PEDro) tool. A level of evidence was assigned to each study according to the modified Sackett Scale. *Results:* Five studies met the inclusion criteria including 3 RCTs (level 1b; PEDro range: 6-8) and 2 uncontrolled pre–post studies (level 4). There were 186 participants with either PSD (n = 40) or VD (n = 146); the majority of the participants were female (52.7%) and had a mean age ranging from 51.9 to 67.9 years. There were no adverse effects reported by any of the studies. Using clinically accepted criteria for the response rate, all studies reported a benefit from rTMS for the treatment of depression. Three studies also demonstrated a benefit on remission rates as well. *Conclusions:* rTMS was reported to be beneficial in treating depression among individuals with cerebrovascular disease over the short term. However, heterogeneous populations and variability in study design and protocol, as well as a limited number of studies to review, challenge the ability to form conclusions as to the effectiveness of rTMS. **Key Words:** rTMS—repetitive transcranial magnetic stimulation—depression—cerebrovascular disease—vascular—stroke.

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Introduction

Depression is well documented among individuals with cerebrovascular disease, including poststroke depression (PSD) and vascular depression (VD). The definition of VD involves major depressive disorder (MDD) according to the *Diagnostic and Statistical Manual of Mental Disorders*[1] with onset at the age of 50 or more, with a history of subcortical stroke or at least three of the following cardiovascular risk factors: arterial hypertension, diabetes mellitus, obesity, hyperlipidemia, and smoking. The criteria for VD are met by 54% of individuals with

late life depression.[2] Stricter criteria for this illness are referred to as magnetic resonance imaging (MRI)-defined VD and require a score of 2 or more on the deep white matter or gray matter hyperintensities on the Coffey-modified Fazekas rating scale.[2,3] Depression can develop after individuals have had a stroke; however, individuals do not necessarily have to meet the aforementioned VD risk factor criteria. A systematic review reported that symptoms of depression have been reported in as much as 30% of a poststroke population living in the community.[4] More specifically, MDD has been shown to be prevalent in up to 23% of individuals in another poststroke community sample.[5]

The combination of cerebrovascular disease and depression cannot be understated; this comorbidity results in greater functional limitations than either impairment alone.[6] PSD has been associated with reduced quality of life[7] and decreased treatment efficacy during rehabilitation,[8] as well as increased mortality.[9] In addition to these consequences, management of PSD and VD may be compounded by improper screening with subsequent undertreatment.[10] Currently, pharmacotherapy is the most commonly prescribed and effective treatment option for major depression of all etiologies, despite the fact that approximately 30% of depressed individuals have treatment-resistant depression.[11] For individuals with PSD and VD, pharmacotherapy may be associated with increased risk of mortality and subsequent stroke.[12] Therefore, these individuals may require novel alternative or adjunctive treatments to optimally manage the condition.

Repetitive transcranial magnetic stimulation (rTMS) has gained considerable interest in the clinical treatment of depression. rTMS was originally introduced in 1986 as an alternative noninvasive central nervous system stimulation treatment.[13] This form of stimulation involves applying a magnetic field to the surface of a patient's head to induce an electric current at the brain; a series of magnetic pulses are delivered during a single rTMS session. Compared to other forms of stimulation, it is has been shown to deliver comparable, but not superior, therapeutic effects as electroconvulsive therapy (ECT) in reducing depressive symptoms.[14] However, ECT has been shown to produce affect cognition,[15] whereas rTMS has been shown to be well tolerated and cognitively benign.[16] In non-CVD populations, rTMS may be favorable compared to pharmacological agents but not ECT; optimal rTMS parameters for treating depression have not yet been determined.

A recent systematic review and meta-analysis examined randomized, double-blind, sham-controlled trials to quantitatively evaluate the efficacy of high-frequency rTMS for MDD.[17] Among the 29 randomized controlled trials (RCTs) included, the overall response rate was high among those receiving active rTMS (29.3%) compared to those in the sham group (10.4%); further, the odds ratio for pooled studies was 3.3 ($P < .0001$) for both the response and remission rates.[17] Positive findings have also been established in various neurological populations, such as Parkinson's disease, where depressive symptoms were reduced with the use of rTMS.[18] To our knowledge, the examination of the effectiveness of rTMS on depression due specifically to cerebrovascular disease as a unique group, including PSD and VD, has yet to be conducted. Hence, the objective of the current study is to systematically review the effect of rTMS on PSD and VD.

Materials and Methods

Literature Search

A literature search of multiple databases (i.e., PubMed, CINAHL, Scopus, Cochrane, and EMBASE) was conducted for English articles published between January 1980 and June 2016. Keywords used for the search included *repetitive*, *transcranial magnetic stimulation*, *rTMS*, *cerebrovascular disease*, *stroke*, *vascular*, *depression*, *biopolar*, *biopolar depression*, *mood disorder*, and *emotional disorder*. Variations of keywords were tailored to each scientific database. Additional references were retrieved by reviewing the references of all relevant articles included for analysis.

Study Selection

Studies were included if they satisfied the following 4 a priori inclusion criteria:

1. There were 50% or more adult humans with VD or PSD.
2. The sample size included 3 or more subjects.
3. The intervention provided was rTMS.
4. Depression was assessed pre- and post intervention using an outcome measure or clinically defined outcomes (e.g., response and remission rates).

A physician (A.B.) trained in the administration of rTMS reviewed each study protocol to ensure that it was conducted appropriately. There were no specified criteria in terms of the timing or intensity of therapy. Because the application of rTMS has not been approved for the treatment of depression in many countries, studies were not excluded if concomitant therapy with an antidepressant drug was used by patients. Studies were not excluded based on research design. However, when information on subject demographics, research design, intervention, and results could not accurately be extracted from the article, it was excluded.

Study Appraisal

Two independent reviewers (A.M.c. and S.T.) evaluated the methodological quality of all RCTs using the Physiotherapy Evidence Database (PEDro) scoring system.[19] The PEDro has been shown to be a more comprehensive measure of methodological quality for trials in the stroke rehabilitation literature compared to others such