Repetitive transcranial magnetic stimulation in the management of poststroke depression

Amgad A.M. Gabr[a], Mohamed Hamed[b], Mohammad Abdul-Fattah[c]

Departments of [a]Psychiatry, [b]Neurology, Faculty of Medicine, Al-Azhar University, Cairo, [c]Department of Neurology, Faculty of Medicine, Misr University for Science and Technology, October City, Giza, Egypt

Correspondence to Amgad A.M. Gabr, MD, Al Mokhaym Al Daem, Al Azhar Unversity, Nasr City, Cairo Governorate 11751, Egypt. Tel: +201004122696; fax:+20222602687; e-mail: dr.amgdgabr@gmail.com

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Background
Poststroke depression (PSD) occurs in nearly 33% of stroke survivors. Noteworthy, PSD might lead to severe consequences such as functional disability, poor rehabilitation outcomes, and quality of life, which in turn contribute noticeably to suicidal tendencies, restroke occurrence, and high mortality rate among survival patients.
Aim
This study was performed to show the psychiatric outcomes of repetitive transcranial magnetic stimulation (rTMS) in the management of PSD survivors.
Patients and methods
Patients with clinical and neuroradiological evidence consistent with either brainstem, hemispheric, or cerebellar ischemic stroke were included in this study. Hamilton depression rating scale and Beck depression inventory scores were performed for psychiatric assessment of these patients.
Results
In all, 40 patients were included in this study who developed PSD and fulfilled the eligibility criteria. There were 22 (55%) women and 18 (35%) men with a mean age of 64.1±9.3 years. All patients suffered from depression, 13 (32.5%) from severe depression, 27 (67.5%) have a complete response to rTMS not only at the end of the treatment protocol, but also after a month from the cessation of rTMS. There was a statistically significant difference regarding the levels of Hamilton depression rating scale 17 Beck depression inventory scores at baseline, end of treatment, and one month after the stoppage of treatment.
Conclusions
This study showed that rTMS is an effective, safe, and promising therapeutic treatment, mostly for severely depressed patients after stroke.

Keywords:
depression, repetitive trans cranial magnetic stimulation, stroke

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Introduction

Stroke is the most leading cause of adult disability, especially in developing countries [1]. The number of stroke-related deaths is nearly 6.5 million worldwide in 2015. Of them, ~46% died as a sequel of ischemic stroke [2].

Stroke is associated with a wide range of morbidities [1]. Poststroke depression (PSD) is a consequence that occurs in nearly 33% of the stroke survivors [3]. Additionally, PSD may occur as a result of minor stroke or transient ischemic attack. Noteworthy, PSD might lead to severe consequences such as functional disability, poor rehabilitation outcomes, and quality of life, which in turn contribute noticeably to suicidal tendencies, restroke occurrence, and high mortality rate among survival patients [4].

In contrast, PSD is associated with complicated pathpsychiatric mechanisms apart from psychiatric issues. These factors might be considered as an eventual impact of neurochemical and functional alterations secondary to brain damage associated with stroke [5]. Prevention of PSD and its potential complications needs the integration of family members, society, and psychiatrists [6].

Antidepressant drugs were the best standard treatment for PSD. On the contrary, they are not associated with the desired benefits. In detail, these drugs take at least 1 month to produce a significant clinical response; subsequently, its efficacy is only 50% with a small proportion of remission (30%) [7]. It was reported that some antidepressive drugs are associated with a high risk of stroke recurrence [7]. Electroconvulsive therapy was an alternative therapy for antidepressive drugs; however, it outraged the cognitive disability among stroke survivors. Thereafter, there was a continuous demand do develop a further effective and safe therapeutic method for PSD [6]. Currently,

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repeated transcranial magnetic stimulation (rTMS) is considered to be an effective treatment for PSD [8].

Noteworthy, rTMS is a successful noninvasive brain stimulation technique. It targeted the distributed brain networks that contributed to the pathogenesis of depression, using rapidly alternating or pulsating, and short-duration magnetic field to generate electrical currents directed to spatially discrete regions of the cerebral cortex [9]. Therefore, rTMS can be implemented painlessly to conscious patients and can be applied as an inpatient or outpatient procedure. Moreover, rTMS neither need anesthesia nor associated with seizures if applied safely [10].

This study was performed to reveal the psychiatric outcomes of rTMS in the management of PSD and its impact on the quality of life subsequently.

Patients and methods

It is a prospective study which was conducted at the Psychiatry Department in coordination with the Neurology Department, Al-Azhar University Hospitals, from September 2016 to April 2018. All clinical and interventional procedures were conducted in accordance with the Declaration of Helsinki and Ethics Research Board approval was assented from the Ethics Unit, Faculty of Medicine, Al-Azhar University before conduction of the study. Confirmed written consents were obtained from the included patients after a clear illustration of the possible benefits and adverse events of intervention.

Eligibility criteria

Patients with clinical and neuroradiological evidence consistent with brainstem, hemispheric, cerebellar ischemic stroke, whereby the lesion was cortical, subcortical of the right hemisphere or posterior cortical or subcortical of the left hemisphere were included in the study. Patients with hemorrhagic stroke or those who had cortical lesions of the left frontal cortex were excluded in order to avoid the risk of seizures associated with rTMS. Severe depression was clarified if the onset of depression preceded the onset of stroke with a significant progression of the depression course. Additionally, patients failed to respond to at least two antidepressant drugs given in an equal dose were considered severely depressed. The diagnosis of severe depression was done using the Diagnostic and Statistical Manual of Mental Disorders-IV (DMS-IV) and Beck depression inventory (BDI) scores.

On the other hand, patients with an intense systemic disorder or neurodegenerative diseases or dementia, or severe aphasia were excluded from the study. Subsequent to that, depressed patients with active suicidal tendencies, those with noticeable psychotic features, or bipolar course were omitted. Patients with drug or alcohol abuse within a year prior to study conduction were excluded. Patients with a history of treatment-induced seizures, idiopathic epilepsy, and major head trauma were excluded. Eventually, patients with metal in the brain, cranial cavity, or skull or those with cardiac pacemaker, or implanted defibrillator were excluded.

Data collection

All patients were subordinated to painstaking history and clinical evaluation by a psychiatrist and a neurologist to achieve the highest levels of quality. This includes the retrieval of the following data: patient's age, sex, marital status, education level, evidence of systemic or neurodegenerative diseases along with the coexisting morbidities such as diabetes, hypertension, smoking, or obesity. The severity of stroke was assessed using the National Institutes of Health Stroke Scale scores. Besides that, MRI was implemented for all participants at the beginning of the study.

Assessment of poststroke depression

The psychiatric diagnosis was done based on the Present State Examination (PSE) which was modified to identify DMS-IV manifestations of depression and anxiety [11]. Additionally, Hamilton depression rating scale (HAM-D), which constituted of 17 items, presented a reliable method to assess the severity of depression manifestations among stroke survivors. In particular, the higher the score, the greater, the level of depression. Additionally, BDI scores were used, whereby patients scored greater than 12 were considered severely depressed [12]. The patients' quality of life was assessed using the World Health Organization Quality of Life-Brief Version questionnaire.

Mini-mental state examination

It evaluated the overall assessment of cognitive function as regards its association with extensive memory testing and cognitive decline among COPD patients. Patients were given a score of between 0 and 30, whereby patients scored greater than 24 were considered of normal cognitive function [13,14].

The protocol of repetitive transcranial magnetic stimulation

Of note, rTMS was performed via a Magstim Super Rapid Stimulator (Jali Medical Inc., Wellesley Hills, Massachusetts, USA) and 70 mm, 8-shaped butterfly coils. Active rTMS was delivered over the left prefrontal cortex at a frequency of 10 Hz, an intensity of 110% of the motor threshold, duration of 5 s, and total of 20 trains

separated by 60 s pauses, five sessions weekly for 4 weeks. Prior to each session, each patient's motor threshold was determined in order to identify the optimal rTMS dose. All patients were strictly observed for early detection of muscle twitching in close temporal relationship to the magnetic stimulus. All patients and investigators wore earplugs to prevent hearing damage.

The response to rTMS was clarified when the total score of HAM-D decreased by 50% coupled with the unfulfillment of DMAS-IV criteria for PSD. In this respect, remission was recognized as a decline of HAM-D scale of at least 50% with a final score of less than 8.

Follow-up protocol

All patients were assessed at the baseline (the day of study enrollment), at the end of the treatment, and after 1 month from cessation of treatment.

Statistical analysis

Normally distributed data were notified as a mean and SD. Nonnormally distributed data were reported using median and range. Qualitative variables were expressed in the form of number and percentage. Repeated measures analysis of variance test was used succeeded by post-hoc test to examine the significant difference between the outcomes at the baseline, at the end of treatment, and after 1 month from the cessation of treatment. Two-sided *P* value was considered significant at a value of less than 0.05. Data synthesis was performed using SPSS v.23 software (IBM SPSS Statistics; IBM Corp., Armonk, New York, USA), and figures were renewed using GraphPad Prism (GraphPad Software Inc., San Diego, California, USA) software version 7.

Results

Patients' demographic characteristics

This study included an overall 40 patients who developed PSD and fulfilled the eligibility criteria. There were 22 (55%) women and 18 (35%) men with a mean age of 64.1±9.3 years. Regarding the comorbidities, there was 38 (95%) and 18 (45%) patients who had hypertension and diabetes mellitus, respectively. Additionally, there were 15 (37.5%) obese patients. The mean duration since the previous stroke was 9.49±4.1 years with a median NIH stroke scale of 1.87 (0.6–3.69) (Table 1).

There were 33 (82.5%) patients who had major depressive features, whereby 12 (30%) patients had a family history of mood disorders. The duration of the current depression episode was 19.4 (2–37.1) weeks. Additionally, the mean HAM-D 17 baseline score was 27.1±8.01, whereas the mean mini-mental state examination score was 27.1±4.02 (Table 2).

Table 1 Patients demographic characteristics

Variables	Mean±SD)/*n* (%)
Age	64.1±9.3
Gender: female	22 (55)
Marital status: married	35 (87.5)
Comorbidities	
Smoking	9 (22.5)
Hypertension	38 (95)
Diabetes mellitus	18 (45)
Obesity	15 (37.5)
Dyslipidemia	34 (85)
Previous stroke-related data	
Time since stroke	9.49±4.1
NIH stroke scale	1.87 (0.6–3.69)

HAM-D, Hamilton depression rating scale; NIH, National Institutes of Health.

Table 2 Baseline psychiatric assessment

Variables	Mean±SD/*n* (%)
Baseline HAM-D 17 score	27.1±8.01
Family history of mood disorders	12 (30)
Duration of current episode (weeks)	19.4 (2–37.1)
Major depressive features	33 (82.5)
MMSE	27.1±4.02

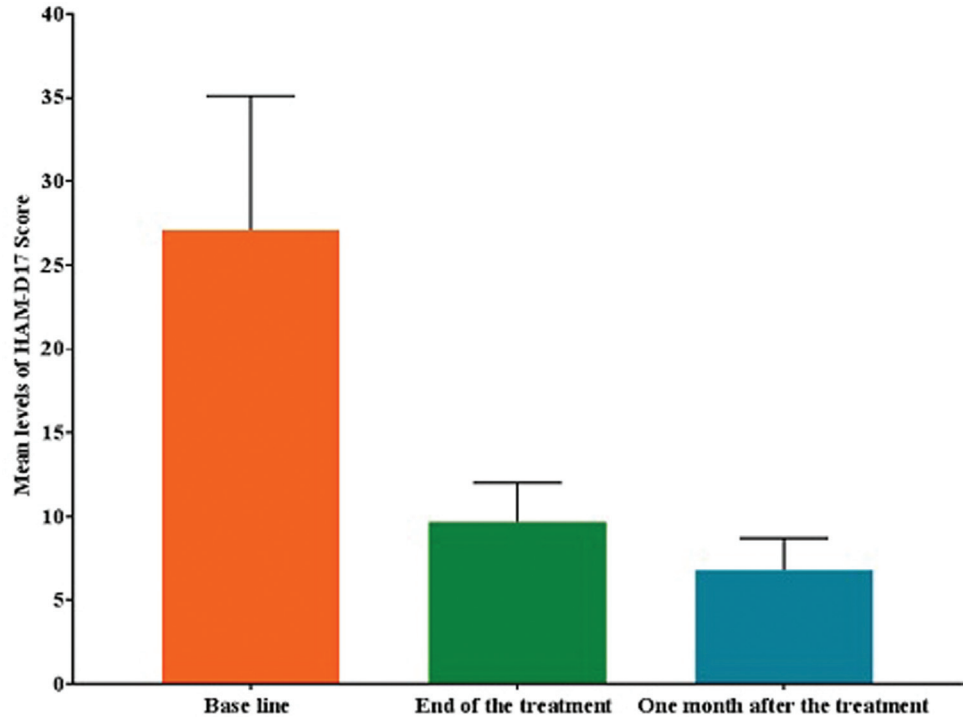
HAM-D, the Hamilton depression rating scale; MMSE, mini-mental state examination.

Outcomes of repetitive transcranial magnetic stimulation

Of note, all patients suffered from depression, 13 (32.5%) of severe depression, 27 (67.5%) experienced a complete response to rTMS not only at the end of the treatment protocol, but also after a month from the cessation of rTMS. In this respect, there was a statistically significant difference ($P<0.001$) regarding the levels of HAM-D17 score with a mean of 27.1±8.01, 9.67±2.35, and 6.8±1.905 at baseline, end of treatment, and 1 month after the cessation of treatment (Fig. 1). Similar to that, the mean score of BDI significantly decreased ($P<0.001$) at the end of treatment (11.18 ±3.06) and at 1 month after the cessation of treatment (9.21±1.14), in contrast to the mean level at the baseline (23.01±6.2) (Fig. 2). The mean levels of World Health Organization Quality of Life-Brief Version score increased significantly ($P<0.001$) 1 month after the cessation of rTMS (67.9±18.09), in contrast to the mean levels at the baseline (19.7±8.105) and at the end of treatment (49.1±12.62) (Fig. 3, Table 3).

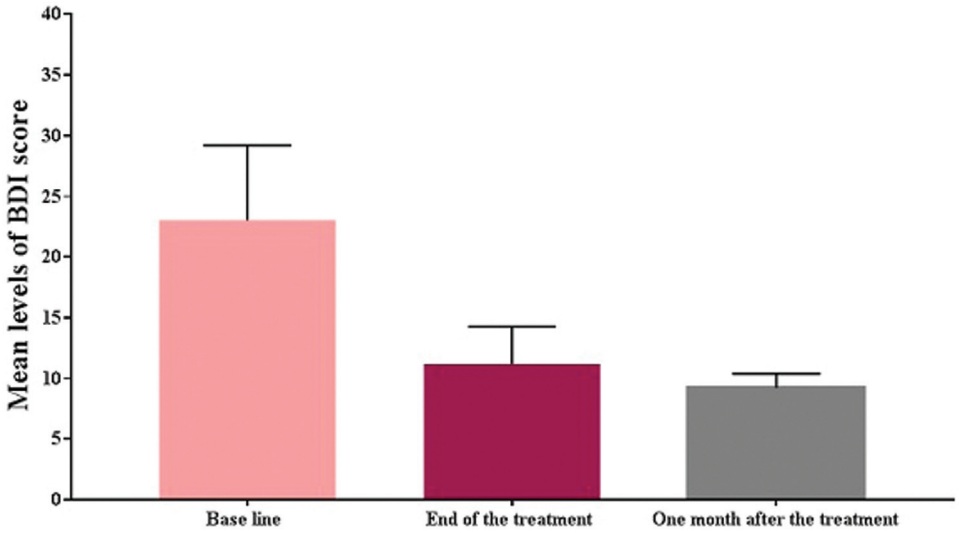
Having post-rTMS complications, 10 (25%) patients suffered from transient headache, whereby seven (17.5%) and three (7.5%) patients had local discomfort and exacerbation of initial insomnia, respectively (Table 4).

Figure 1



Error bar chart displayed the mean differences of Hamilton depression rating scale 17 score at different assessment periods.

Figure 2



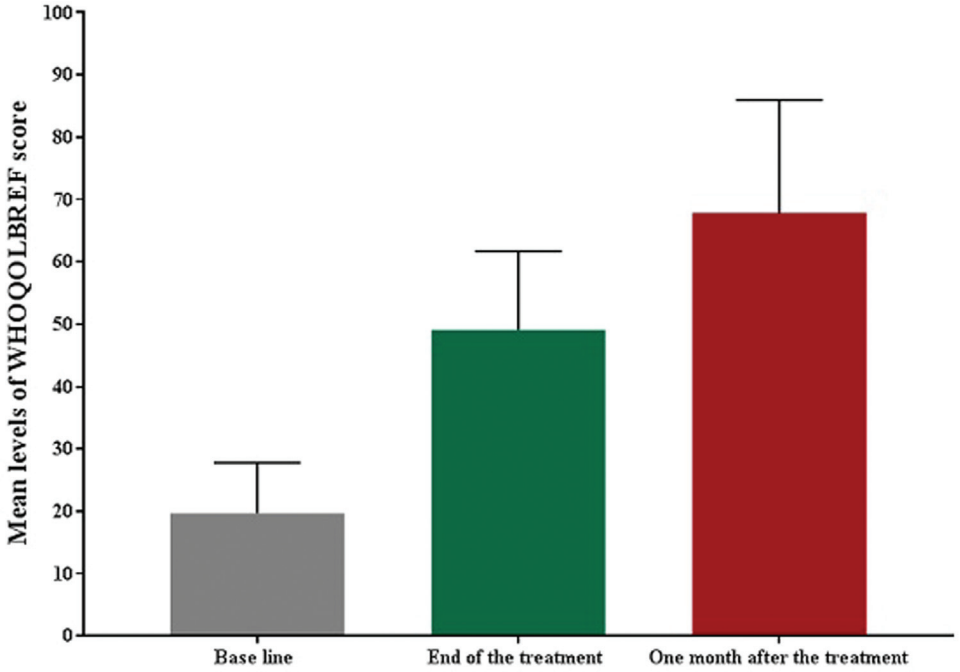
Error bar chart displayed the mean differences of Beck depression inventory score at different assessment periods.

Discussion

Depression is a life-threatening and often neglectable sequel of stroke, despite its effects on rehabilitating, quality of life, and mortality rates among poststroke survivors [15]. Herein, safe and effective treatment strategies for controlling PSD manifestations are extremely important to boost the psychiatric and physical outcomes among stroke survivors [16]. There was plenty of treatment approaches in the management of PSD; however, the majority of these strategies are often not associated with the expected functional and psychiatric outcomes [17]. Thereafter, the present study was performed to reveal the psychiatric outcomes and their impact on the overall quality of life of rTMS in the management of PSD among stroke survivors.

The current investigation showed that rTMS is an effective treatment in the management of PSD which was established based on clinical manifestations, HAM-D17, and BDI scores, which eventually had a considerable impact on the quality of life. These

Figure 3



Error bar chart displayed the mean differences of World Health Organization Quality of Life-Brief Version score at different assessment periods.

Table 3 Functional outcomes of repetitive transcranial magnetic stimulation

Variables	Baseline [*n* (%)]	End of the treatment [*n* (%)]	1 month following the treatment [*n* (%)]	*P* value
Depressed patients	13 (32.5)	0 (0)	0 (0)	_
Severely depressed patients	27 (67.5)	0 (0)	0 (0)	_
HAM-D17 score	27.1±8.01	9.67±2.35	6.8±1.905	<0.001
BDI score	23.01±6.2	11.18±3.06	9.21±1.14	<0.001
WHOQOLBREF score	19.7±8.105	49.1±12.62	67.9±18.09	<0.001

BDI, Beck depression inventory; HAM-D, Hamilton depression rating scale; WHOQOLBREF, World Health Organization Quality of Life-Brief Version.

Table. 4 Postrepetitive transcranial magnetic stimulation complications

Variables	*n* (%)
Transient headache	10 (25)
Local discomfort	7 (17.5)
Exacerbation of initial insomnia	3 (7.5)
Seizures	0 (0)

prospective results continued even after cessation of the treatment and the presence of mild adverse events.

In 2008, rTMS was approved as a therapeutic option of major depression in the USA. Since then, it has been widely applied, principally among patients who did not respond adequately to traditional treatments [18]. Noteworthy, PSD is linked to the frontal lobe and basal ganglia lesions, white matter hyperintensities, and disruption of the connecting pathways. Besides that, PSD is associated with the decline of the concentration of serum and plasma brain-derived neurotrophic factor [19,20].

The effectiveness of rTMS might be evolved owed to several factors. In detail, rTMS can promote fractional anisotropy value, stimulate the left frontal lobe, increase the concentrations of brain-derived neurotrophic factor, and enhance the reconstruction of the destructed neural network, which ultimately restores the neuronal structure. Despite these explanations, detailed mechanisms of the efficacy of rTMS have not been completely understood [21].

In compliance with our results, Shen *et al.* [22] conducted a meta-analysis comprehending a total of 1764 patients who developed PSD and treated by rTMS and reported that rTMS significantly improved HAMD scale [mean deviation (MD)=−6.09, 95% confidence interval (CI):−7.74,−4.45, $P<0.001$], remission rates (odds ratio: 0.99, 95% CI: 0.56, 1.75, $P<0.00001$), and activities of daily living (SMD=−1.20, 95% CI: 0.68, 1.72, $P<0.001$). In this respect, da Silva Júnior *et al.* [23] showed that rTMS was noticeably effective in

decreasing the PSD manifestations and that reflected dramatically in the patients' quality of life. Similarly, Gu *et al.* [24] showed that rTMS accomplished effectiveness in the management of PSD superior to sham treatment regarding BDI ($P<0.05$) and HAM-D17 ($P<0.017$) scores.

Regarding the safety of rTMS, there was a small proportion of post-management complications; however, all of them were mild and temporary and relived either spontaneously or by low doses of analgesics in case of transient headache. This pattern of complications was in line with Jorge *et al.* [25].

Liu *et al.* [26] conducted a meta-analysis of 17 clinical trials which included 1171 patients and revealed that rTMS significantly improved the clinical symptoms of PSD [Standard deviation (SD),−1.01; 95% CI: −1.36 to −0.66; $P<0.001$]. Additionally, patients treated by rTMS were more susceptible to headache relative to the control group (odds ratio: 3.53; 95% CI: 1.85–8.55; $P<0.001$).

The current study had some limitations. In particular, the relatively small sample size and the lack of randomization which may lead to selection bias. Additionally, the relatively short follow-up period limited our capability to evaluate the long-term psychiatric and functional outcomes of rTMS. Thereafter, it is necessary to implement further randomized clinical trials to address the potential limitations of our investigation.

Conclusion

This study provided an effective, safe, and promising therapeutic option, especially for severely depressed patients after stroke and these advantages were sustained for at least 1 month after cessation of the treatment. Besides that, the use of rTMS reflected dramatically in the quality of life.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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