Repetitive Transcranial Magnetic Stimulation Improves Depressive Symptoms and Quality of Life of Poststroke Patients—Prospective Case Series Study

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Hercílio Barbosa da Silva Júnior[1], Marcos Rassi Fernandes[1] and Ângela Maria Costa Souza[2]

[1]Medicine Faculty, Federal University of Goiás, Goiânia, Brazil. [2]Dr. Henrique Santillo State Rehabilitation Centre (CRER), Goiânia, Brazil.

ABSTRACT

BACKGROUND: Poststroke depression (PSD) is a serious psychiatric complication often reported after a stroke. Nearly a third of stroke survivors experience depressive symptoms at some point, affecting their functional recovery and quality of life. In recent years, repetitive transcranial magnetic stimulation (rTMS) has been studied by many researchers and found to be a safe supporting tool for the treatment of PSD.

OBJECTIVE: We aim to evaluate the effects of rTMS on PSD and on the quality of life of poststroke patients.

METHOD: A prospective clinical case series, performed at CRER Rehabilitation, Brazil, between June 2016 and May 2017. A nonprobabilistic sample (n = 15) was divided into 2 groups (excitatory stimulation in F3, n = 8; inhibitory stimulation in F4, n = 7) and underwent 20 sessions of rTMS. Individuals were assessed according to the 17-item Hamilton Depression Rating Scale (HAM-D17) and World Health Organization Quality of Life-Brief Version (WHOQOL-BREF) questionnaire at 3 different moments: baseline, at the end of the treatment, and in a 1-month follow-up meeting.

RESULTS: Both groups presented a significant change in the score of all WHOQOL-BREF domains and in HAM-D17. In the group that received inhibitory stimulation (F4), score changes were continuous and gradual, comparing the 3 moments. In the excitatory stimulated (F3) group, however, the improvement in scores was more expressive between baseline and the second moment, without significant changes in the follow-up.

CONCLUSIONS: The findings of this clinical study suggest that rTMS can be a promising tool, capable of relieving depressive symptoms and helping in the improvement of poststroke patients' quality of life.

KEYWORDS: Transcranial magnetic stimulation, depression, stroke, quality of life

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CORRESPONDING AUTHOR: Hercílio Barbosa da Silva Júnior, Medicine Faculty, Federal University of Goiás, Rua Pedro José de Carvalho, 241, Centro, Nerópolis, Goiânia 75460-000, Goiás, Brazil. Email: herciliopsi@gmail.com

Introduction

Poststroke depression (PSD) is a psychiatric complication that occurs in nearly one-third of the cases of stroke survivors, eventually, affecting their functional recovery and quality of life.[1] Poststroke depression may be associated with increased physical disabilities, cognitive and social impairment, poorer outcome in motor rehabilitation, poor quality of life, and increased risk of recurrence of stroke or suicide.[2-7]

Antidepressants, especially selective serotonin reuptake inhibitors (SSRIs), are indicated as the primary therapeutic intervention, even though their benefits are not expressive in PSD remission.[8] In addition to that, recent studies have shown that the use of tricyclic antidepressants (ADTs) and SSRIs may increase the risk of stroke recurrence in some patients.[9]

In 2008, the Food and Drug Administration of the US Health and Human Services Department approved repetitive transcranial magnetic stimulation (rTMS) as a safe tool for the treatment of depression in patients who have not found relief from antidepressant medication.[10] Regarding PSD, some significant evidence of the effectiveness of rTMS has been reported[11] but further studies are required to validate protocols.

The rTMS is a noninvasive neuromodulation and neurostimulation technique capable of modulating excitability between the cerebral hemispheres.[12] Among its benefits, rTMS is relatively painless, noninvasive, simple to apply, and presents low risk for research with human beings.[13] Barker and his team demonstrated this technique for the first time in 1985, in Sheffield, England.[14] Since its discovery, scientists around the world are studying rTMS effects for treatment in psychiatry, neurology, and perhaps other clinical specialties, such as depression.[15] Depending on the frequency—measured in Hertz—rTMS can result in inhibitory or excitatory effects. The low-frequency rTMS (≤1 Hz) is commonly used to decrease cortical excitability, whereas the high-frequency rTMS (≥5 Hz) is used to stimulate it.[16]

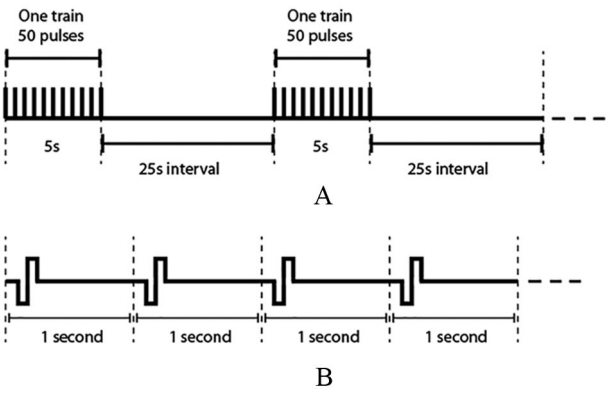

Figure 1. (A) The rTMS excitatory protocol—10 Hz on the left DLPFC (F3) using 100% to 110% of motor threshold—20 minutes session: 40 trains, 50 pulses per train, 2000 pulses in total. (B) The rTMS inhibitory protocol—1 Hz on the right DLPFC (F4) using 80% to 90% of motor threshold—20 minutes session: 1 stimulus per second (1200 pulses in total). DLPFC indicates dorsolateral prefrontal cortex; rTMS, repetitive transcranial magnetic stimulation.

In this study, we applied and compared 2 different protocols using high- or low-frequency rTMS depending on the location of the brain lesion. Our aim was to evaluate the effects of rTMS on PSD symptoms and its impact on the quality of life of poststroke patients.

Methods

This was a prospective clinical case series, performed at the Neuromodulation Laboratory of the Dr. Henrique Santillo State Rehabilitation Centre (CRER), in the state of Goiás, Brazil, from June 2016 to May 2017.

Charts review and patients' selection

The charts review included patients registered on the internal management system of CRER. All patients registered to the system were previously assessed by the multidisciplinary staff and then referred to the waiting list of the proper care department. To find the subjects of this study who would undergo treatment for depression using rTMS, we looked for the charts of those who were waiting for psychiatric outpatient treatment. We searched through the system using the keywords "depression" and "stroke."

Among these patients, we recruited the ones (a) with a history of stroke either in the right or left hemispheres, (b) at least 6 months past the stroke episode, (c) confirmed by nuclear magnetic resonance, (d) aged between 21 and 80 years, (e) diagnosed with Major Depression Disorder according to *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.; *DSM*-V) criteria, and (f) with absence of severe cognitive dysfunction or aphasia.

We considered patients those who (a) scored ⩽18 on the 17-item Hamilton Depression Rating Scale (HAM-D17), (b) were already on outpatient therapy at any other department of CRER, (c) had other psychiatric or neurological disease associated with stroke, (d) had a history of epilepsy, (e) had any metal in their skull or a cardiac pacemaker, (f) had a history of depression before stroke, and (g) underwent previous treatment with rTMS as ineligible for the study.

The rTMS intervention was discontinued for patients who (h) presented nontolerance to the stimulation side effects and (i) attended less than 75% of the treatment program sessions.

Clinical assessments

After the charts review, all preselected patients underwent a more detailed clinical evaluation by a neuropsychologist prior to the first day of treatment. They were interviewed about their medical records, considering the selection criteria of this study. They were offered a treatment with rTMS, and after receiving a full explanation of the study and its procedures, the selected patients, who met all the inclusion criteria, signed a written informed consent statement approved by the ethics committee.

All selected subjects for this study were assessed at baseline, at the end of the treatment, and during a follow-up meeting 1 month following the treatment. Poststroke depression was measured using HAM-D17, which was applied as an interview. The instrument evaluates the intensity of depressive symptoms, meaning that the higher the score, the greater the level of depression. Response to the treatment was considered if there was an improvement in at least 13 points from the baseline score. Remission was considered for scores ⩽7. The patients' quality of life was measured using the WHOQOL-BREF questionnaire. This instrument's score ranges from 0 to 100, meaning that the higher the score, the better the patient's quality of life level. WHOQOL-BREF was applied as a self-administered questionnaire.

In this series, baseline HAM-D17 and WHOQOL-BREF scores were used as the primary outcome measure. The following assessment scores (end of treatment and follow-up) were used as secondary outcomes measurement.

The rTMS procedures

The rTMS was delivered using a high-speed magnetic neuro stimulator (Neurosoft Company, Neuro/MS, Russia) equipped with a figure-8-shaped coil and intermittent cooling. The protocol consisted of 20 rTMS sessions, each one lasting 20 minutes. The protocol was ministered by the physician responsible for the neuromodulation laboratory of CRER for 4 weeks (1 session per business day).

The nonprobabilistic sample was divided into 2 groups with different treatment frequencies (Figure 1), excitatory (10 Hz), or inhibitory (1 Hz), according to the location of the injury. When the patient's lesion was located in F3—left dorsolateral prefrontal cortex (DLPFC)—or in regions near that target, we applied the low-frequency protocol (inhibitory), with 1 Hz on F4—the right DLPFC—using 80% to 90% of the motor

threshold (MT) and 1 stimulus per second with no interval in between (1200 pulses in total). When the injury was on the right hemisphere or in other regions that were not F3, the high-frequency protocol (excitatory) was applied, with 10 Hz on F3, using 100% to 110% of MT, at 25 second intervals, stimuli every 5 seconds, and trains of 50 pulses (2000 pulses in total). Both protocols are based on a previous study conducted by Ciobanu et al.[17]

The respective targets, F3 or F4, were located using electroencephalography parameters and the international 10 to 20 system. The intensity of the stimulus was defined using the MT, which is the minimum of intensity necessary to produce visible movements of the contralateral hand musculature in at least 3 of 5 simple pulses applied to the motor cortex. There was no other therapy going on during the rTMS sessions.

Independent variables were as follows: (a) age—in years, (b) sex—male/female, (c) marital status—with/without partner, (d) injury time—from 7 months to 15 years, (e) number of children—none/1 or 2, and (f) type of intervention—F3-stimulation or F4-inhibition.

Statistical Analysis

The software used to analyze all collected data was Statistical Package of Social Sciences (SPSS 23.0). General characteristics of the group were presented by means of absolute and relative frequency for qualitative variables and mean/standard deviation and median/interquartile range for continuous variables. We applied nonparametric statistical tests, considering the data set conditions (assumptions) which were not sufficient for an eventual use of parametric tests, such as Shapiro-Wilk test for normality, for example.

The reliability of the WHOQOL-BREF questionnaire was tested by Cronbach alpha coefficient (α) to verify the internal consistency of the instrument for the studied sample. Before and after the intervention, the Friedman test followed by the Wilcoxon test—represented by letters, in which different letters indicated significant differences—was used for comparing the quality of life and Hamilton Depression Rating Scale (HAM-D) scores. The clinical status comparison with the HAM-D score was performed based on the χ^2 test. The level of significance was 5%.

Regarding the ethical aspects, the Research Ethics Committee of the Federal University of Goiás approved our study under the following protocol number: CAAE 50623315.3.0000.5083. This study was also in compliance with Resolution 466 of the Helsinki Treaty, and all participants signed a free and clarified term of consent.

Results

Using the internal management system of CRER, we searched for the keywords "depression" and "stroke." The system retrieved a list of 1080 individuals on the waiting list for psychiatric outpatient treatment. After analyzing their charts, we excluded 1040 who did not meet the selection criteria for the study. The 40 preselected candidates were called for a detailed pretreatment clinical evaluation. From these interviews, 20 individuals were also excluded due to the selection criteria and 20 were eligible to undergo the treatment with rTMS. Of them, 5 patients did not adhere to the treatment, being absent for more than 2 sessions in a row or more than 5 sessions during the whole process. Thus, 15 individuals completed the treatment procedures. The only reported side effect during the course of the rTMS experiment was a transient headache.

Table 1 lists the demographic and clinical profile of the patients, as well as the type of protocol used, whether inhibitory or excitatory. Most of the participants were adults and only 5 were older than 65 years of age (elderly). The intervention was homogeneous in relation to the sample data.

Figure 2 compares the mean/standard deviation and minimum/maximum values of HAM-D17 scores before and after the intervention with rTMS. There was a significant difference between the scores of baseline (min = 20; max = 31; mean: 24.60 ± 3.27) and the assessment at the end of the treatment (min = 3; max = 9; mean: 5.27 ± 1.79) and also between the scores of baseline and the 1-month follow-up assessment (min = 3; max = 6; mean: 4.33 ± 0.82). There was no significant difference when comparing the score at the end of the treatment and at the 1-month follow-up.

Figure 3 compares the quality of life evaluation at the 3 moments (baseline, end of treatment, and 1-month follow-up). There was a significant improvement in all WHOQOL-BREF domain scores. The psychological domain scores showed a greater difference in mean values after the intervention. At baseline, the psychological domain score was 28.34 ± 19.05; at the end of the treatment, it increased to 63.34 ± 9.74; and in the follow-up assessment 1 month after the treatment, it changed to 71.95 ± 9.12.

Table 2 presents the comparison of HAM-D17 scores before and after rTMS intervention. At the baseline, 73.3% of the patients had very severe depression (score ≥ 23); at the end of treatment, only 20% had mild depression ($8 <$ score < 13); and at the 1-month follow-up assessment, 100% already showed a stable mood (score < 7).

Table 3 presents the comparison of HAM-D17 and WHOQOL-BREF psychological domain scores at the 3 evaluation moments, separating the sample by the type of protocol that was applied (1 Hz inhibitory and 10 Hz excitatory) and by age groups (adults and elders).

Discussion

In this prospective case series clinical study, we aimed to evaluate the effects of rTMS in the treatment of PSD and how they affect the patient's quality of life. Our results suggest that both protocols, excitatory (10 Hz on F3, n = 8) and inhibitory (1 Hz in F4, n = 7), were effective in reducing depressive symptoms in

Table 1. Demographic and clinical profile of the sample/type of protocol (n = 15).

SAMPLE	TYPE OF PROTOCOL, NO. (%)		TOTAL	*P* VALUE[a]
	F4 (46.7)	F3 (53.3)		
Age (55.20 ± 12.45)				
Adult	6 (85.7)	4 (50.0)	10 (66.7)	.14
Elder	1 (14.3)	4 (50.0)	5 (33.3)	
Sex				
Female	4 (57.1)	4 (50.0)	8 (53.3)	.78
Male	3 (42.9)	4 (50.0)	7 (46.7)	
Marital status				
With partner	3 (42.9)	5 (62.5)	8 (53.3)	.45
Without partner	4 (57.1)	3 (37.5)	7 (46.7)	
Time since stroke (y)				
7-15	4 (57.1)	3 (37.5)	7 (46.7)	.45
Up to 6	3 (42.9)	5 (62.5)	8 (53.3)	
Number of kids				
1-2 kids	3 (42.9)	6 (75.0)	9 (60.0)	.20
None	4 (57.1)	2 (25.0)	6 (40.0)	

Abbreviations: F3, excitatory protocol; F4, inhibitory.
[a]Pearson χ^2 test.

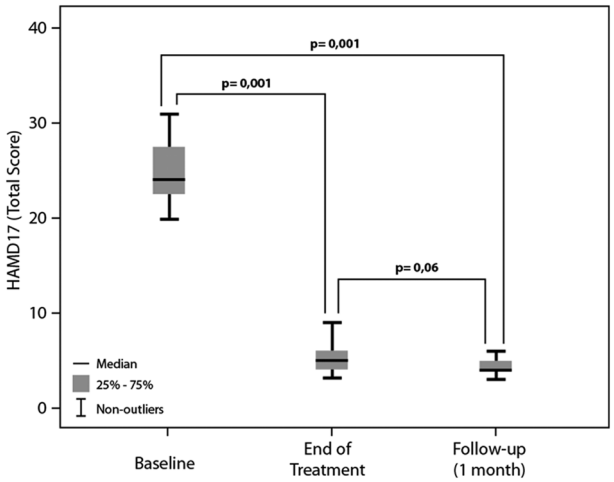

Figure 2. Boxplot graph: comparison of mean/standard deviations, maximum/minimum scores of HAM-D, at 3 moments of evaluation (n = 15). HAM-D17 indicates Hamilton Depression Rating Scale.

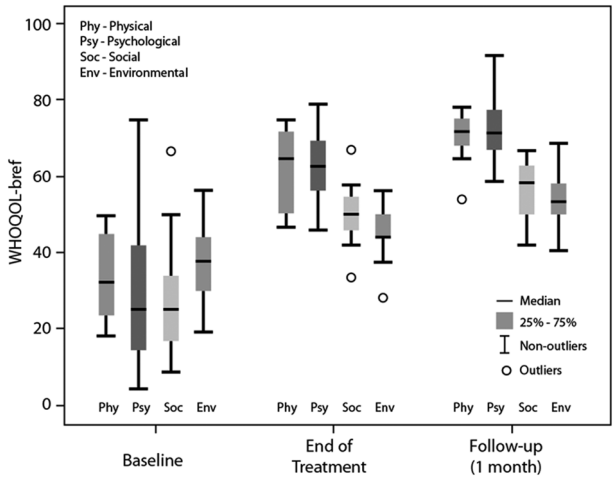

Figure 3. Boxplot graph: comparison of mean/standard deviations, maximum/minimum scores of WHOQOL-BREF, at 3 moments of evaluation (n = 15). WHOQOL-BREF indicates World Health Organization Quality of Life-Brief Version.

the treatment of PSD and in the improvement of the individual's quality of life. In both groups, there was a significant change in HAM-D and WHOQOL-BREF scores and the changes could be observed up to 1 month after the treatment with rTMS.

In our sample (n = 15), 5 patients were ⩾65 years old and all of them responded well to the rTMS treatment regardless of the protocol, inhibitory (n = 1) and excitatory (n = 4). Compared with the group of younger adults, there were no notable differences in the way patients responded to the intervention. Previous studies have discussed the relationship between the atrophy of the frontal cortex, which is a normal process of aging in the brain, to a weaker antidepressant response to

Table 2. Comparison of clinical status before and after transcranial magnetic stimulation (n = 15).

STATUS	INTERVENTION, NO. (%)			*P* VALUE[a]
	BASELINE	END OF TREATMENT	FOLLOW-UP	
Stable mood	0 (0.0)	12 (80.0)	15 (100.0)	<.001
Mild depression	0 (0.0)	3 (20.0)	0 (0.0)	
Severe depression	4 (26.7)	0 (0.0)	0 (0.0)	
Very severe depression	11 (73.3)	0 (0.0)	0 (0.0)	

[a]χ^2 test.

Table 3. Comparison of HAM-D17 and WHOQOL-BREF psychological domain scores according to the protocol (inhibitory and excitatory) and the age group (adults and elders).

	PROTOCOL (M ± SD)		AGE GROUP (M ± SD)	
	INHIBITORY F4 (N = 7)	EXCITATORY F3 (N = 8)	ADULTS (<65 Y) (N = 10)	ELDERS (>65 Y) (N = 5)
HAM-D17				
Baseline	26.00 ± 3.65a	23.38 ± 2.50a	25.10 ± 3.35a	23.60 ± 3.21a
End of treatment	6.43 ± 1.90b	4.25 ± 0.89b	5.60 ± 1.71b	4.60 ± 1.95b
1-month follow-up	4.57 ± 0.79c	4.13 ± 0.83b	4.30 ± 0.67b	4.40 ± 1.14b
P[a]	.001	.001	<.001	.010
WHOQOL-BREF—psychological domain				
Baseline	17.86 ± 12.90a	37.51 ± 19.42a	23.75 ± 13.50a	37.52 ± 26.50a
End of treatment	58.94 ± 7.78b	67.19 ± 10.08b	61.67 ± 8.76b	66.68 ± 11.77a,b
1-month follow-up	70.23 ± 6.57c	73.46 ± 11.12b	71.25 ± 7.97c	73.36 ± 12.01b
P[a]	.001	.001	<.001	.020

Abbreviations: HAM-D17, 17-item Hamilton Depression Rating Scale; F, [a]Friedman test; WHOQOL-BREF, World Health Organization Quality of Life-Brief Version. Different letters indicate significant differences when comparing subsequent evaluations (Wilcoxon test).

rTMS stimulation.[18-20] The authors have also been discussing whether adjustments in the intensity of the stimuli would be necessary, considering this atrophy.[21,22]

With age, the reduction of brain volume occurs disproportionately, affecting the frontal cortex much more than the motor cortex.[23] Thus, it can be argued that the individual's MT may become a faulty reference to calculate the appropriate intensity to stimulate the frontal cortex in rTMS protocols for depression.[24] Although some authors propose adjusting the stimulus intensity considering the distance between the cortex and the scalp generated by atrophy,[25-27] other studies report this correlation is still inconclusive and inconsistent.[24,28] Besides that, List et al[29] and Sabesan et al[24] noted that there may be a relationship between the lower motor cortical thickness and lower MT in older people. This indicates that, despite causing a reduction in the strength of the magnetic field that reaches the cortex, brain atrophy also increases the cortical excitability, so that even smaller intensities are enough to stimulate the brain.[24,28]

Regarding the type of protocol (1 Hz inhibitory, n = 7 and 10 Hz excitatory, n = 8), patients of both groups responded similar to the intervention, when comparing their scores at each moment of assessment. The group that received the 1 Hz inhibitory protocol significantly reduced the HAM-D17 scores (from 26.00 ± 3.65 to 6.43 ± 1.90) by the end of the 20 sessions. The follow-up evaluation also indicates a continuous improvement until 1 month after the end of the treatment, when the score decreased to 4.57 ± 0.79. In practice, subjects who were either severely or very severely depressed at baseline presented with a stable mood at the end of treatment, with a slight improvement of the scores 1 month after the end of treatment. Similarly, in the group that received the 10 Hz

excitatory protocol (n = 8), scores decreased considerably (from 23.38 ± 2.50 to 4.25 ± 0.89) from severe or very severe depression to stable mood at the end of treatment. In the follow-up evaluation, the scores remained stable (4.13 ± 0.83), without significant change.

Our results resonate with previous findings of studies in which the rTMS high-frequency protocol over the left DLPFC improved mood of patients with stroke sequelae[30,31] and of patients who had major depressive disorders (MDDs).[32,33] A systematic review and meta-analysis of controlled clinical trials on the use of rTMS for the treatment of PSD analyzed 22 clinical trials with 1764 patients.[30] Their findings indicated the improvement of the depressive condition and significant differences in HAM-D scores after the intervention, leading to the conclusion that rTMS may indeed have a positive effect on PSD treatment. Seo Gu and Chang[31] also conducted a study to verify the efficacy of the 10 Hz protocol on the left DLPFC (F3) to treat PSD and improve motor function. As a result, the authors report that rTMS was able to relieve depressive symptoms and that the results were also maintained up to 1 month after the end of treatment.

Similarly, Caulfield et al[34] reported 2 cases of elderly patients with a history of stroke in the left hemisphere who had a good response to the 1 Hz inhibitory protocol of rTMS over the right DLPFC (F4). One of the subjects' 24-item Hamilton Depression Rating Scale (HAMD-24) score decreased from 23 in the initial state to 6 after 30 rTMS session and her Beck Depression Inventory (BDI) scores decreased from 31 to 1. Although limited to 2 cases, their data resonate with our findings, suggesting that the low-frequency rTMS over the right DLPFC may also be effective in the treatment of depression in patients with left frontal stroke.

The cortical activity of the prefrontal brain regions, specifically the right and left DLPFCs, has been the subject of medical imaging studies on MDD. Studies using positron emission tomography, functional magnetic resonance imaging (fMRI), and rTMS show hypoactivity on the left DLPFC (F3) and hyperactivity on the right DLPFC (F4) in patients with MDD, supporting the hypothesis that the neuropsychological foundations of MDD can be related to an asymmetry and imbalance of the prefrontal cortical activity between both hemispheres.[35-37] This understanding of the imbalance of the prefrontal cortex has guided researchers into testing rTMS with inhibitory and excitatory protocols, and their results have revealed that both choices are effective, not only for treating depression,[38,39] but also for generalized anxiety disorder, aphasia, and poststroke motor sequels.[40]

Studies in healthy individuals have shown that both cerebral hemispheres process emotions. Although the left DLPFC processes positive emotions, the right side is responsible for the negative ones. Thus, when the left DLPFC is injured, the individual develops depression.[41,42] Neuroimaging studies also report that in patients with MDD, the left DLPFC hypoactivity is associated with a worse emotional judgment and the right DLPFC hyperactivity is associated with more severe depressive symptoms.[43]

Our results also corroborate the assumptions raised by Nitschke and Mackiewicz,[41] Gainotti,[42] and Grimm et al.[43] At the baseline of the group receiving the low-frequency (inhibitory) rTMS in the right DLPFC (F4), WHOQOL-BREF's psychological domain score was much lower (17.86 ± 12.90) than the score of the group receiving the excitatory protocol (37.51 ± 19.42) in F3. In addition, the HAM-D score was higher, indicating that depressive symptoms were more pronounced in this group.

It is worth noting that, in our study, the location of the brain injury defined the protocol of rTMS to be used in the PSD treatment, applying the stimulus always in the healthy hemisphere (contralateral to the injury). Following a similar line of reasoning, previous studies of patients with stroke sequels have shown clinical benefits from using rTMS. Olivieri et al[44] stimulated the healthy hemisphere of patients with hemi-spatial neglect and perceived improvements in their clinical condition; likewise, Martin et al[45] stimulated the healthy hemisphere of patients presenting aphasia and also reported improvement in their naming skills.

Also corroborating our data, a study conducted with the same population and same excitatory protocol compared the response of 20 patients to the treatment with the high-frequency rTMS. A total of 10 individuals received active stimulation and 10 received sham stimulation. The group that received active stimulation presented a significant difference in HAM-D and BDI scores. The same difference could not be observed in the group of patients who received sham stimulation, leading to the conclusion that the excitatory rTMS intervention could be considered effective for the treatment of PSD and that this improvement continued for at least until 1 month after the end of the intervention.[31]

All individuals in our study responded to the treatment and achieved remission of depressive symptoms, regardless of the protocol. This is a higher rate than what other studies have previously found. In a systematic review and meta-analysis of randomized controlled clinical trials (RCT) on the use of rTMS for the treatment of PST, Shen et al analyzed 12 RCTs that reported qualified data about response rates. The authors found that 64.4% and 39.7% of subjects in the experiment or control groups were classified as responders, respectively. Eleven RCTs reported a number of 28.8% remitters of experiment groups and 30.2% of control groups.[30] It is hard to compare our findings with the studies included in this meta-analysis, though, due to their heterogeneous samples, methodologies, and protocols.

Bucur and Papagno[11] also conducted a recent systematic review of studies that used noninvasive brain stimulation for PSD. Of the 7 articles that were analyzed in full, only 3 studies used rTMS. Regarding their response and remission rates, (a) Jorge et al[46] reported that 3 out of the 10 patients that received

active rTMS were considered responders, and only 1 patient met the criteria for remission; (b) El Etribi et al[47] reported a response rate of 60%, but no remitters; and (c) Gu and Chang[31] did not set response or remission criteria.

Considering the aforementioned, the reasons behind the expressive response and remission rates in our study remain uncertain and inconclusive.

Limitations of the study

It is worth mentioning that our study was limited to a small sample and lacked a control or sham-rTMS group. Future clinical trials should be conducted on poststroke patients with depressive disorder, with an appropriate sample, blinding, control group, and fMRI images of the brain, to validate the efficiency of the rTMS protocols, as well as their effects in a longer-term follow-up.

Conclusions

A deeper understanding of the results that rTMS treatments can achieve may be fundamental to promote public health policies and more effective strategies and protocols for the treatment of PSD, thus improving patients' quality of life, providing them with better assistance, and reducing their vulnerability to the impact of a neurological sequel.

The current scientific repertory lacks effective alternatives to treating PSD, as many individuals recovering from brain injuries remain resistant to pharmacologic therapy. Our brief clinical study suggests that both inhibitory and excitatory protocols of rTMS may be effective in reducing depressive symptoms in PSD and improving their quality of life, thus becoming a promising alternative to accomplish this task.

Author Contributions

HBSJr and AMCS conceived and planned the trials. HBSJr was the responsible for the selection and assessment of the patients with the HAM-D17 and WHOQOL-BREF. AMCS helped with the design of the study and she was also the medical doctor responsible for the application of the rTMS protocol. HBSJr and AMCS colaborated to the interpretation of data. HBSJr wrote the manuscript with support from MRF. All authors contributed to the final version of the manuscript, providing critical feedback and helping to shape the research. MRF supervised the project.

ORCID iD

Hercílio Barbosa da Silva Júnior https://orcid.org/0000-0003-1873-4865

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