Repetitive Transcranial Magnetic Stimulation Treatment in Post Stroke Depression

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ABSTRACT

Introduction: The prevalence of post stroke depression (PSD) ranges between 20% and 65%. It may be associated with functional disability of stroke patients Appropriate treatment of PSD might facilitate their rehabilitation and improve their quality of life. To assess the efficacy of repetitive Transcranial Magnetic Stimulation (rTMS) as treatment modality in post stroke depression.

Patients and Methods: We conducted this study on twenty patients diagnosed as post stroke depression according to DSM-VI treated with rTMS at low frequency (1HZ) applied over the left dorsolateral prefrontal cortex for ten sessions in two weeks at 100% of motor threshold. Hamilton Depression Rating Scale (HDRS) was used for rating depression and cognitive assessment for memory, attention and concentration was done before and after TMS treatment.

Results: About 60% of our patients showed drop of at least 41.3 % from the relevant phase baseline in scores on the 21-item Hamilton depression scale associated with clinical improvement, pointing that repetitive transcranial magnetic stimulation significantly improved mood in patients with post stroke depression. This effect appears to be maintained over time for one month. Moreover, rTMS showed significant improvement of cognitive tests assessed in this group of patients.

Conclusions: TMS could be a promising treatment for patients with stroke complicated by depression with the privilege of fewer side effects previously known to be associated with electroconvulsive therapy and pharmacotherapy. Further studies are indicated to study effects of TMS in large patient population in relation to other technical variables.

Key words: Post stroke depression, transmagnetic stimulation.

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INTRODUCTION

In 1831, Michael Faraday discovered that electrical currents can be converted into magnetic fields and vice versa. His principle of mutual induction is the basis of transcranial magnetic stimulation (TMS). In TMS, a bank of capacitors is rapidly discharged into an electric coil to produce a magnetic field pulse. When the coil is placed near the head of a human or animal, the magnetic field penetrates the brain and induces an electric field in the underlying region of the cerebral cortex. An electrical field of sufficient intensity will depolarize cortical neurons, generating action potentials. These then propagate to exert their biological effects[1].

TMS can affect underlying brain tissue at several levels. Positron emission tomography (PET) has revealed changes in cortical metabolism and dose-dependent changes in regional cortical blood flow in response to TMS which extends to sites distant from the magnetic stimulus, showing that the effects of TMS propagate to other parts of the brain and correspond to known neural networks[2]. Similarly, TMS to one brain region can alter neurotransmitter release elsewhere. For example, TMS to the left prefrontal cortex has been shown to increase release of dopamine in the ipsilateral caudate nucleus[3]. Last, TMS might directly alter gene expression patterns. A study of TMS-induced activation of c-fos expression in the thalamic Para ventricular nucleus of rats[4].

Several uncontrolled studies tested the effects of high-frequency (3–20 Hz) rTMS to the left prefrontal cortex in depressed patients but did not include depressed comparison subjects[5]. Also studies of low-frequency (<1 Hz) rTMS applied to the right prefrontal cortex showed >50% decrease in the Hamilton depression scale score after 10 treatments. Preliminary evidence for a beneficial effect of low-frequency, repetitive transcranial magnetic stimulation in patients with major depression and schizophrenia[6].

In comparison sham controlled studies used the TMS coil positioned such that less of the magnetic stimulus penetrates the brain[7].

Pascual-Leone et al.[8] tried to examine the maintained response of TMS. He conducted a crossover study of patients with relapsing unipolar psychotic depression that was

refractory to pharmacotherapy. In this study, rTMS applied to the left prefrontal cortex was compared to rTMS applied to other locations as well as to sham TMS. Patients were given five daily treatments and then evaluated over the next 4 weeks. During the first 2 weeks, rTMS to the left prefrontal cortex produced significantly better results than both rTMS to other locations and sham TMS. However, the benefit became insignificant by the 3rd week. In a later open phase study better results were found with increased treatment duration and stimulus intensity[9].

Other studies have examined the effects of high-frequency rTMS to the left prefrontal cortex as a stand-alone treatment for depression in patients who were not receiving antidepressant medications. George et al.[10] treated non psychotic depressed outpatients with rTMS at 5 Hz, rTMS at 20 Hz, or sham rTMS. A decrease in Hamilton depression scale score of >50% was observed in 9 of 20 (45%) RTMS patients. (The 5Hz group did twice as well as the 20Hz group, although the difference was not statistically significant).

PATIENT AND METHODS

Twenty right- handed patients diagnosed as mood disorder due to general medical disease (stroke) according to Schedule for Affective Disorders and Schizophrenia[11] and the Structured Clinical Interview for DSM-IV[12]. participated in the study. Their mean age (51.94.77+), male/female ratio as (128/). They all underwent careful general, psychiatric and neurological examination. All patients with past history or comorbid other major psychiatric disorder or drug abuse, as well as patients with pacemakers or a history of seizures or major head trauma were excluded from the study. Diagnosis was established by means of laboratory and imaging investigation. They had comorbid medical illnesses as diabetes mellitus (n=11), hypertension (n=14) and heart disease (n=3). Half the patients (n=10) had left hemisphere lesions and half (n=10) had right hemisphere lesions. 75% of the patients (n=15) had anterior circulation strokes, while 25% (n=5) had posterior circulation strokes. Fifty percent of the patients (n=10) had frontal lobe lesions, 20% (n=5) had parietal lobe lesions, 15% (n=3) had occipital lobe lesions and 5% (n=1) had temporal lobe lesions. The 21-item Hamilton Depression Rating Scale (HDRS)[13] was used for rating depression at four points of the study: just before treatment, at the end of treatment sessions, 2 weeks after and one month after. The mean score on HDRS at entry of the study was 24.4 (SD=5.09). Modified Rankin Scale (MRS) score for physical disability was zero in three patients, 1 in six patients, 2 in eight patients and 3 in three patients.

The patients were recruited from the Stroke Unit, Ain Shams University Specialized Hospital. After complete description of the study to subjects, written informed consent was obtained through a protocol approved by the Staff Board of the Neuropsychiatry department. No other antidepressant treatment was given to the studied group of patients. Repetitive magnetic stimulation was delivered by using the Mag Pro X100 magnetic stimulator (Medtronic A/S) capable of producing 2 tesla magnetic power and up to 100 pulses per second. On the initial visit, the motor threshold of the right abductor pollicis brevis muscle (the thumb) for the subjects was determined as the lowest intensity that gives motor response[14]. Then all subjects received stimulation at 100% of this level, 5 sessions per week for two successive weeks. All patients received low frequency stimulation (LFS) 1HZ (each session=10 trains, duration of the train=10 seconds, 10 pulses /train, intertrain interval=2 seconds, with total duration of the session=2 min, pulses/session=100, pulses in whole therapy =1000). Stimulation occurred over the left dorsolateral prefrontal cortex, which was defined for each person as the site 5 cm anterior and in a parasagittal plane from the point of maximum stimulation of the right abductor pollicis brevis muscle. We used a figure 8-shaped coil, biphasic (full sine) waveform with the extensions of the coil perpendicular to a line running from the site to the subject's nose. All subjects were repeatedly rated (at baseline, at the end of treatment,after 2 weeks and after one month) with the 21-item Hamilton depression scale by trained investigators who were blind to the treatment phase. Hamilton depression scale scores were analyzed as means and standard deviation and difference change from baseline were used to assess improvement response across time of the study. Cognitive assessment including: assessment of visual memory using Visual associate learning test, Taping forward test and Taping backward test. Assessment of verbal memory using Verbal associate learning, Digit span forward test and Digit span backward test. Assessment of attention and concentration was done using Vigilance continuous performance test. To Compare significant differences before and after TMS treatment we used paired t-test with $p<0.05$ considered significant (*).

RESULTS

Table 1 shows changes in Hamilton Depression Rating Scale scores from baseline, at the end of treatment, 2 weeks after and 1 month after end of treatment. We found drop of equivalent to 41.3% that could be maintained over 1 month time in about 60% of the patients group as shown in Table 2. Cognitive testing were compared before and after rTMS treatment and showed significant improvement in verbal and visual memory and continuous vigilance performance tests in favor of after treatment (Tables 3a,b,c).

Table 1: Changes in HDRS across time of the study for all patients

Timing of the study	HDRS (Mean+SD	Differences
Baseline	24.4+5.09	
End of the study	14.3+5.46	10.1(41.39%)
Two weeks after	15.0+7.00	9.4(38.52%)
One month after	14.6+6.57	9.8(40.16%)

The above data shows drop of the HDRS scores at the end of the study which indicate response to treatment. This effect although maintained over 1 month appear to decrease over time.

Table 2: Shows percentage of responders to TMS treatment among the whole patient group.

Response to treatment	Number	Percentage
Responders	12	60%
Non-responders	8	40%

About 60% of post stroke patients showed response as indicated by change in HDRS and clinical improvement to low frequency Stimulation with rTMS pointing to the efficiency of this type of treatment.

Table 3: Shows cognitive assessment before and after rTMS.
Table 3a : Verbal Memory Tests.

		Mean (+/-Std.)	P value
Paired Associate learning	before	14.2 (+/-3.5)	< .001*
	after	18.75 (+/-2.8)	
Digit Span forward	Before	5.2 (+/-2)	< .001*
	After	6.75 (+/-2)	
Digit Span backward	Before	4.55 (+/-1.5)	< .001*
	After	6.58 (+/-3.2)	
Total of Digit Span	before	9.5 (+/-2.8)	< .001*
	after	11.15 (+/-3.2)	

*P-value >0.05 considered significant.

Table 3a: Mean (+/- SD) of verbal memory tests before and after rTMS sessions with significant improvement of all tests after rTMS.

Table 3b: Visual memory tests.

		Mean (+/-Std.)	P value
Paired Associate learning	before	7.3 (+/-2.9)	.006*
	After	9.6 (+/-4)	
Taping forward	Before	6 (+/-1.5)	.483
	After	6.2 (+/-2)	
Taping backward	Before	4.8 (+/-2)	.465
	After	5.03 (+/-1.5)	
Taping total	Before	10.45 (+/-2)	.037*
	after	11.2 (+/-2.7)	

*P-value >0.05 considered significant.

Paired t-test comparing scores of visual memory tests showing statistically significant difference between before and after rTMS in favor of after treatment.

Table 3c: Continuous vigilance performance tests.

		Mean (+/-Std)	P value.
Average delay	before	487.336 (+/-46.72)	.000*
	After	460.9 (+/-41.1655)	
Total commission	Before	14.4 (+/-12.537)	.019*
	After	11.15 (+/-9.317)	
Total omission	Before	11.9 (+/-12.008)	.037*
	After	9.3 (+/-10.818)	

*P-value >0.05 considered significant.

Table 3c: Mean of continuous vigilance performance tests before and after RTMS sessions with significant improvement of after RTMS.

DISCUSSION

Post stroke depression:

Depression is a major and often underrecognized problem after stroke. The prevalence of post stroke depression (PSD) ranges between 20% and 65% [15]. It may be associated with reduced satisfaction with life as well as with lowered functional ability of stroke patients and appropriate treatment of PSD might facilitate their rehabilitation and improve their quality of life[16].

Recent evidence suggests that post stroke depression is associated with the location of the brain infarct, proximity to the frontal pole being associated with greater depression following left hemisphere injury and an opposite relationship being seen with injury to the right hemisphere[17]. In our study half of the patients had left sided lesions with location in the frontal lobe.

Cognitive impairment is a common complication after stroke, with a prevalence varying from 13.6% to 35.2%. The impairment may range from a minimal deficit in memory to a transient disturbance of orientation to an irreversible dementia[18].

It is a challenge during selection of treatment modality to have the least side effects in such group of patients with medical complications as diabetes mellitus, hypertension and heart diseases in addition to the brain insult.

Tricyclic antidepressants (TCAs) have alpha adrenergic blockade, anticholinergic, antihistaminic and cardiac side effects. Selective Serotonin Reuptake Inhibitors (SSRIs) have drug interactions related to cytochrome P-450 isoenzyme inhibition. In addition Fluoxetine may prolong bleeding time[19].

The severity of brain vessel arteriosclerosis and frequency of brain vascular lesions were not significantly different between cases with post stroke depression and those without. Earlier death was the only variable significantly associated with post stroke depression. Neuropathological data confirm that depression is associated with worse prognosis in elderly stroke patients and tend to support the hypothesis that psychological rather than neurological factors are the main determinants of post stroke depression[20].

Response to TMS in elderly patients:

Figiel et al.[5] observed that in older patients, onset of depression after age 65 was also associated with less response to treatment. Janicak et al.[21] in a trial of high-intensity and longer rTMS treatments, found a correlation between age and the number of treatments required to achieve a clinical response. In our group of patients the mean age was 51.94.7+. The treatment course was ten sessions over two weeks.

Comparing effect of high and low frequency TMS:

Low-frequency (≤1Hz) rTMS has been examined in sham-controlled studies. Padberg et al.[22] conducted a three-armed study of 18 patients comparing the effects of high-frequency,

low-frequency and sham rTMS to the left prefrontal cortex on pharmacotherapy-resistant major depression. They found a significant decrease in the mean Hamilton depression scale score only in the low-frequency (0.3Hz) group after 5 days of daily treatment. In our study we applied low frequency 1Hz on the left dorsolateral prefrontal cortex. Fourty percent of patients complained of headache few hours after the session which responded well to treatment with paracetamol.

TMS versus ECT:

Studies comparing high-frequency rTMS to the left prefrontal cortex with ECT found that 16 (80%) of 20 patients responded to ECT but that only nine (45%) of 20 responded fully to rTMS. However, when the data were stratified by the presence or absence of psychotic features, a different picture emerged. For psychotic patients, ECT was clearly superior to rTMS, with 10 of 10 patients responding to ECT but only two of nine responding to rTMS. But among nonpsychotic patients, both treatments met with similar success rates, with six (60%) of 10 patients responding to ECT and seven (64%) of 11 responding to rTMS[23].

However no data available to assess the effect of rTMS or ECT in post stroke depression. In our study 60% of patients showed clinical improvement after RTMS treatment. Yet, TMS shows preferable side effect profile. Our study showed improvement of cognitive tests assessing verbal and visual memory and vigilance performance following rTMS.

Maintained effect of TMS:

A significant limitation of TMS is how durable its antidepressant effect over time. In a recent study they followed a group of patients randomly assigned to receive ECT or rTMS at 3- and 6-month time points. They found no significant difference in the relapse rate between the two groups[24].

Relation of TMS response and physiological changes in the brain:

Kimbrell et al.[25] used PET analysis to measure cerebral glucose metabolism in depressed patients undergoing TMS to the left prefrontal cortex. They found that hypo metabolism in the cerebellum, both temporal lobes and the occipital and anterior cingulate regions were associated with a positive response to 20-Hz treatment, but that hyper metabolism was associated with improvement with 1-Hz treatment.

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