TRANSCRANIAL MAGNETIC STIMULATION THERAPY IN REFRACTORY DEPRESSION

Tarhan N (*), Tan O (**), Baripoğlu SK (**), Coban DA (**)

* Professor in Psychiatry, Memory Center Neuropsychiatry Clinics, Istanbul.

**Specialist in Psychiatry, Memory Center Neuropsychiatry Clinics, Istanbul.

SUMMARY

Neuroscientists have become increasingly concerned with brain stimulation techniques. Electroconvulsive treatment (ECT) is a traditional therapeutic method that stimulates the brain electrically. In recent years, transcranial magnetic stimulation (TMS) treatment has emerged as a promising research and clinical tool. In TMS, short and but powerful magnetic currents are directed into the brain by means of coils located on the skull. Improvement in depression, loss of energy and cognitive decline has been observed with safe and painless magnetic stimulation activating the neural circuit. In repetitive TMS (rTMS), the current is sent in a 'pulsed' fashion.

In our clinic, 53 outpatient cases diagnosed as having depression according to the DSM-IV were applied rTMS with a total of 2000-10.000 pulses. The patients had treatment-resistant depression and were continuing to take medicine. Before and after the rTMS treatment, the patients were given HAM-17, and quantitative EEGs (QEEG), were taken.

After 10 sessions of rTMS, HAM scores were decreased by 30-50 percent. This was evaluated as a rapid improvement. Cognitive decline and loss of energy were the most rapidly improving symptoms. In QEEG, a general increase in delta and theta power was observed, an effect that is seen following antipsychotic administration.

These results suggest that rTMS enhances recovery from depression in patients who continue to use antidepressive drugs. rTMS lead to neuroleptic-type changes in neuronal activity.

High frequency (25Hz) was fixed. The group which was applied with 10.000 pulses in total sessions demonstrated higher remission than the group which was applied with 5.000 pulses in total sessions. The difference of the psychotic groups was not significant after treatment to rTMS.

Key words: rTMS, Transcranial Magnetic Stimulation, Depression, Drug resistant Depression, QEEG, Brain Mapping

INTRODUCTION

The interaction of psychiatry and technology has aimed at changing brain functioning for a century without harming the scalp and without causing any apparent adverse effect. Transcranial magnetic stimulation therapy has been studied to improve mental disorders since 1985. Many animal and sham trials have been conducted. (Klein, Kreinin, 1999, Barker, Jalinous 1985, George 1994, Grisaru 1994, Hotlich 1993, Kozel 2002, Little 2000, Gershon 2003)

A magnetic coil is employed in TMS to stimulate the cortex safely and no invasively. Such methods as quantitative electroencephalography (QEEG) and brain mapping having localizing value may be used to measure alterations in cortical activity. So, changes in specific cortical regions caused by given stimulation parameters (rate, frequency, duration) can be investigated.

Effects of repetitive TMS (rTMS) of prefrontal region were detected in normal volunteers, in whom left prefrontal application caused an increase in sadness but right application an increase in happiness.(Pascual-Leone 1996; Martin, George 1997) Prefrontal cortex dysfunction shows positive correlation with brain imaging studies (George, Keller 1994). So how can these results be observed in patients clinically? Would we attain good response especially in treatment-resistant patients?

George et al. demonstrated in a 1995 study that rTMS in high frequency (25 Hz) was significantly effective in drug-resistant patients.

We investigated effects of rTMS in subgroups of treatment resistant major depression. In addition, we used the findings emerging from psychopharmacological and QEEG studies by Itil et al. as a biological marker. It is known that psychotropic drugs lead to significant changes in brain wave activities (Itil 1977, Itil, Saletu 1972). We investigated the effects of rTMS on QEEG results. Boutros (2000), Nikulin (2003) used ongoing QEEG in rTMS.

METHODS

We enrolled 53 treatment-resistant patients having depression in a prospective design. 29 were females and 24 were males. 34 had non-psychotic unipolar depression, 15 had psychotic unipolar depression and 4 had nonpsychotic bipolar depression. The average age was 36,9 %. All were right-handed. None had a history of drug abuse or neurological and physical local pathology.

The diagnosis of depression was made according to the DSM-IV. The 17-item Hamilton Depression Rating Scale (HDRS) was employed. Treatment-resistant depression was described as a failure to respond adequately to two successive courses of monotherapy with pharmacologically different antidepressants given in adequate doses for sufficient time.

Patients received ten daily sessions of rTMS for two weeks in a high frequency (25 Hz) and with a total of either 5.000 or 10.000 pulses. All 53 patients completed the trial.

The diagnosis and rating were made by two psychiatrists. All patients gave written informed consent. None of the patients discontinued their drugs and none received psychotherapy.

MATERIALS

A magnetic stimulator (Magstim, rapid, superrapid high frequency magnetic stimulator) and QEEG (Neurocorp, 10-20 system, HZI database) were used. A two-holed standard coil was applied to the left prefrontal cortex in all patients. Its power was that of the motor threshold which caused muscular contraction when applied over the left parietal lobe. Stimulation parameters were 25 Hz and 200-500-1000 pulses for each session. 210-250-500-1000 stimuli were given per train. Each session lasted approximately ten minutes.

DATA ANALYSIS

Patients were divided into three groups: Major depression (34), psychotic depression (15) and bipolar depression (4). 29 were males, 24 were females. As variance analysis technique (ANOVA), parametric t test was used, and/or as Kruskal Wallis technique, non-parametric "t" test was used. (Tables I-IV).

RESULTS

The average HDRS scores of 53 patients completing the trial decreased from 28.6 to 11.3, which was a significant decrease ($p<0.001$). Both females and males had similar significance ($p<0.001$). HDRS decreased from 29.1 to 12.2 in non-psychotic unipolar depression ($p<0.001$), 28.4 to 10.3 in psychotic unipolar depression ($p<0.001$) and 25.2 to 7.2 in non-psychotic bipolar depression ($p<0.001$).When three groups were compared with each other, the results were not significant. ($P > 0,05$). Tables (I-IV)

Tonic-clonic epileptic seizure lasting for two to three minutes developed immediately after the session with a patient receiving 10.000 pulses. No other adverse effect was observed. Neither a headache requiring medication nor cognitive difficulties occurred. Patients had previously been informed about contractions of facial muscles and the power was generally low in the first session regarding the intolerance of patients.

QEEG results were evaluated according to Z scores. Increase in delta power was observed in 34 out of 53 patients. They were those patients who received high pulses. Delta power decreased in 9 patients, and no change in QEEG power spectrum was observed in 10 patients. Two out of 53 patients showed a significant increase in beta power according to Z score data.

Out of 53 patients, 35 (%66) showed moderate recovery (HDRS 8 to 15) . After rTMS sessions HDRS was < 8 in 9 patients (%16.9) and was >16 in 9 (%16.9).

5 out of 14 patients (%35.7) who received 10.000 pulses had a complete recovery. 5 out of 39 patients (%10.2) who received about 5000 pulses had a complete recovery. This finding was significant ($p<0.001$).

After rTMS it is significant that the correlation coefficient increased to 0,175. As age increased, response to the treatment decreased (Table III).

9 of 14 patients (%64.2) who received 10.000 pulses had an increase in delta power. 21 of 39 patients (%53.8) who received about 5000 pulses had an increase in delta power. The Relation between delta increase and pulses given was not significant.

DISCUSSION

Many studies showed that rTMS had modest benefits in depression. There had not been sufficient data about the effect of rTMS in psychotic depression in literature. Frequency, intensity, duration and number of magnetic pulses remains to be analyzed. On the other hand, efficacy of rTMS as an augmentation strategy must be clarified/elaborated.

Controlled studies demonstrated antidepressant efficacy of rTMS (George et al. 1999, Post et al. 1999, Pridmore et al. 1999). Epstein et al. (1998) reported 50 percent decrease in HDRS after daily 500 pulses per day of rTMS to the left prefrontal cortex for five days in 56 cases with refractory depression. Pasqual-Leone (1998) observed recovery lasting for two weeks after active rTMS to the left prefrontal cortex in 17 patients with psychotic depression.

In the present study 53 patients with treatment-resistant major depression lasting for at least 6 months were enrolled. 34 had non-psychotic unipolar major depression, 15 had psychotic unipolar major depression, 4 had non-psychotic bipolar major depression. HDRS scores decreased significantly after the treatment. Among depression subtypes, there was not a statistically significant difference. Only one patient (who had received 25 Hz and had frontal dysrhythmic discharges,) had convulsive seizure immediately after the last session. In the analysis of QEEG and brain mapping, delta power increased significantly after the treatment. This change is similar to that caused by neuroleptics. This finding suggests that a slowdown in energy transfer due to neuronal depolarization caused by rTMS can be demonstrated electrophysiologically. Electrophysiological dysrhytmia resulting from an increase in the cortical excitability after the high-frequency rTMS was evaluated as an effect similar to that caused by ECT.

As a result, we observed that application of high frequency rTMS with an average of 5000 pulses and an intensity of 80-100 percent power over the prefrontal cortex for ten days as an augmentation strategy resulted in significant improvement in medication-resistant depression within a short time (two weeks); therefore rTMS may be a valuable therapeutic tool in refractory depression. In addition, it is important that rTMS led to a significant improvement in psychotic depression. (Table I)

CONCLUSION

1. rTMS application with constantly high frequency (25 Hz) but with varied pulses (5000 or 10.000) showed that the rate of complete remission was significantly higher in the group receiving 10.000 pulses than in the group receiving 5000 pulses. (Table IV)

2. rTMS application resulted in an increase in delta power in QEEG, independently of doses.

3. Rate of response did not show significant difference among the three subtypes of cases (psychotic and non-psychotic unipolar and non-psychotic bipolar depression) (Table II).

4. Response to the treatment decreased as the age of the patient increased. (Table III)

TABLE I The Comparison of the Groups

	N	%	Before rTMS	After rTMS	t	P
Major Depression*	34	64,2	29,1	12,2	15,221	P < 0,001
Psychotic Depression*	15	28,3	28,4	10,3	11,187	P < 0,001
Bipolar Depression	4	7,5	25,2	7,2	7,919	P < 0,001
Total	53	100	28,6	11,3	20,275	P < 0,001
Women	29	54,7	28,6	11,8	14,111	P < 0,001
Men	24	45,31	28,7	10,6	14,557	P < 0,001

(*) Because the distribution was normal, parametric techniques were used. The parametric "t" test and the wilcoxon non-parametric test produced similar results.

TABLE II The Comparison within the Groups

	N	Before rTMS	After rTMS	Chi square	df.	P.
Major Depression	54	29,1	12,2	5,04	2	0,80
Psychotic Depression	15	28,4	10,3			
Bipolar Depression	4	25,2	7,2			
Total	53	28,6	11,3			

According to the ANOVA (F 0,576, F: 2,955), Kruskel Wallis statistical analyses, the results are not significant. P > 0,05

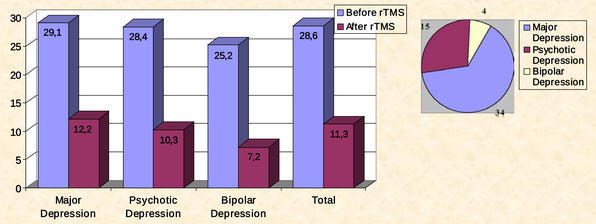
TABLE III The Correlation of Age and the Treatment Results

	N	Correlation	Sig.
AGE + B rTMS	53	0,091	0,519
AGE + A rTMS	53	0,175	0,211

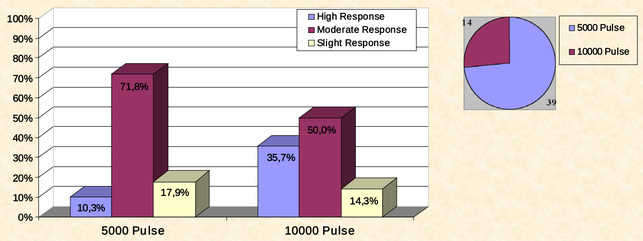
TABLE IV Comparison of the Pulse Groups and the Degree of Improvement

	N.	%	HDRS 8 or less (High response) N:9 (16,9 %)	HDRS 8-158 (Moderate response) N:35 (66,2 %)	HDRS 16 or more (Slight response) N:9 (16,9 %)	100 %
The group receiving pulses to a maximum of 5.000	39	73,6	N:4 (% 10,3)	N:28 (% 71,8)	N:7 (%17,9)	100 %
The group receiving 10.000 pulses	14	26,4	N:5 (% 35,7)	N:7 (% 50)	N:2 (% 14,2)	100 %
Total	53	100	P < 0,001	P < 0,001	P > 0,05	

GRAPHIC I The Comparison of the Groups (Table I)



GRAPHIC II Comparison of the Pulse Groups and the Degree of Improvement (Table IV)



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