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Efficacy of Transcranial Magnetic Stimulation (TMS) in depression: naturalistic study

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Transcranial magnetic stimulation (TMS) is a technique in which the evidence has been confirming its efficacy. Repetitive stimulation (rTMS) of the left prefrontal dorsolateral (LPFDL) area with frequencies between 10 and 20 Hz has been shown to be effective in major depression.

This article presents the prospective analysis of the treatments performed using TMS on LPFDL at 20 Hz with an intensity of 70% in a protocol of 10 sessions on 107 patients (41 male and 61 female) due to drug treatment resistant depressive symptoms in different conditions. The patients had previously undergone two psychopharmacological attempts with adequate dosage and time, who had been considered candidates for electroconvulsive therapy (ECT) if they did not respond to any conventional treatment. A total of 62.7% had mood disorder, 13.1% obsessive-compulsive disorders (OCT), 7.5% cognitive disorders, 4.7% personality disorders and 3.7% were psychiatric disorders. Mean age of the group was 49.98 years (SD = 17.09).

The global results showed that the TMS provided some degree of improvement in 48.6%, although only half, that is 24.3%, maintained it beyond week 12. Efficacy by diagnoses showed a significant difference in favor of affective disorders. In the case of bipolar disorders in the depressive phase, there was improvement in 88.9%, which was maintained in 66.7% of the patients treated. No differences in efficacy were found within each one of the groups diagnosed based on gender, age or presence of personality disorders. The efficacy of the ECT was similar to the TMS in the group in which it had to be applied in comparison with the general group. New studies are proposed with the inclusion of the TMS for resistant-depression treatment protocols in a step prior to the ECT and even before all the

drug treatments had been attempted, combining it with them for their potentiation.

Key words:
 Transcranial Magnetic Stimulation, Depression, ECT

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Eficacia de la Estimulación Magnética Transcraneal (TMS) en depresión: Estudio naturalístico

La estimulación magnética transcraneal (TMS) es una técnica cuya eficacia va quedando confirmada con la evidencia. La estimulación repetitiva (rTMS) del área dorso-lateral prefrontal izquierda (LDLPF) con frecuencias entre 10 y 20 Hz se ha mostrado eficaz en depresión mayor.

En el presente artículo se analizan retrospectivamente los tratamientos realizados mediante TMS sobre LDLPF a 20 Hz con una intensidad del 70% en un protocolo de 10 sesiones sobre 107 pacientes (41 varones y 66 mujeres) por presentar sintomatología depresiva resistente al tratamiento farmacológico en distintas patologías. Los pacientes habían realizado previamente dos intentos psicofarmacológicos adecuados en tiempo y dosis, y en caso de no responder a ningún tratamiento convencional eran considerados candidatos para terapia electroconvulsiva (TEC). El 62,7% eran trastornos del humor, un 13,1% trastornos obsesivo-compulsivos (TOC), un 7,5% eran trastornos cognoscitivos, un 4,7% trastornos de personalidad y un 3,7% fueron trastornos psicóticos. La edad media del grupo fue de 49,98 años (d.e. = 17,09).

Los resultados globales muestran que la TMS aportó algún grado de mejoría en el 48,6%, aunque sólo la mitad, el 24,3% la mantenía más allá de la semana 12. La eficacia por diagnósticos aporta diferencias significativas a favor de los trastornos afectivos; en el caso de los trastornos bipolares en fase depresiva presentan una mejoría del 88,9%, mantenida en el 66,7% de los pacientes tratados. No se encontraron diferencias de eficacia dentro de

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cada uno de los grupos diagnósticos en función del sexo, edad o presencia de trastornos de la personalidad. La TEC presentó una eficacia similar a TMS en el grupo en el que se tuvo que aplicar en comparación con el grupo general. Se propone la realización de nuevos estudios con la inserción de la TMS en los protocolos de tratamiento de depresión resistente en un escalón previo a la TEC e incluso sin haber agotado las vías farmacológicas, con las que podría combinarse para su potenciación.

Palabras clave:
estimulación magnética transcraneal, depresión, TEC

INTRODUCTION

Transcranial magnetic stimulation (TMS) is a technique which is being progressively implemented and which has been approved for use in resistant depression¹ in the European Union, Canada, Australia and United States. This procedure is well-tolerated and has few side effects with scant intensity that rarely lead to treatment withdrawal in adults^{2,3} or in children.⁴ The TMS, which is hardly 20 years old, was initially conceived for the noninvasive study of the conduction of corticospinal tract, spinal cord roots and peripheral nerve in humans.⁵ Its repetitive use (rTMS) has a therapeutic action in neuropsychiatric diseases linked to excitability alterations.⁶

The basics of the therapeutic action of this technique continue to be linked to the principle of electromagnetic induction discovered by Faraday in 1831 by which electrical energy and magnetic fields are related. To simplify, it can be stated that transcranial magnetic stimulation produces electrical currents specifically in certain areas of the brain, which based on the type of the field applied, will increase or decrease neuronal excitability. Thus, the classical studies of Pascual-Leone⁷ advocated an increase of excitability linked to the increase of the magnetic field frequency. However, recent studies⁸ have indicated that this increase in excitability is linked to a consecutive period of decrease of excitability due to refractoriness for about 30 minutes. Neurochemically, the TMS is associated to changes in tryptophan and serotonin metabolism in the limbic areas⁹ and to normalization of the brain-derived neurotrophic factor (BDNF),¹⁰ as occurs in effective treatments of depression.

TMS studies on the activity of the dorsal lateral prefrontal (DLPF) cortex have detected an asymmetry with hypoactivation of the left side versus the right.¹¹⁻¹³ Thus, according to the investigations of Pascual-Leone (1995), high frequencies (10-20 Hz) can be used on the left hemisphere and low frequencies (1-2 Hz) on the right hemisphere in order to achieve the same effect of recovery of the symmetry. Multiple studies have been making progress regarding the efficacy of this technique with high frequencies on the left

DLPF or with low frequencies on the right DLPF,¹⁴⁻¹⁶ even in cases of bipolar depression.¹⁷

The side effects are limited and not very important and generally do not generally go beyond typical dermal sensations. No deaths due to this technique have been recorded in more than 10,000 sessions of the treatments performed,^{2,3} so that studies have been progressively appearing that prolong the application period beyond the classical 10 initial sessions, improving the results of the TMS rescue and maintenance of effect.^{17,18}

Drug wash-out in the patients in the real clinical situation is frequently complicated, and for this reason, studies including them have been designed. These studies have demonstrated an efficacy similar to them, but inferior to ECT,¹⁹ that improved when used in combination.²⁰

In order to enhance the resources, predictors of positive response have been investigated. Among them are younger age,²¹ absence of anxious comorbidity and less duration of the current episode,²² certain polymorphisms of the BDNF²³ or the already mentioned prefrontal electroencephalograph asymmetry.²⁴

Depression is a disease that frequently does not occur alone but rather as a part of a syndromic complex. For this reason, studies have also been performed that show the efficacy in these cases, such as in Parkinson's disease with depression.²⁵ Affective symptoms such as autistic concern of schizophrenia showed improvement in some studies.²⁶ In this disease, its possible utility in auditory hallucinations^{27, 28} has also been indicated, although there are some discordant studies²⁹ in this regard. There are also open lines of study on the efficacy of TMS in post-traumatic stress disorder (PTSD),^{30, 31} on its lack of effect in obsessive-compulsive disorders (OCD)^{32, 33} or of the physiology and possibilities of treatment in attention deficit hyperactivity disorders (ADHD).³⁴ The TMS has also been studied in non-psychiatric fields such as those of pain decrease³⁵ or tinnitus.³⁶

MATERIAL AND METHODS

In order to evaluate the true efficacy of the application of the TMS in the real clinical practice, it was decided to reevaluate all of the cases in which it had been applied between January 2003 and June 2008. In this way, its efficacy could be evaluated in different diagnoses of the depressive spectrum in other conditions for which there is little information.

Inclusion criteria were being over 16 years of age, having affective symptoms that did not respond to two psychopharmacological attempts that were adequate in time and dose, having signed the informed consent and absent-

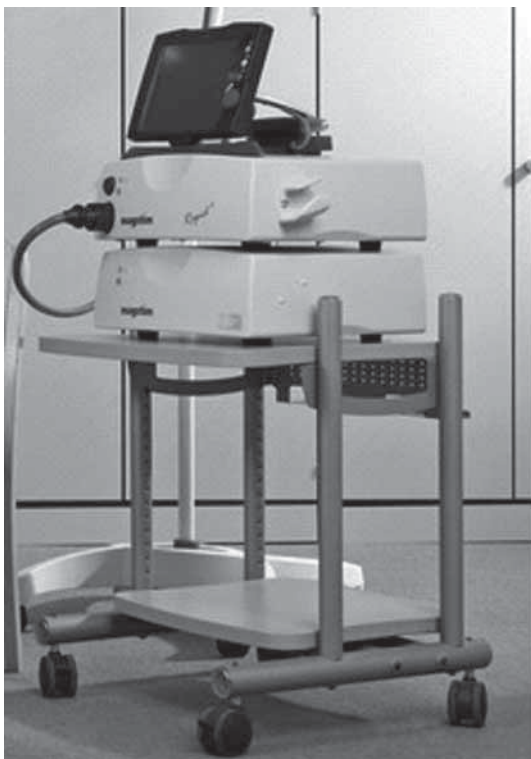


Figure 1 Transcranial Magnetic Stimulator.

ce of exclusion criteria. Exclusion criteria were presence of irritative brain disease secondary to the different forms of epilepsy or of intracranial masses or bleeding, in addition to being under 16 years of age.

Standard treatment consisted in ten sessions, one per day, of stimulation (9.37 mean; SD = 2.93) with an intensity of 70% of the motor threshold (69.93 mean; SD = 2.28) with the signal frequency of 20 Hz (19.49 mean; SD = 2.96). The intentionally stimulated zone corresponded with the left prefrontal dorsolateral area (LPFDL). One hundred percent of the patients were receiving drug treatment with different antidepressants and no changes had been made during the two weeks prior to the TMS or in the four weeks following it. In this way, the drug factor was randomized and it could not be considered that it had an influence or could be analyzable regarding the results of the technique. The machine used was the Magstim Rapid with Booster Set-up (figure 1).

Response to the TMS was considered as absent in clinical terms if there were no changes in the affective symptoms in the 4 weeks following the treatment according to the evaluation of the responsible psychiatrist. Positive response was when there were changes and these changes continued beyond 12 weeks. Unstable improvement was that exceeding week 4 but not week 12. Response to the ECT in the cases

Table 1		Diagnoses of the sample	
Diagnoses	n	%	
Mood Disorders (affective)	68	62.7	
Dysthymia	10	9.3	
Single Episode Depressive Disorder	26	24.3	
Recurrent Episode Depressive Disorder	22	20.6	
Bipolar Disorder	9	8.4	
Obsessive-Compulsive Disorder	14	13.1	
Cognitive Disorders	8	7.5	
Delusion	2	1.9	
Cognitive Deterioration	6	5.6	
Other Anxiety Disorders	9	8.4	
Generalized Anxiety Disorder	4	3.7	
Conversion Disorder	3	2.8	
Dissociative Disorder	1	0.9	
Psychotic Disorders	5	3.7	
Schizophrenia	3	2.8	
Schizoaffective Disorder	1	0.9	
Adaptive Disorder	1	0.9	
Personality Disorder	5	4.7	

requiring such technique due to the absence of response to TMS was evaluated in the same way.

In order to perform the statistical study, the techniques appropriate to effect were applied using the computer program SPSS 14.0.

RESULTS

The total number of patients who accepted treatment was 107, 41 (38.3%) males and 66 (61.7%) females. Mean age of the patients was 49.98 years ([16 -87]; SD=17.09), no significant differences being found between genders, 50.83 years ([22-87]; SD=18.03) in males and 49.45 ([16-81]; SD=16.59) in females. There was a significant difference between cognitive disorders (76.50 years; [66-87]; SD=7.45) and the rest of the group (t=-9.32; p<0.01). No patient had side effects due to the technique that made it necessary to discontinue the transcranial stimulation treatment.

The most frequent diagnoses by group were those of the group of affective disorders (62.7%), as can be observed in table 1. Following in order was obsessive-compulsive disorder (13.1%), cognitive disorders (7.5%), personality disorders (4.7%) and psychiatric disorders (3.7%). A significant difference appears between genders in the greater frequency of cognitive disorders (delusions and dementia) ($\chi^2=18.79$; p<0.001) in males (14.6%) versus females (3.0%) and in affective disorders (dysthymia, single or recurrent depressive episode disorder, and bi-

Results after transcranial magnetic stimulation	n	Improvement	Partial improvement	Maintained improvement	No improvement
Global	107	48.6	24.3	24.3	51.4
Dysthymia	10	70.0	60.0	10.0	30.0
Single Episode Depressive Disorder	26	46.2	15.4	30.8	53.8
Recurrent Episode Depressive Disorder	22	63.6	18.2	45.5	36.4
Bipolar Disorder	9	88.9	22.2	66.7	11.1
Adaptive Disorder	1	100.0	100.0	0.0	0.0
Delusion	2	0.0	0.0	0.0	100.0
Cognitive deterioration	6	16.7	16.7	0.0	83.3
Dissociative disorder	1	0.0	0.0	0.0	100.0
Schizophrenia	3	0.0	0.0	0.0	100.0
Schizoaffective disorder	1	0.0	0.0	0.0	100.0
Generalized anxiety disorder	4	50.0	50.0	0.0	50.0
Conversion disorder	3	0.0	0.0	0.0	100.0
Obsessive-compulsive disorder	14	35.7	28.6	7.1	64.3
Personality disorder	5	40.0	40.0	0.0	60.0

Results after electroconvulsive therapy	n	Improvement	Partial improvement	Maintained improvement	No improvement
GLOBAL	20	75.0	40.0	35.0	25.0
Women	15	73.3	46.6	26.7	26.7
Men	5	80.0	20.0	60.0	20.0
Dysthymia	1	0.0	0.0	0.0	100.0
Single Episode Depressive Disorder	7	85.7	57.1	18.6	15.3
Recurrent Episode Depressive Disorder	6	83.3	66.6	16.7	16.7
Delusion	2	50.0	0.0	50.0	50.0
Schizophrenia	1	100.0	100.0	0.0	0.0
Schizoaffective disorder	1	0.0	0.0	0.0	100.0
Obsessive-compulsive disorder	1	100.0	100.0	0.0	0.0
Personality disorder	1	100.0	100.0	0.0	0.0

polar depressive episode disorder) ($\chi^2=13.64$; $p<0.001$) in females (72.73%) versus males (46.34%). The presence of personality disorders was 22.4%, with no difference in accordance to gender in general or specifically in any of the axis 1 diagnoses.

The global results of the TMS showed some type of improvement in 48.6%, which was stable in 24.3%. Results by diagnoses (table 2) showed greater efficacy of this technique in affective disorders ($\chi^2=8.92$; $p<0.01$), especially in recurrent depression and bipolar disorder. In fact, in bipolar disorder, improvement reached 88.9%, which was stable in 66.7%. No difference in the efficacy of the TMS could be found in any of the affective disorders based on gender or the presence of personality disorders.

No statistically significant decrease of efficacy was found for the results of the TMS in the presence of personality disorders, as principal diagnoses or as comorbid condition (table 2), when considering the general group or the groups diagnosed of greater efficacy, as affective disorders, either separately or in combination.

The ECT (table 3) was applied to a total of 20 patients, 15 women and 5 men, with a global result of improvement of 75.0%, which was maintained in 35.0%. In the depressive disorders, it was depressive in 7 of the 26 single episodes and in 6 of the 22 recurrent ones, with no significant changes being shown in the distribution by genders between the treatments applied. In the affective disorders, the ECT provided improvement and 84.6%, that was maintained in 17.5%

of the cases. Significant differences could not be seen in the result of the ECT among the different conditions.

DISCUSSION

In retrospective studies, especially naturalistic ones, it is not possible to control many of the variables that escape the control that can be performed in clinical trials. However, with these studies, many groups with a much larger sample size can be formed, thus allowing for the possibility of obtaining a more realistic idea of the true efficacy of the technique. Thus, although more controlled and directed groups can be used, the screening would eliminate comorbidity or the consideration of the time factor in form of stable improvement and subsequent response to other treatments in non-responder cases. Our study has made it possible to study clearly the importance of the time factor and stability of the positive response to TMS.

The stimulated zone, the left DLPF cortex, and the way it is stimulated, with high-frequency, is that used the most in clinical trials conducted in depressive conditions.^{14,15,18} Progressively, after having demonstrated the efficacy of TMS, the studies performed tend to seek the sequence in which the technique is performed within the protocol. Therefore, they include the use of drugs, as is done in the real clinical practice.^{19, 20} For this reason, we believe that our treatment protocol using TMS has been supported by the literature in this regard.

Our group has a similar age to that of other studies on depression^{14,15,18-20} or in other conditions.^{26,29,32,33} Even though age is considered as a negative prognostic factor for the efficacy of TMS,^{21,22} we have not been able to replicate this observation, not even when we purify the groups by diagnoses and analyze it in those having the greatest efficacy, such as affective disorders. It is possible that age as a negative prognostic factor found in other studies is a confounding factor associated to the presence of early affective symptoms in the initiation of a future cognitive disorder. We have also not found prognostic importance in the results of the TMS for the presence of personality disorder as a primary or secondary diagnosis. It seems that the action mechanism of TMS is highly linked to the pathophysiology of the depressive disorder, as indicated by the prognostic factors found in the studies of Cheeran²³ and Funk.²⁴

In the clinical trials performed on depression with the TMS as the only technique,^{14,15,18} treatment has been restricted only to right-handed subjects. Given the age range of the sample^{37,38} and the irregularity in the distribution of regulatory regions or their intercommunication with left-handed subjects^{43,44,45} it was decided to not consider dominance of the patients. In this age range, there is high prevalence in

the Spanish population of left-handed patients who were obligated to switch due to educational factors tending to the correction of left-handedness in the pursuit of a supposed social normalization.^{37,38} Thus, it must be considered in this population that lateralization in the tasks does not adequately correlate with brain lateralization.

The results obtained in our experience agree with the literature on the subject. Thus, the practical absence of side effects recorded in the clinical trials^{2,3} is maintained in ours, in which no treatment had to be withdrawn due to intolerance. On the other hand, the low global efficacy that we have recorded seems to be because the TMS was not effective on the depressive symptoms independently of the disease in which it was found. This is true especially when we focus on techniques in which negative results have been obtained, such of OCD or psychotic pictures, as in the previous studies.^{26, 29, 32, 33}

The positive results in the group of affective disorders were similar to those of the study with TMS in depression.^{14,16,35} The efficacy found in our series in the depressive phases of bipolar disorder, as occurred in the work of Dell'Osso,¹⁷ is especially significant. In accordance with that work, the magnificent tolerance of the technique and its efficacy makes it possible to propose the use of the TMS as a maintenance treatment in the prevention of relapses in depressive phase or in an early sequence of the treatment.

In our treatment schedule, the TMS was performed prior to the ECT. If we consider the global results, the ECT seems to be superior to the TMS. However, when we analyze its efficacy by diagnoses, no difference is observed with the TMS in the affective disorders. Thus, given the low prevalence of side effects of the TMS and its ease of application, its use should be considered prior to the ECT, as has been previously proposed.^{16, 19} It is precisely for the same reasons that it would not be necessary to perform more than three drug treatments appropriately, including pharmacological potentiation, before considering magnetic stimulation.

CONCLUSIONS

The TMS is a safe and reliable technique that does not have side effects or severe complications. This makes it a technique that is easy to apply, especially when compared with the ECT.

Stimulation of the left hemisphere dorsolateral prefrontal area (LPFDL) by TMS in patients with depressive symptoms is more effective if they correspond to affective disorders than if they correspond to other conditions.

The TMS on the LPFDL shows similar efficacy to that of the ECT in the affective disorders in which it had to be applied.

Due to all of this, the TMS could be included in resistant depression treatment protocols in a step prior to ECT, even as a coadjuvant form to an appropriate third pharmacological study. In this regards, it could be interesting to identify the areas to stimulate or inhibit through the use of neuroimaging diagnostic techniques.

Studies must continue to be performed, both naturalistic as this current one, as well as randomized, multicenter clinical trials with large samples that confirm that data herein provided and that can confirm possible factors of positive prognoses or negative response.

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