BRIEF REPORT

Transcranial Magnetic Stimulation in depression: results of bi-weekly treatment

Raphael Boechat-Barros[a] e Joaquim Pereira Brasil-Neto[a]

[a]Laboratório de Neurociências e Comportamento, Departamento de Ciências Fisiológicas, Instituto de Biologia – Universidade de Brasília, DF, Brasil

Abstract

***Objective**: Transcranial Magnetic Stimulation (TMS) has been shown to be a useful therapy for depression. This paper evaluates the results of bi-weekly low-frequency TMS of 4 weeks duration, in 10 patients with depression who do not respond or are intolerant to antidepressive medication.*

***Methods**: This is a case series study. DMS-IV criteria were used to diagnose depression. In order to disclose possible improvements in depressive symptoms, the 17 items Hamilton scale was used at three different moments: at the beginning, middle and end of the treatment period. Results were analysed using Friedman's x^2 test.*

***Results**: Hamilton's scale score improvement was ≥ 50% in five patients and ≥ 75% in 3 of these.*

***Conclusions**: TMS may be efficacious, safe and easily performed as an adjunct to medical treatment of depression. We cannot differentiate a potentiation of the effect of antidepressive medication from an intrinsic effect of TMS alone, since we did not treat any subjects without the concurrent use of medication.*

***Keywords**: Neurophysiology (instrumentation). Depression. Magnetics (therapeutic use).*

Introduction

Transcranial magnetic stimulation (TMS) was introduced by Barker et al. in 1985.[1] This technique uses a device capable of producing an electromagnetic field, rapidly variable in time, usually of nearly 2 tesla (40,000 times the Earth's magnetic field and having approximately the same intensity of the static magnetic field produced by a magnetic resonance device), which is conducted through a coil contacting the subject's scalp. This electromagnetic field passes through the skull stimulating a cortical area nearby, by means of the inducement of electrical loads in the brain parenchyma (electromagnetic induction – Faraday's Law). It is a form of electrical stimulation without electrodes, without the need for craniotomy.

Initially used in propedeutic, providing a series of information regarding the normal physiology of the human motor pathways,[2,3,4] TMS has started to be also used as a therapeutical tool in conditions such as Parkinson's disease[5] and epilepsy,[6] and research in the treatment of depression have begun 8 years ago.[7,8] Currently, other psychiatric pathologies such as mania,[9] schizophrenia,[10,11] obsessive-compulsive disorder[12] and post-traumatic stress-disorder[13] already have results with TMS.

Regarding the number of pulses per time unit, there are two types of TMS, low-frequency - < 1Hz , and high frequency - ≥ 1Hz, with diverse effects. The use of high-frequency magnetic stimulation increases the brain blood flow in the area, as measured through PET (positron emission tomography), with consequent increase in the brain activity, whereas low-frequency stimulation decreases it.[14]

In 1999, Daniel Menkes[15] published one of the first studies suggesting the efficacy of low-frequency TMS on depression. However, in that study they had not set the application days; it was only said that the treatment was composed of 8 sessions, lasting for 6 weeks, and there was no interval longer than 1 week between the applications and no more than two weekly applications were performed. In our protocol, which is similar to that of Menkes,[15] we have pre-established two weekly sessions, with a three-day interval between them. Except for this, we have used the same parameters of his study (described below).

Method

This is a descriptive study, that is, non-controlled, a case series study.

We have also used a Dantec® Maglite device, which was approved for use by the Food and Drug Administration in 1993 under the registration - K931923.

This study was approved by the Ethical Research Committee of the School of Medical Sciences of the University of Brasilia - CEP/FS UNB, according to the guidelines of the resolution 196/96 of the National Health Agency – Secretary of Health.

Ten patients have been studied, 8 males and 2 females (the initial sampling had 11 patients, being one female patient excluded for having missed one session), aged 19 to 54 years (mean of 34.9 years), with a diagnosis of major depressive episode according to the DSM - IV (Diagnostic and Statistical Manual of the American Psychiatric Association).[16] Patients were considered as difficult to be controlled by their psychiatrists, who decided to refer them to this experimental treatment as they had no psychopharmacological options, be it for the lack of response or for the intolerance to the medications used (pertaining to the several pharmacological classes of antidepressants). The response to electroconvulsotherapy was not assessed, as no patient was submitted to this kind of therapeutical modality. All subjects were from outpatient settings, upon whom the seventeen-item Hamilton scale was applied[17] in three moments: T1 - before the first application, T2 - in the middle of the study and T3 – at its end, by the same psychiatrist on all subjects, aiming to quantify a possible improvement. The intensity of depression, considering the scale's punctuation and following Blacker's classification,[17] was moderate in 2, severe in 3, and very severe in 5 patients. These patients were referred by psychiatrists of the public and private network of the Federal District and after the application they were referred back to their clinicians.

Patients under 18 years and above 55 years of age were excluded, as well as those with pacemakers or other metallic implants (due to the magnetic stimulation) and women who were pregnant or at risk of pregnancy. It was also ascertained that there was no psychiatric comorbidity or any concomitant disease which could prevent regular attendance to TMS sessions. Patients should also be able to understand and sign the informed consent form.

A 'butterfly' magnetic coil (more focal than round ones) was used. On each patient, 8 low-frequency transcranial magnetic stimulation sessions were carried out at a frequency of 0.5 Hz: 2 per week, each one with 5 series of 20 stimuli, with intervals of 1 minute between each series, applied on the right dorsolateral prefrontal cortex, 5 cm ahead of the optimal point to stimulate the first dorsal interrosseus muscle.[18]

In order to establish stimulus intensity, we have used the motor threshold as a reference; it is the minimal intensity of stimulus capable of producing visible movements in the musculature of the contralateral hand in at least 3 out of 5 simple pulses applied to the motor cortex. In this study we used stimuli up to 100% of the motor threshold.

All patients used the same medication, at the same doses as before enrollment in the study, throughout the whole rTMS treatment period.

Results

Evolution of the Hamilton scale score in the 10 patients and mean motor thresholds are shown in Table 1.

The mean stimulus intensity applied (determined by the motor threshold) was 34.56 % of the maximal stimulator output.

For the statistical analysis we have used Friedman's non-parametric repeated measures comparisons (Friedman's x^2), which showed significant results ($p < 0.01$). Ranks were assigned to Hamilton scale's scores corresponding to the moments T1, T2 and T3 and the null hypothesis was that there were no significant differences between the scores at the beginning, middle and end of treatment. With two degrees of freedom, xp^2 was higher than critical value x^2, what rejected the null hypothesis.

Analyzing the four-week treatment, we observed a pattern considered as response, i.e., improvement of $\geq$ 50% in the punctuation in the Hamilton scale in 5 patients. Three patients had a pattern considered as remission,[15] with a punctuation below 8 in the same scale.

Considering the set of all patients, the mean percentage of improvement during the treatment was 50.45%.

Discussion

The main advantages of this TMS protocol are:

1) Safety: There are no cases of convulsive crisis triggered by low-frequency TMS;

2) Practicality: Patients do not need to come to the service daily, being treated only twice a week;

3) Cost: The cost of the low-frequency TMS device is significantly lower than the high-frequency one, as it does not need a complex refrigeration system.

In this study, we have observed different response profiles to the same treatment. Patients 4, 7 and 9 showed an initial improvement with subsequent worsening, what may suggest

Table 1 – Scores of the 10 patients at T1, T2, T3 and percentage of improvement between T1 and T3

Patients	Score At T-1	Score At T-2	Score At T-3	Percentage of Improvement Between T1 And T3
1	38	35	34	10.52%
2	34	20	13	61.76%
3	22	9	2	90.90%
4	24	18	21	12.5%
5	17	9	2	88.23%
6	14	8	6	57.14%
7	20	12	13	35%
8	30	16	17	43.33%
9	20	15	16	20%
10	27	8	4	85.18%

some kind of placebo effect, as the rapid improvement obtained was not sustained during all the treatment period, configuring a response pattern classically associated to placebo-responsive subjects.

The continuous decrease in the punctuation of 6 out of 10 patients along the study led us to speculate if a higher number of sessions or the extension of the treatment could improve even further their clinical condition.

As this treatment method is still very recent, the optimal parameters of stimulation and frequency of application have not yet been defined. In our study, we have initially used bi-weekly applications, as there were previous reports in the literature which had used this protocol.[15] As there was an improvement, we have chosen to augment it through the increase in the frequency of applications in future studies. This study was discontinued at this point precisely due to its positive results, which authorize and encourage us to use more frequent stimulations. On the other hand, if daily stimulation demonstrates to be no better than bi-weekly ones, the latter regime is much more practical and less costly for the patient.

It is important to highlight that those patients were deemed difficult to treat by their clinical psychiatrists. Thus, it is conceivable that with a random population of depressed patients the results would be better.

In this study, for ethical reasons, we did not use a control group with sham stimulation, as subjects were severely depressed patients. Besides, at that moment (nearly two years and a half before we wrote this article) therapeutical TMS was described in the literature with very promising results, and it did not seem ethical to us to deprive severely depressed patients of such a promising treatment. Once established that the beneficial effects of this treatment are not so remarkable, placebo may be used in further studies, even in severely ill patients.

These results suggest that bi-weekly low-frequency TMS is a valuable treatment for depression, although further studies are required. We cannot define whether the results are due to an augmentation of the antidepressive effect or to an isolated effect of TMS, as we have not tested it in patients without concomitant pharmacological treatment. We suggest that in the current state of knowledge on this therapeutic it should not be used alone, without the use of antidepressants.

Sponsor: None
Received 29.09.2003
Accepted 30.01.2004

References

1. Barker AT, Jalinous R, Freeston IL. Noninvasive magnetic stimulation of human motor cortex. Lancet 1985;i:1106-7.

2. Brasil-Neto JP. Uma interação promissora entre a neurociência básica e a terapêutica em psiquiatria. Rev Bras Psiquiatr 2001;23(2):61.

3. Brasil-Neto JP, McShane LM, Fuhr P, Hallett M, Cohen LG. Topographic mapping of the human motor cortex with magnetic stimulation: factors affecting accuracy and reproductibility. Electroencephalogr Clin Neurophysiol 1992;85:9-16.

4. Pascual-Leone A, Tormos JM, Keenan J, Tarazona F, Canete C, Catala MD. Study and modulation of human cortical excitability with transcranial magnetic stimulation. J Clin Neurophysiol 1998;15:333-43.

5. Pascual-Leone A, Valls-Sole J, Brasil-Neto JP, Cohen LG, Hallet M. Akinesia in Parkinson's disease. I. Shortening of simple reaction time with focal, single-pulse transcranial magnetic stimulation. Neurology 1994;44:884-91.

6. Chen R, Classen J, Gerloff C, Wassermann EM, Hallett M, Cohen LG. Depression of cortex excitability by low-frequency transcranial magnetic stimulation. Neurology 1997;48:1398-403.

7. George MS, Wassermann EM, Williams WA. Daily repetitive transcranial magnetic stimulation (rTMS) improves mood in depression. NeuroReport 1995;6:1853-6.

8. Brasil-Neto JP, Boechat-Barros R, Mota-Silveira DA. O uso da estimulação magnética transcraniana de baixa freqüência no tratamento da depressão no Hospital Universitário de Brasília: achados preliminares. Arquivos de Neuropsiquiatria 2003;61(1):83-6.

9. Grisaru N, Chudakov B, Yaroslavsky Y, Belmaker RH. TMS in mania: a controlled study. Am J Psychiatry 1998;155(11):1608-10.

10. Feinsod M, Kreinin B, Chistyacov A, Klein E. Preliminary evidence for a beneficial effect of low-frequency, repetitive transcranial magnetic stimulation in patients with a major depression and schizophrenia. Depress Anxiety 1998;7:65-8.

11. Hoffman RE, Boutros NN, Berman RM, Roessler E, Belger A, Krystal JH, Charney DS. Transcranial magnetic stimulation of left temporal cortex in three patients reporting hallucinated "voices". Biol. Psychiatry 1999;46(1):130-2.

12. Greenberg BD, George MS, Martin JD, Benjamin J, Schlaepfer TE, Altemus M, Wassermann EM, Post RM, Murphy DL. Effect of prefrontal repetitive transcranial magnetic stimulation in obsessive-compulsive disorder: a preliminary study. Am J Psychiatry 1997;154:867-9.

13. Grisaru N, Amir M, Cohen H, Kaplan Z. Effects of transcranial magnetic stimulation in posttraumatic stress disorder: a preliminary study. Biol Psychiatry 1998;44(1):52-5.

14. Speer AM, Kimbrell TA, Wassermann EM, Repella JD, Willis MW, Herscovitch P, Post RM. Oppositive effects of high and low frequency rTMS on regional brain activity in depressed patients. Biol Psychiatry 2000;48:1133-41.

15. Menkes DL, Bodnar P, Ballesteros RA, Swenson MR. Right frontal lobe slow frequency repetitive transcranial magnetic stimulation (SFr-TMS) is an effective treatment for depression: a case-control pilot study of safety end efficacy. J Neurol Neurosurg Psychiatry 1999;67:113-5.

16. Kaplan H, Sadock B, Greeb J. Compêndio de Psiquiatria, Ciências do Comportamento e Psiquiatria Clínica. 7ª Ed. Batista D. Porto Alegre: Artes Médicas 1997:493-544.

17. Moreno RA, Moreno DH. Escalas de Avaliação para Depressão de Hamilton (HAM-D) e Montgomery-Asberg (MADRS). In: Gorenstain C, Andrade LHSG, Zuardi AW, editores. Escalas de Avaliação Clínica em Psiquiatria e Psicofarmacologia. São Paulo: Lemos-Editorial;2000. p. 65-87.

18. Pascual-Leone A, Rubio B, Pallardó F, Catalá MD. Rapid-rate transcranial magnetic stimulation of left dorsolateral prefrontal cortex in drug-resistant depression. Lancet 1996;347: 233-7.

Correspondence
Joaquim Pereira Brasil-Neto
ICC sul, módulo 8 - Universidade de Brasília
70910-900 Brasília, DF, Brasil
Tel.: (61) 307-2175 ramal 25 fax: (61) 346-1870
E-mail: jbrasil@unb.br