ORIGINAL ARTICLE

An evaluation of factors affecting duration of treatment with repetitive transcranial magnetic stimulation for depression

Avaliação de fatores associados à duração do tratamento com a estimulação magnética transcraniana repetitiva na depressão

Roni Broder Cohen[1], Felipe Fregni[2], Paulo Sergio Boggio[3]

ABSTRACT

Objective: To investigate the effects of repetitive transcranial magnetic stimulation in patients with major depression who were submitted to this treatment during the period from 2000 to 2006. **Methods:** A retrospective study with 204 patients who underwent treatment with repetitive transcranial magnetic stimulation, collecting data from those who experienced remission (defined as a HDRS score equal to or lower than 7). The patients were followed for up to 6 months after treatment. Mean duration of remission for this cohort of patients was 70.2 (± 58.4) days. **Results:** The only variable associated with the duration of remission in the linear regression model was number of repetitive transcranial magnetic stimulation sessions. **Conclusion:** Our findings suggest that the greater the number of sessions, the longer the duration of repetitive transcranial magnetic stimulation effects. Consequently, future research investigating the effects of repetitive transcranial magnetic stimulation should explore this variable in order to maximize the therapeutic effects of this new brain stimulation technique.

Keywords: Depression/therapy; Deep brain stimulation; Transcranial magnetic stimulation; Risk factors

RESUMO

Objetivo: Investigar os efeitos da estimulação magnética transcraniana repetitiva em pacientes com depressão maior que se submeteram a esse tratamento durante o período de 2000 a 2006. **Métodos:** Realizou-se um estudo retrospectivo com 204 pacientes, que se submeteram ao tratamento com a estimulação magnética transcraniana repetitiva, coletando os dados daqueles que tiveram remissão do quadro (definido como escore da HAM-D menor ou igual a 7). Os pacientes foram seguidos até seis meses após o tratamento. A duração média da remissão para essa coorte de pacientes foi 70,2 dias (± 58,4). **Resultados:** A única variável que foi associada com a duração da remissão no modelo de regressão linear foi o número de sessões com a estimulação magnética transcraniana repetitiva. **Conclusão:** Nossos achados sugerem que, quanto maior o número de sessões, mais longa a duração dos efeitos da estimulação magnética transcraniana repetitiva. Conseqüentemente, pesquisas futuras que investiguem os efeitos da estimulação magnética transcraniana de repetição precisam explorar essa variável para maximizar os efeitos terapêuticos dessa nova técnica de estimulação cerebral.

Descritores: Depressão/terapia; Estimulação encefálica profunda; Estimulação magnética transcraniana; Fatores de risco

INTRODUCTION

Transcranial magnetic stimulation (TMS) was introduced in 1985 by Anthony Barker et al.[1] and has been investigated for the treatment of depression since mid 1990s[2]. Several studies were published evaluating the efficacy of this therapy for major depression. The meta-analyses of these studies suggest that active repetitiveTMS (rTMS) is effective in reducing depression as compared with sham rTMS[3-6]. Although these studies showed that rTMS induces a significant improvement in depressive symptoms, so far, these investigations only assessed the short-term effects of rTMS. Therefore the question whether the effects of rTMS are long-lasting remains unanswered.

We therefore conducted a large retrospective study with 204 patients who remitted depression after rTMS treatment. In this study patients were followed up to 180 days after the end of rTMS treatment. To our knowledge, this is the longest follow-up period with a large sample size. We initially analyzed duration of remission and then performed further models to analyze the factors that

Study carried out at the Centro Brasileiro de Estimulação Magnética Transcraniana – CBREMT, São Paulo (SP), Brazil.

[1] Director of the Centro Brasileiro de Estimulação Magnética Transcraniana –CBREMT, São Paulo (SP), Brazil.

[2] Post-doctorate in Neurology; Professor at the Harvard Medical School, Center for Noninvasive Brain Stimulation, Boston (MA), USA.

[3] PhD in Psychology; Lecturer and researcher at the Centro de Ciências Biológicas e da Saúde – CCBS, Universidade Presbiteriana Mackenzie – UPM, São Paulo (SP), Brazil.

Corresponding authors: Roni Broder Cohen – Rua Itambé, 341 – Casa 12 – Higienópolis – CEP 01239-001 – São Paulo (SP), Brazil – Tel.: 11 3255-7537 – e-mail: dr.broder@uol.com.br

Received on May 14, 2007 – Accepted on Nov 08, 2007

were associated with an increased duration of remission. This study adds to the results of our previous analysis using survival models in the same sample size that are described elsewhere.

OBJECTIVE

To investigate the therapeutic effects of rTMS in major depression patients who underwent treatment with rTMS.

METHODS

Subjects

The study was a retrospective analysis of patients from the Centro Brasileiro de Estimulação Magnética Transcraniana – CBrEMT – undergoing treatment of transcranial magnetic stimulation for the treatment of depression from the period of 2000 to 2006. The diagnosis of major depression was made using the criteria of DSM-IV Axis I Disorders (SCID) by an experienced senior psychiatrist (R.B.C.). Although rTMS treatment was performed with clinical purposes, patients signed an informed consent form acknowledging that their data might be used for publication.

This study was approved by the local and also national research ethics committee (SISNEP number CAAE – 0040.0.272.000-07.

Data on overall depression remission (according to Hamilton Depression Rating Scale 17 –items [HDRS] score less or equal 7) was determined for each patient. HDRS scores were analyzed at baseline, after 10, 20, 30, 60, 120, 150 and 180 days of treatment. Remission time was calculated from the session that remission was achieved to the date of relapse.

In order to investigate the risk factors associated with relapse, we performed a linear regression model (note that we performed a survival analysis with these data that is described elsewhere). The advantage of using the linear regression method is that this method has less assumptions and an easier interpretability. The following variables were entered in our model: demographic variables (age, sex); clinical variables (baseline HDRS, medications, duration of depression, number of episodes, previous use of ECT and depression refractoriness) and rTMS variables [rTMS intensity (dichotomized as 100% of less or higher than 100%), rTMS frequency (dichotomized as high (> 1 Hz) or low frequency (≤ 1 Hz) and number of rTMS sessions]. Patients were considered as being refractory if they were using more than three antidepressants, had more than three episodes of depression, the duration of the current episode was longer than two years or had undergone ECT treatment in the past.

RTMS treatment sessions were given only on weekdays. Repetitive TMS was administered using a figure-eight coil and applied over the dorsolateral prefrontal cortex (DLPFC) (5 cm anterior to the motor spot that elicited motor evoked potentials in either the abductor pollicis brevis or the first interosseous dorsalis muscle of the right hand). Two strategies of stimulation were performed (high-frequency of left DLPFC or low-frequency of right DLPFC). We addressed the influence of these two strategies and also rTMS intensity in our model. Finally the number of rTMS sessions varied from 10 to 30 consecutive weekdays.

Our goal was to model the relation between these predictors and the duration of remission time using a linear regression analysis. We considered our dependent variable as normally distributed using the central limit theorem for large sample sizes as our sample had 204 patients. Therefore the use of linear regression was adequate and means and standard deviation are reported.

The first step of modeling was selection of covariates. We performed a univariate analysis for each one of our predictors using linear regression with only one variable and we obtained the values for the unadjusted beta coefficients and 95% confidence intervals. We decided to include in our model building process all variables that had a p-value lower than 0.1 in order to include potential confounders that did not reach the 0.05 significance level in the univariate analysis.

We used a forward selection process (with the option stepwise selection) to build our model. This methodology is well-suited to exclude collinear terms, but risks excluding non-significant confounders. To correct for this caveat, we examined the potential confounding effect of each one of the excluded variables by adding them individually to the model. Confounding was defined by changes of ± 10% or higher in the beta coefficient of any variable from the forward selection model. Confounders were included in our final model.

All reported P values are two-tailed. Mean and standard deviation are reported, unless otherwise specified. Statistical analyses were performed with use of the SAS system for Windows, version 9.13 (SAS Institute, Cary, N.C.).

RESULTS

We included 204 subjects in this analysis. Forty-nine percent of these subjects were men (101 males and 103 females) and the mean age was 43.3 (± 13.4) years. Mean HDRS scores at baseline were 22.0 (± 4.3). Patients had, on average, 2.2 (± 2.8) previous episodes of depression and the mean duration of the current episode was 14.8 (± 15.9) months. Finally 29% of patients were determined as being refractory (60/145 patients) according to our

criteria and 22 patients (10.0%) had undergone ECT treatment.

Adverse effects were reported in 22 occasions. The following adverse effects were reported: nightmares (12 patients), headache (5 patients), increased anxiety (2 patients), tingling (2 patients) and increased somnolence (1 patient). There were no seizures or any other serious adverse event.

Psychotropic drugs were being taken by 80.0% of patients. The following drugs were being taken: benzodiazepines (BDZ) (51.0%), selective serotonin reuptake inhibitors (SSRI) (31.8%); novel antidepressants with serotoninergic and adrenergic action (venlafaxine, bupropion, reboxetin, mirtazapine) (new AD) (25.9%); neuroleptics (NEU) (18.1%); mood stabilizers (antiepileptic drugs – AED) (13.3%); tricyclics (TCA) (12.7%); MAO inhibitors (6.7%) and lithium (LTM) (4.3%).

The mean remission duration was 70.2 (± 58.4) days. In order to select the variables for the multivariate analysis, we performed an univariate analysis in which we calculated the association between remission time and each variable using a linear regression model. We selected the variables that had a P value lower than 0.1 in order to include potential confounders that did not reach the 0.05 significance level in the univariate analysis. This univariate analysis yielded only one predictor significantly associated with remission time – number of sessions ($p < 0.001$) (Table 1). We therefore did not proceed with our model selection as there was only one variable that showed to be significant in the univariate analysis. Interestingly the model with the variable number of sessions showed a beta coefficient of 1.96; indicating that each additional day of treatment increased the remission time by two days on average.

Table 1. Univariate analysis

Variable	DF	Parameter estimate	Standard error	P-Value
Age	1	0.17	0.30	0.56
Gender	1	5.82	8.18	0.47
Baseline HDRS	1	0.75	0.95	0.43
rTMS intensity	1	10.79	10.20	0.29
rTMS frequency	1	4.49	7.59	0.55
SSRI	1	-2.72	8.79	0.75
New AD	1	6.93	9.33	0.45
TCA	1	-12.04	12.27	0.32
Neuroleptics	1	-5.39	10.52	0.61
BDZ	1	11.82	8.15	0.15
Lithium	1	11.51	16.20	0.48
MAO	1	-10.03	19.97	0.61
AED	1	-2.47	11.92	0.83
Meds	1	8.02	10.31	0.43
ECT	1	-13.38	14.14	0.34
Number of sessions	1	1.96	0.46	< 0.001
Refractoriness	1	-11.46	8.96	0.20

HDRS = Hamilton Depression Rating Scores; SSRI = selective serotonin reuptake inhibitors; New AD = novel antidepressants with serotoninergic and noradrenergic action (ex: reboxetin and mirtazapine); TCA = tricyclic antidepressants; BDZ = benzodiazepines; MAO = monoamine oxidase inhibitor; AED = antiepileptic drugs; Meds = use of psychotropic medications; ECT = electroconvulsive therapy; Refractoriness = depression refractoriness as defined in methods.

DISCUSSION

Our findings showed that the number of rTMS sessions was associated with long duration of remission according to the model selection procedure. Finally adverse effects were not frequent and they were mild in this study.

An important finding in this study is that the number of rTMS sessions is a risk factor for relapse, and less sessions is associated with a greater chance of early relapse. Other studies showed a relation between antidepressant response and number of rTMS sessions. In a previous meta-analysis, Martin et al.[6] showed that whereas 5 days of active stimulation is associated with a small non-significant effect size, 10 days of stimulation is associated with a significant effect size favoring the active treatment. In addition, further studies using up to 30 sessions of rTMS showed a linear, cumulative effect, such as that the effects of rTMS increase over time[7-9]. It is also important to note that in our study as in other studies that applied rTMS up to 30 sessions of stimulation, the frequency and severity of adverse effects did not increase; however, this matter has not been assessed systematically.

One important point here is that rTMS sessions should be applied consecutively. Indeed in a previous study, Baumer et al.[10] showed that whereas two consecutive sessions of rTMS of the motor cortex in healthy subjects lead to after-effects on cortical excitability that lasts for two hours, when the second session is performed seven days after the first session this effect is not observed[10]. Therefore consecutive daily rTMS sessions can induce memory in the stimulated networks resulting therefore in an increase in the magnitude of the effect. As suggested, this effect might be similar to the phenomenon of long-term potentiation (LTP) and long-term depression (LTD) observed in animals[11].

An important matter when using rTMS treatment is the definition of parameters of stimulation, particularly frequency and intensity of stimulation (number of sessions was discussed above). We showed that frequency and intensity of stimulation were not predictors of the remission time. Previous studies show that these two factors are not independent predictors of the antidepressant response. In a recent study, Herrmann et al.[4] analyzed whether parameters of stimulation could predict the outcome pooling data from 33 studies on rTMS for the treatment of depression. There were no significant predictors of the effect size. The authors concluded that either parameters of stimulation do not play a significant role or the study was not powered adequately to detect significant predictors. In another study, Fregni et al.[12], in a study in which data from six different clinical trials were merged, showed these two parameters of

stimulation – frequency and intensity of stimulation – are not significant predictors of the antidepressant response[12]. An important issue is that, in our study, the majority of stimulation sessions were performed using low-frequency rTMS that might have reduced the power of this analysis. However, a previous study comparing high and low-frequency rTMS for the treatment of depression showed no difference in depression scores reduction between these two strategies of stimulation[13], however, remission time was not compared. Finally, although the frequency of stimulation also does not appear to be significantly associated with antidepressant effects, rTMS studies used intensity of stimulation in a small range (usually from 80% to 120% of motor threshold). Therefore, intensities outside this range might produce different results.

Finally, two other variables that were not associated with remission duration should be discussed – refractoriness and medications. Although we have previously shown that refractoriness is associated with a significant effect on antidepressant response[12] and greater duration of disease is also associated with a smaller antidepressant response[14], after achieving remission, it appears that it is not important if the patient was previously refractory to determine the duration of remission. Another potential explanation is that our method to determine refractoriness did not capture all variance of this factor and therefore we could not show a potential relationship. Future prospective studies should explore this question further. Finally we showed that medications are not associated with duration of remission. However, it should be noted here that medications were kept constant and not introduced after rTMS treatment. The question whether medications introduced after remission with rTMS influence the duration of remission is yet to be determined.

CONCLUSION

This study is the first to explore the factors that are associated with remission duration in patients who underwent rTMS treatment for depression. Further studies should explore this question further and also investigate whether maintenance treatment can maintain the effects of rTMS for a longer period of time in order to develop rTMS as a clinical tool.

REFERENCES

1. Barker AT, Jalinous R, Freeston IL. Non-invasive magnetic stimulation of human motor cortex. Lancet. 1985;1(8437):1106-7.
2. Pascual-Leone A, Rubio B, Pallardo F, Catala MD. Rapid-rate transcranial magnetic stimulation of left dorsolateral prefrontal cortex in drug-resistant depression. Lancet.1996; 348(9022):233-7.
3. Burt T, Lisanby SH, Sackeim HA. Neuropsychiatric applications of transcranial magnetic stimulation: a meta analysis. Int J Neuropsychopharmacol. 2002; 5(1):73-103.
4. Herrmann LL, Ebmeier KP. Factors modifying the efficacy of transcranial magnetic stimulation in the treatment of depression: a review. J Clin Psychiatry. 2006; 67(12):1870-6.
5. Holtzheimer 3rd PE, Russo J, Avery DH. A meta-analysis of repetitive transcranial magnetic stimulation in the treatment of depression. Psychopharmacol Bull. 2001;35(4):149-69.
6. Martin JL, Barbanoj MJ, Schlaepfer TE, Thompson E, Perez V, Kulisevsky J. Repetitive transcranial magnetic stimulation for the treatment of depression. Systematic review and meta-analysis. Br J Psychiatry. 2003;182:480-91.
7. Avery DH, Holtzheimer 3rd PE, Fawaz W, Russo J, Neumaier J, Dunner DL, et al. A controlled study of repetitive transcranial magnetic stimulation in medication-resistant major depression. Biol Psychiatry. 2006;59(2):187-94.
8. Fitzgerald PB, Benitez J, de Castella A, Daskalakis ZJ, Brown TL, Kulkarni J. A randomized, controlled trial of sequential bilateral repetitive transcranial magnetic stimulation for treatment-resistant depression. Am J Psychiatry. 2006;163(1):88-94.
9. Rumi DO, Gattaz WF, Rigonatti SP, Rosa MA, Fregni F, Rosa MO, et al. Transcranial magnetic stimulation accelerates the antidepressant effect of amitriptyline in severe depression: a double-blind placebo-controlled study. Biol Psychiatry. 2005;57(2):162-6.
10. Baumer T, Lange R, Liepert J, Weiller C, Siebner HR, Rothwell JC, et al. Repeated premotor rTMS leads to cumulative plastic changes of motor cortex excitability in humans. Neuroimage. 2003;20(1):550-60.
11. Chen SJ, Sweatt JD, Klann E. Enhanced phosphorylation of the postsynaptic protein kinase C substrate RC3/neurogranin during long-term potentiation. Brain Res.1997;749(2):181-7.
12. Fregni F, Marcolin MA, Myczkowski M, Amiaz R, Hasey G, Rumi DO, et al. Predictors of antidepressant response in clinical trials of transcranial magnetic stimulation. Int J Neuropsychopharmacol. 2006;9(6):641-54.
13. Fitzgerald PB, Brown TL, Marston NA, Daskalakis ZJ, De Castella A, Kulkarni J. Transcranial magnetic stimulation in the treatment of depression: a double-blind, placebo-controlled trial. Arch Gen Psychiatry. 2003;60(10):1002-8.
14. Holtzheimer 3rd PE, Russo J, Claypoole KH, Roy-Byrne P, Avery DH. Shorter duration of depressive episode may predict response to repetitive transcranial magnetic stimulation. Depress Anxiety. 2004;19(1):24-30.