

Update on the electroconvulsive therapy (ECT) efficacy in the treatment of manic episodes of bipolar disorder

Atualização sobre a eficácia da eletroconvulsoterapia (ECT) no tratamento dos episódios maníacos do transtorno bipolar

Monique Almeida Vaz¹, Felipe Rocha Silva¹, Bruna Evellyn de Lima Alves¹,
Daniele Oliveira Ferreira da Silva²

Abstract

Bipolar disorder (BD) is a mood disorder characterized by manic, hypomanic and depressive episodes, which cause social, professional, financial or physical damage, and is a risk factor for suicide. Electroconvulsive therapy (ECT) has been well established as a treatment for refractory depression to drugs, but studies addressing the ECT effectiveness in the treatment of mania are scarce. This study evaluated studies published in the last 10 years on the ECT effectiveness in the treatment of manic episodes of bipolar disorder, and for this purpose, 4 articles were analyzed. Two randomized studies found that groups submitted to ECT showed significant response to treatment criteria. Another study showed inconclusive results regarding the ECT efficacy in manic episodes, but a positive outcome for the usefulness of the method. The other study analyzed the use of ECT in pregnant women, showing that the treatment was effective, but that further studies in relation to maternal and fetal risks should be conducted. It was therefore concluded that ECT can be a viable option for the treatment of manic episodes.

Key words: Electroconvulsive therapy, bipolar disorder, manic episodes

Resumo

O transtorno bipolar (TB) é uma alteração de humor caracterizada por episódios maníacos, hipomaníacos e depressivos, que acarretam prejuízos sociais, profissionais, financeiros ou físicos, além de ser fator de risco para o suicídio. A eletroconvulsoterapia (ECT) já está bem estabelecida como tratamento para depressão refratária a medicamentos, mas os estudos que tratam sobre a eficácia da ECT no tratamento da mania são escassos. O presente trabalho avaliou estudos publicados nos últimos 10 anos sobre a eficácia da ECT no tratamento dos episódios maníacos do

1. Acadêmicos do curso de Medicina da Universidade Católica de Brasília

2. Docente da disciplina de psiquiatria na Universidade Católica de Brasília

E-mail do primeiro autor: moniquevazz@gmail.com

transtorno bipolar, para tal fim, foram analisados 4 artigos. Dois estudos randomizados apontaram que os grupos submetidos a ECT apresentaram significativa resposta aos critérios de tratamento. Outro estudo apresentou resultados pouco conclusivos em relação à eficácia de ECT no episódio de mania, porém com desfecho positivo para a utilidade do método. O último estudo analisou o uso de ECT em gestantes, mostrando eficácia no tratamento, mas exigindo análises mais profundas em relação aos riscos materno-fetais. Compreende-se, então, que a ECT pode ser uma opção viável para o tratamento dos episódios maníacos.

Palavras-chave: Eletroconvulsoterapia; Transtorno bipolar; Episódios maníacos

Introduction

Bipolar disorder (BD) is a mood disorder characterized by manic, hypomanic and depressive episodes¹. BD can be divided into types I and II^{1,2}. Type I BD is defined as the occurrence of at least one manic episode at any time of life¹. Type II BD is defined as the occurrence of at least one hypomanic episode and a major depressive episode.

Major depressive episode is characterized as a depressed mood or loss of pleasure associated with other symptoms such as change in body weight, changes in sleep patterns, agitation or psychomotor retardation, fatigue, loss of energy, feelings of guilt or worthlessness and death thoughts¹. The initial episode of BD presentation is depression in 59% of times². Mania is a state in which the individual, in addition to presenting expansive or irritable mood, can also show high self-esteem, talkativeness, hypotenacity, low need for sleep, psychomotor restlessness, racing thoughts and potentially harmful behaviors. The main feature that differs mania from

hypomania is the social or professional damage that affects the individual: if it is severe, the episode is defined as mania; otherwise, it is defined as hypomania³.

A study with 61,392 patients in 11 countries suggests that bipolar disorder may be underdiagnosed⁵. Classical statistics reveals a worldwide prevalence of 1.1% for bipolar disorder¹. However, this prevalence may increase to 2.4% when considering the diagnosis of bipolar spectrum disorder, which also includes patients who do not completely meet the DSM-5 criteria for type I or type II⁵. Many of these patients, even without the full criteria, are subject to damage from bipolarity⁵.

Bipolar disorder, besides causing social, professional, financial or physical damage, is also a risk factor for suicide⁴. People with BD have a suicide risk over the life of 8%⁴, reaching 25% in the early stages of the disease³.

The Electroconvulsive therapy (ECT) is well established as a treatment for

refractory depression to drugs⁶. However, studies addressing the effectiveness of ECT in the treatment of mania are scarce.

According to Resolution No. 1.640 / 2002 of the Federal Council of Medicine, ECT is a procedure that takes place in the hospital environment by written consent of the patient. It is administered under general anesthesia and under the use of neuromuscular blockers, and the seizure must be recorded by electroencephalogram.

The classical techniques of placing electrodes are bilateral and right unilateral⁹. In bilateral ECT, two electrodes are positioned, one on each frontotemporal region of the patient. In right unilateral ECT, one electrode is positioned in the frontotemporal region and the other adjacent to the skull vertex. Studies indicate that bilateral ECT is more effective compared to right unilateral ECT¹⁰, although it has higher incidence of adverse effects in the short term such as retrograde amnesia¹¹. Thus, most patients initiate right unilateral technique and if there is no response after 3-6 sessions, electrode placement changes to bilateral⁶. More serious patients may start directly with bilateral technique.

Currently, bifrontal technique has also been studied. In this technique, electrodes are positioned in frontal region of the patient close to the eyebrows, with efficacy and adverse effect profile similar to bitemporal technique⁶.

One of the most common adverse effects of this procedure is headache, which occurs in up to 48% of cases¹². The most feared adverse effect of ECT is retrograde amnesia¹³. In general, there is an improvement over the months following the end of ECT, though some effects may remain^{12,13}.

The aim of this study was to evaluate studies published in the last 10 years on the ECT effectiveness in the treatment of manic episodes of bipolar disorder.

Methodology

A literature review of studies published between 2006 and 2016 addressing the efficacy of electroconvulsive therapy in the treatment of manic episodes of bipolar disorder was performed. Studies published in the PubMed, LILACS and SciELO databases were analyzed.

The criteria used for the search in PubMed were articles containing in title or abstract both "Electroconvulsive Therapy" and "Bipolar Disorder" or "Electroconvulsive Therapy" and "Mania". The type of article was limited to clinical trials, observational studies and comparative studies. In LILACS, articles containing health descriptors "Electroconvulsive Therapy" and "Bipolar Disorder" were searched. In SciELO, articles containing these two terms in "all indexes" were searched.

In total, 37 distinct articles were found. Of these, it was not possible to access the full text of 3 potentially eligible. After excluding case reports and literature reviews, only 4 articles met the selection criteria and were evaluated.

Discussion

A randomized double-blind study conducted by Hiremani et al.¹⁴ evaluated 36 patients aged 18-45 years in India, all of which had manic episodes. The study aimed to compare the effectiveness of bifrontal and bitemporal Electroconvulsive therapy (ECT) in patients with acute mania episodes. Of the 36 patients, none had rapid-cycling bipolar disorder (BD) or had undergone ECT in the previous month. In the clinical history of patients, ECT was indicated as the treatment of choice for 29 of the study patients; six were non-responsive to pharmacotherapy with valproate (n = 4), lithium (n = 1) and carbamazepine (n = 1); and one patient was intolerant to the use of lithium and chlorpromazine.

A group of 19 patients were randomized to receive bifrontal ECT (ECT-BF), and 17 bitemporal ECT (ECT-BT). ECT was held for three times a week over a period of 21 days with a pause in the administration of mood stabilizers in the three days retrospective to ECT, as well as lorazepam and haloperidol in the previous 12 hours.

However, the use of antipsychotics remained in both groups. The severity of mania episodes was measured by the Young Mania Rating Scale (YMRS), applied one day prior to ECT and on days 3, 7, 11, 14 and 21 after treatment.

At the end of the study, difference in mean YMRS score between groups were found (Group x occasional effect, quadratic trend: $F = 13.05$, $df = 1.33$ $p = 0.03$). Group submitted to ECT-BF showed faster improvement in manic episodes than ECT-BT. In the survival analysis, it was found that a significant proportion of ECT-BF group patients had earlier response compared to the ECT-BT group (Breslow statistic = 5:52; $df = 1$; $p = 0.019$), and 87.5% of patients in the first group and 72.2% in the second group showed response criteria to treatment. This result showed that ECT-BF may be preferable when rapid control of the acute manic episode is needed.

In order to analyze differences in improvement time and remission of manic episodes after treatment with differentiated ECT administration, Mohan et al.¹⁵ conducted a randomized clinical trial. This study was developed in India with the participation of 52 patients aged 20-45 years diagnosed with manic episodes (minimum score of 26 on YMRS), with severe symptoms according to the Clinical Global Impression (CGI) scale without response to conventional drug therapy

and who were indicated for ECT. Prior to the study, all patients were treated with antipsychotics (Risperidone 6-8 mg / day and Olanzapine 15-30 mg / day), which were maintained during treatment with ECT.

Of the 52 patients, two could not be submitted to ECT, since one had abnormalities on echocardiography, and the other received no consent for participation from the family. The remaining 50 patients were randomized into two groups, one with 26 patients who underwent ECT therapy threshold intensity for stimulating seizure, and another group of 24 patients, who received different ECT therapy with threshold intensity 2.5 times above that conducted in the second treatment session (supra-threshold) bilaterally twice a week. Anticonvulsants and lithium were suspended before therapy. In addition, all patients received benzodiazepines (lorazepam above 8mg / day) and intramuscular haloperidol (5-10 mg + promethazine 25-50mg) in order to reduce agitation or behavioral disorders. Patients were followed for one month after the end of ECT sessions.

The results showed that 92% (46/50) of patients treated with ECT had significant improvement in mania symptoms, with CGI \leq 2. Of all patients, 88% had remission of mania episodes after the end of therapy, with no significant difference between groups (OR = 1.1, 95% CI: 0.2-6.0; $p = 1.0$). The mean

time to symptom improvement response ($>$ 50% of the basic score on the YMRS) after ECT was $9.9 + 4.9$ days. The number of sessions to obtain the same clinical result was $2.8 + 1.3$ days. The number of days for the remission of symptoms (YMRS <10) after the end of treatment was $12 + 6.1$ days for the entire sample, with average of $3.4 + 1.7$ ECT sessions. There was no significant difference in the results between groups regarding the time of improvement, remission of symptoms or adverse effects.

Mohan et al.¹⁵ reported that the use of ECT in acute manic episodes is effective, and its management with bilateral electrodes with supra-threshold twice a week and combined with antipsychotics is as safe as ECT used with intensity threshold for stimulus to seizure.

In a mental health institute in southern India, where 500 patients are annually treated with ECT, Virupaksha et al.⁷ conducted an observational study comparing the therapeutic effects and adverse effects of ECT use combined or not with antiepileptic drugs (MAE) in patients with non-epileptic bipolar disorder. The analysis was done by CGI. Of the 201 patients, about 60% were treated with ECT unassociated with MAE.

Of the 201 patients, 40.8% underwent bifrontal ECT and 59.2% bitemporal ECT. According to CGI, 2.6% of patients on concomitant use of MAE and none of subjects

treated only with ECT showed improvement of bipolar symptoms; respectively, 3.8% and 1.6% had minimal improvement of the condition; 88.5% of individuals who used MAE associated with ECT had significant improvement of symptoms, as well as 93.5% submitted only to ECT; 5.1% and 4.9% had marked improvement of symptoms, respectively. Of patients using MAE, 59.5% received antiepileptic associated with treatment reduced response to ECT, however, at least 95.7% of study subjects had good response to previous treatment with ECT.

The study did not classify response to treatment within the different signs and symptoms of bipolar disorder, but it is possible to infer conclusions focused on the mania stage, since about 79% of patients had mania and the others depression or situation ranging from mania to depression. Therefore, the study confirms the efficacy of ECT to treat mania.

In a prospective study by Bulbul et al.¹⁶, women with bipolar disorder who were planning their pregnancies were analyzed, and for this purpose, they suspended the use of mood stabilizers during the six months prior to conception due to the risks to the fetus and complications that can occur during the pregnancy period. Thirty-three patients with mean age of 29.73 years were followed from the beginning of pregnancy up to 12 months after birth. Of the 33 women, 38.2% had

depression, 29.2% had depression and mania, 16.8% had hypomania and 6.7% had mania episodes.

ECT is used as a treatment for several severe psychiatric disorders in pregnant women due to the low risk to both mother and fetus. ECT was performed in the first trimester of pregnancy in 39.4% of patients, 45.5% were submitted during the second quarter and 15.1% in the third. According to CGI criteria, in 11 out of 12 patients with bipolar disorder, scores decreased to 2 or less after ECT. About 89% of children were born without any health problems, 2 children (7.4%) were born with comorbidities (congenital hip dysplasia and temporary heart failure) and one child (3.7%) died due to unknown causes. Approximately 63.6% of pregnant women associated psychotropic medications with ECT. The author concluded that ECT is an effective treatment for psychiatric disorders including manic episodes during pregnancy despite offering pregnancy risks, particularly in the second quarter.

Conclusions

From the analysis of the four described studies, it appears that there is evidence of the electroconvulsive therapy administration for manic episodes of bipolar disorder. Two randomized studies, one double-blind, showed that both groups submitted to ECT showed a significant

response to treatment criteria. It could also be concluded from these favorable outcomes that bifrontal ECT may be the option of choice for acute mania episodes, requiring further studies with a sample containing greater number of individuals to confirm if the result remains positive. With regard to safety and efficacy, there is no difference in the administration of threshold or supra-threshold stimuli in ECT. Furthermore, supra-threshold stimuli do not imply in higher incidence of adverse cognitive effects; however, there is insufficient evidence relating to other effects such as headache.

It is noteworthy that ECT association with the use of antipsychotics analyzed in this study showed good results. Thus, further trials should be carried out to determine the potential benefits of combination therapy. A study presented inconclusive results regarding the ECT efficacy in manic episode, but a positive outcome showing the usefulness of the method. Regarding the use of ECT in pregnant women, although being favorable in our assessment, it was observed that further more comprehensive correlational studies in relation to maternal and fetal risks are necessary. It was therefore concluded that ECT already used with benefits for depression, can also be a viable option for the treatment of manic episodes.

References

1. American Psychiatry Association. Diagnostic and Statistical Manual of Mental disorders - DSM-5. 5th ed. Washington: American Psychiatric Association, 2013.
2. Baldessarini, R.J., Tondo, L., Visioli, C. First-episode types in bipolar disorder: predictive associations with later illness. *Acta Psychiatr. Scand.* 2014;129:383–392
3. Frye, MA. Bipolar Disorder – A Focus on Depression. *N Engl J Med.* 2011;364:51-9
4. WHO. Preventing suicide: a global imperative. World Health Organization, Geneva; 2014.
5. Merikangas KR, Jin R, He J, Kessler RC, Lee S, Sampson NA, et al. Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. *Arch Gen Psychiatry.* 2011;68(3):241-51.
6. Kellner CH, Greenberg RM, Murrugh JW et al. ECT in treatment-resistant depression. *Am J Psychiatry.* 2012;169(12):1238-44
7. Virupaksha HS, Shashidhara B, Thirthalli J, et al. Comparison of electroconvulsive therapy (ECT) with or without anti-epileptic drugs in bipolar disorder. *J Affect Disord* 2010;127:66-70.
8. Oremus C, Oremus M, McNeely H, et al. Effects of electroconvulsive therapy on cognitive functioning in patients with depression: protocol for a systematic review and metaanalysis. *BMJ Open.* 2015;5: 1-5.
9. Rosa MA, Rosa MO. Fundamentos da Eletroconvulsoterapia. Porto Alegre: Artmed; 2015

10. Carney S, Cowen P, Dearness K, Eastaugh J. Efficacy and safety of electroconvulsive therapy in depressive disorders: a systematic review and meta-analysis. *Lancet*. 2003;361(9360):799-808.
11. Semkowska M, Keane D, Babalola O, McLoughlin DM. Unilateral brief-pulse electroconvulsive therapy and cognition: effects of electrode placement, stimulus dosage and time. *J Psychiatr Res*. 2011;45(6):770-80.
12. Datto CJ. Side effects of electroconvulsive therapy. *Depress Anxiety*. 2000;12(3):130-4.
13. Antunes PB, Rosa MA, Belmonte-de-Abreu PS, Lobato MIR *et al*. Eletroconvulsoterapia na depressão maior: aspectos atuais. *Rev. Bras. Psiquiatr*. 2009;31(Suppl 1): S26-S33.
14. Hiremani R. M., Thirthalli J., Tharayil B. S. *et al*. Double-blind randomized controlled study comparing short-term efficacy of bifrontal and bitemporal electroconvulsive therapy in acute mania. *Bipolar Disorders*. 2008; 10 (6) :701-7.
15. Mohan, T. S., Tharyan, P., Alexander, J. *et al*. Effects of stimulus intensity on the efficacy and safety of twice-weekly, bilateral electroconvulsive therapy (ECT) combined with antipsychotics in acute mania: a randomised controlled trial. *Bipolar Disorders*. 2009; 11: 126-134.
16. Bulbul, F., Copoglu, U. S., Alpak, G. *et al*. Electroconvulsive therapy in pregnant patients. *General Hospital Psychiatry*. 2013; 35: 636-39.