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Safety and acceptability of transcranial direct current stimulation for the acute treatment of major depressive episodes: Analysis of individual patient data

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ABSTRACT

Background: Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation modality that has been increasingly used for major depressive disorder (MDD) treatment. Although studies in healthy volunteers showed that the technique is well-tolerated, tDCS safety and acceptability have not been sufficiently explored in patients with MDD.

Methods: We collected individual patient data from 6 randomized clinical trials that had been previously identified in a systematic review and meta-analysis. Primary outcomes were safety (rate of adverse events) and acceptability (rate of dropouts). Secondary outcomes were clinical, demographic and treatment predictors of the primary outcomes.

Results: Dropout rates between active (8.8%) and sham (12%) groups were not significantly different (OR = 0.7, p = 0.38). Adverse event rates between active (73.5%) and sham (68.3%) groups were not significantly different (OR = 1.4, p = 0.23). Higher current densities were associated with lower adverse event rates.

Limitations: Dropout reasons were not systematically reported and adverse events were not collected using questionnaires standardized across studies.

Conclusions: Active tDCS is as acceptable and safe as sham tDCS, as found in randomized clinical trials of MDD.

1. Introduction

Depression is a prevalent and debilitating clinical condition that is predicted to be the second leading cause of disability worldwide in 2020 (Eaton et al., 1997). The available treatment alternatives are mainly pharmacological, presenting limited efficacy – for instance, only one third of patients achieve remission after a first-line antidepressant treatment, and another third is refractory even after multiple antidepressant treatments (Rush et al., 2006). Moreover, even the newer generation antidepressant drugs exhibit several adverse effects (*e.g.* gastrointestinal symptoms, weight gain, sexual dysfunction and sleep disturbance) that may abate after a few weeks of treatment initiation but, in some cases, also persist in the long term (Carvalho et al., 2016).

Therefore, there is an urgent need to develop and optimize novel treatments for major depressive disorder (MDD) including non-invasive brain stimulation (NIBS) approaches such as transcranial direct current stimulation (tDCS). TDCS uses weak (1–2 mA), direct electric current applied into the brain through electrodes placed in the scalp to induce neuromodulatory changes that outlast the period of stimulation, ultimately inducing neuroplasticity (Nitsche and Paulus, 2001). TDCS is

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also relatively cheap, portable, and ease to use.

Recent randomized, sham-controlled clinical trials (RCTs) conducted so far have presented mixed, albeit positive, results regarding tDCS efficacy in MDD. Moreover, although there is overall evidence that tDCS is well-tolerated and acceptable (Bikson et al., 2016), it is important to further assess the safety, acceptability and tolerability of tDCS considering individual patients' demographic, clinical and treatment characteristics.

To this end, we pooled data from 6 randomized clinical trials evaluating tDCS efficacy in MDD. Our goals were: (1) to perform an individual patient data (IPD) analysis regarding safety and acceptability in patients with MDD treated with tDCS; and (2) to explore whether clinical, demographic and treatment characteristics were associated with these outcomes.

2. Methods

2.1. Study selection

The present study uses data from the most actual and detailed report (Brunoni et al., 2016), in which we performed a systematic review and individual patient data meta-analysis focusing on the acute efficacy of tDCS for MDD. That study was conducted according to the recommendations of the Cochrane group and PRISMA guidelines (Liberati et al., 2009). Our original search was performed using MEDLINE, EMBASE, Web of Knowledge and Scopus databases. We now expanded our search from the first date available until 1 October 2016 and only included randomized, sham-controlled trials with at least ten patients per arm in which IPD were available.

2.2. Data extraction

Two authors (ARB and AHM) extracted the data using a checklist that was elaborated *a priori*. Differences were resolved by consensus and the original authors were also consulted if necessary.

2.3. Quality assessment

We assessed methodological quality of each trial using two standard checklists: the Cochrane risk of bias tool (Higgins, 2009) which assesses selection, performance, detection, attrition and reporting biases; and the Physiotherapy Evidence Database (PEDro) scale (de Morton, 2009) in which ten criteria are used for internal validity.

2.4. Outcome measures

Our primary outcomes were safety and acceptability of tDCS. Acceptability was the dropout rate due to all causes (*i.e.*, attrition rate). This definition has already been adopted in recent meta-analyses published in major journals (Samara et al., 2016) as well as in Cochrane studies and protocols (*e.g.*, PROSPERO protocol CRD42015025643). Safety was assessed as the rate of all AEs.

Data were also extracted on the following clinical, demographic and treatment variables: (a) gender; (b) age ($\leq$50 years *versus* > 50years); (c) severe depression (MADRS$\leq$30 *versus* > 30 or HAM-D$\leq$24 *versus* > 24, according to the scale of the primary outcome); (d) treatment resistant depression (< 2 *versus* $\geq$2 failed antidepressant trials); (e) anxiety disorder as comorbidity; (f) stimulation group (sham *versus* active); (g) current intensity (1 mA *versus* 2 mA); (h) current density ($\leq$0.57 A/m^2 *versus* 0.8 A/m^2) and (i) response ($\geq$50% improvement from baseline to endpoint depression scores). Group allocation guess was not included because not all studies collected these data.

2.5. Data analysis

Analyses were performed in Stata 12 (Statacorp, College Station, TX, USA) using the command *xtmelogit* with 'study' as a random-effects variable and 'stimulation group' (active/sham) nested in the variable 'study'. The between-study heterogeneity was addressed as the variable 'study' was forced into all models. All results are presented using the random-effects odds ratio (OR) with the 95% confidence interval (95% CI).

To explore the influence of each clinical, demographic and treatment variable on the primary outcome variables (safety and acceptability) we ran several univariate analyses, initially using only one at a time. Variables that were present in all studies and were associated with the outcome variables at $p < 0.15$ were further included in the multivariate analyses. In this step, initially all variables which achieved the significance threshold in the univariate analyses were imputed and then successively removed if they were not significant at a two-tailed p threshold of 0.05 (stepwise backward method). Current intensity and current density were analyzed separately in the multivariate stage (as they are redundant). Values between groups were compared using the Chi2 test. Best fits were chosen based on the likelihood method (log likelihood) and the significance of variables in the models were evaluated by the Wald statistics.

For the predictors of safety analyses, we analyzed only the trials that used standard questionnaires to assess AEs (Loo et al., 2010, 2012; Brunoni et al., 2013) – *i.e.*, RCTs that collected AEs based on spontaneous reporting were not included, as these different approaches produce different estimation of AEs.

Based on these same studies, a separate logistic regression tested if side effects (AEs for any reason) were associated with clinical efficacy, coded as response ($\geq$ 50% improvement in depression scores) *versus* non-response.

Serious AEs (*i.e.*, hospitalization, suicide attempts, manic induction) are described qualitatively due to the low number of cases.

3. Results

3.1. Overview

According to our eligibility criteria, six randomized clinical trials (RCTs) were identified and included in our analysis (Loo et al., 2010, 2012; Brunoni et al., 2013; Palm et al., 2012; Blumberger et al., 2012; Bennabi et al., 2015) (Supplementary Material).

3.2. Study description and quality assessment

All trials presented low risk of bias per the Cochrane risk of bias tool and achieved maximum scores on the PEDro scale (Supplementary Material).

3.3. Outcome measures

Data from 289 patients were analyzed. The mean age was 47.2 years with standard deviation (SD) of 13.4 and 62.3% were female; 55.4% presented severe depression; 42.6% had anxiety as a comorbidity; 51.6% presented a treatment-resistant depression, with a mean of 2.3 (SD = 2.4) previous antidepressant failed trials. Only the study of Brunoni et al. (2013) had antidepressant drug free patients (but allowed the use of benzodiazepines). The distribution of patient characteristics across the six studies was significantly different for almost all baseline clinical and demographic variables (Supplementary Material).

3.4. Acceptability

The dropout rates between active (13 out of 147, 8.84%) and sham (17 out of 142, 11.97%) groups were not significantly different (OR = 0.70, 95% CI 0.32– 1.54; p = 0.379) (Table 1).

Age (OR = 0.47, 95% CI 0.19–1.14; p = 0.096), current density (OR = 2.23, 95% CI 0.82–6.07; p = 0.115) and response (OR = 0.23,