Brain Stimulation 12 (2019) 1332–1334

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: http://www.journals.elsevier.com/brain-stimulation

Cortico-spinal tDCS in ALS: A randomized, double-blind, sham-controlled trial

Keywords:
Motor neuron disease
Amyotrophic lateral sclerosis
Transcranial direct current stimulation
Transcranial magnetic stimulation
Short interval intracortical inhibition
Clinical trial

Amyotrophic lateral sclerosis (ALS) is a progressive disease which affects both upper and lower motor neurons, with a fatal prognosis, for which no curative treatment is currently available. Glutamate-driven excitotoxicity is supposed to be involved in its pathophysiology, and drugs such as riluzole or edaravone have shown to reduce disease progression in ALS to a limited extent.

Recent studies using non-invasive brain stimulation have shown promising results on muscle strength and quality of life in patients with ALS [1–7]. However, stimulation has been limited to the motor cortex, somehow neglecting the involvement of spinal motor neurons. Thus, it may be argued that the concurrent stimulation of both structures might be synergic in improving symptoms in this group of patients.

These observations defined the objective of this work, aimed at assessing long-term effects of repeated sessions of tDCS with concurrent bianodal motor cortex and cathodal spinal stimulation (cortico-spinal tDCS) in patients with ALS. To this, we assessed *a)* clinical outcomes and *b)* intracortical inhibitory and excitatory measures in a randomized, double-blind, sham-controlled clinical trial.

Full written informed consent was obtained from thirty patients according to the Declaration of Helsinki. The study protocol was approved by the local ethics committee (Brescia Hospital), #NP2743 approved 20.09.17 and has been registered at ClinicalTrials.gov (NCT03293394).

Patients were randomized to receive real or sham cortico-spinal tDCS for 5 days/week for 2 weeks, in a 2:1 ratio respectively. Two separate anodes were placed on the scalp over the motor cortex areas and the cathode over the spinal cervical enlargement (over C6). This montage was chosen after evaluating current density distribution with computer simulations. During real stimulation a constant current of 2 mA per each anodal electrode positioned over each motor cortex (4.0 × 6.5 cm2, current density 0.077 mA/cm2) and 4 mA per cathodal spinal electrode (5.0 × 7.5 cm2, current density 0.107 mA/cm2) was applied simultaneously for 20 minutes in a single session.

Detailed inclusion and exclusion criteria, as well as precise study design and methodology are reported in the Supplementary Data.

Each patient underwent a clinical evaluation and TMS analysis at baseline (pre-stimulation, T0), after two-weeks of either real or sham tDCS (post-stimulation, T1), at two-months (T2) and at six-months follow-up (T3).

Six patients dropped-out from the study: two receiving sham stimulation (both cases for pneumonia after T1) and four receiving real stimulation (one respiratory failure after T1, one respiratory failure and one pneumonia after T2, and one worsening of general clinical conditions after T2). This could be secondary to the relative unbalanced distribution of the site of disease onset (53% bulbar onset in the real group and 0% in the sham group).

No statistically significant association between type of stimulation and patients' perception were observed, as assessed by Fisher's exact test, $p = 1.000$, suggesting that real tDCS could not be distinguished from sham stimulation.

Clinical characteristics and baseline/follow-up clinical scores are reported in Supplementary Tables 1 and 2.

In the intention-to-treat analysis, repeated measures ANCOVA performed on total MRC scores revealed a significant TIME × TREATMENT interaction ($F(1.67,44.95) = 9.53$, $p = 0.001$, partial $\eta^2 = 0.26$, $\varepsilon = 0.56$), with a significant improvement in the real stimulation group compared to baseline and to sham stimulation (see detailed results in Fig. 1A).

For EQ-VAS and CBI, there was also a statistically significant TIME × TREATMENT interaction (EQ-VAS: $F(2.56,60.90) = 4.59$, $p = 0.011$, partial $\eta^2 = 0.15$, $\varepsilon = 0.75$; CBI: $F(2.46,66.43) = 5.63$, $p = 0.003$, partial $\eta^2 = 0.17$, $\varepsilon = 0.82$) (see detailed results in Fig. 1B and C).

For ALSFRS-R, ALSAQ-40 and EQ-5D-5L, there was not a statistically significant TIME × TREATMENT interaction.

Twenty-one patients underwent a TMS paired-pulse protocol, while nine patients had an unexcitable motor cortex and were thus excluded from TMS analysis.

Repeated measures ANOVA performed on peak SICI (ISI 3 ms) and peak ICF (ISI 10 ms) revealed a statistically significant TIME × TREATMENT interaction (SICI: $F(1.83,34.69) = 5.34$, $p = 0.011$, partial $\eta^2 = 0.22$, $\varepsilon = 0.61$; ICF: $F(3,57) = 6.33$, $p = 0.001$, partial $\eta^2 = 0.25$) (see Fig. 1D–E).

No significant TIME × TREATMENT interaction was observed for RMT.

A significant correlation was observed between the percentage of improvement in global MRC and CBI scores and the restoration of SICI (global MRC scores: $r_s = 0.612$, $p = 0.003$; CBI scores: $r_s = 0.513$, $p = 0.017$); a significant correlation was also observed between improvement in global MRC and ALSFRS-R scores and

https://doi.org/10.1016/j.brs.2019.06.011

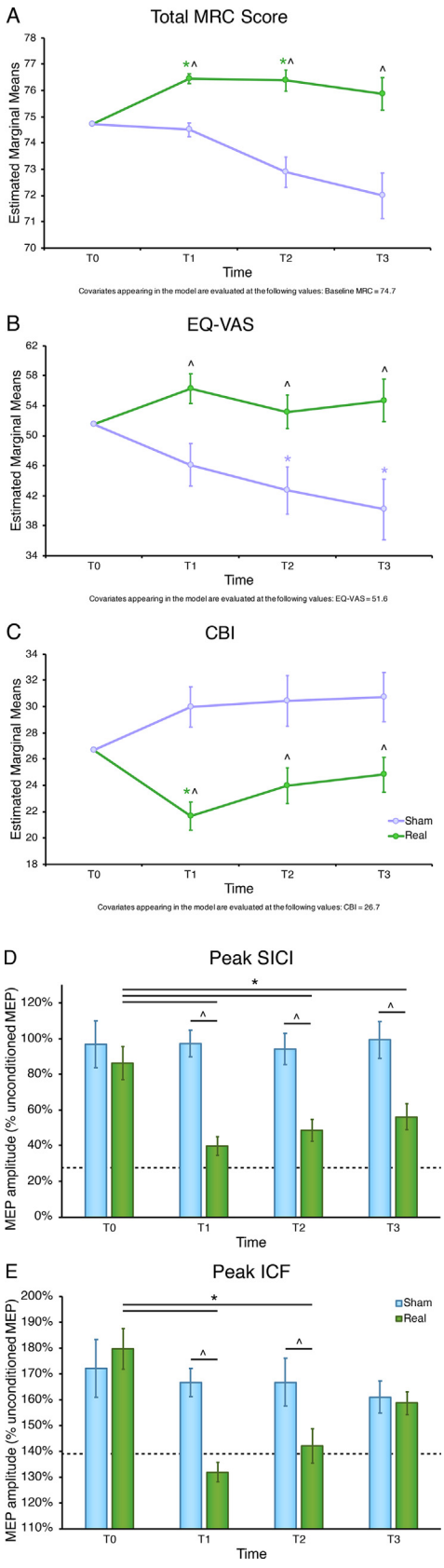

Fig. 1. Clinical and neurophysiological measures of included patients at different time points. **Legend. A-C:** Total MRC, EQ-VAS and CBI scores, pre- and post-sham and real tDCS at different time points (T0: baseline; T1: after 2-weeks' treatment; T2: at 2-months follow-up; T3: at 6-months follow-up); Error bars represent standard errors. Real stimulation is reported in green; sham stimulation is reported in light blue. **D-E:** Data are plotted as a ratio to the unconditioned motor evoked potential (MEP) amplitude. Error bars represent standard errors. Black dotted line represents the mean value of average SICI (panel A) and average ICF (panel B) of 21 age- and gender-matched healthy controls. Real stimulation is reported in green; sham stimulation is reported in light blue. MRC: Medical Research Council; EQ-VAS: EQ visual analogue scale; CBI: caregiver burden; tDCS: transcranial direct current stimulation. ISI: inter-stimulus interval.*significant difference from baseline (T0); ^significant difference compared to sham stimulation. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

the restoration of ICF (global MRC scores: $r_s = 0.568$, $p = 0.007$; ALSFRS-R: $r_s = 0.664$, $p = 0.001$).

In the present study we observed a significant improvement/stabilization in clinical scores of muscle strength, in self-reported quality of life scores, and in proxy-reported caregiver burden, after a two-weeks' treatment with cortico-spinal tDCS in patients with ALS. These findings were further corroborated by the restoration of TMS parameters of intracortical circuits, with a significant correlation between the improvement in global MRC and CBI scores and the restoration of SICI and ICF.

One of the main strengths of the present study is that clinical outcomes encompass three very relevant aspects in the natural history of ALS, and represent independent measures assessed by the clinician (MRC score), the patient (EQ-VAS) and the caregiver (CBI), respectively.

These changes, which were still detectable up to 6 months, were associated and correlated with the restoration of intracortical circuits measures of short interval intracortical inhibition and intracortical facilitation. SICI, which is considered to reflect short-lasting postsynaptic inhibition mediated through the $GABA_A$ receptor at the level of local interneurons, has been shown to be altered in ALS and to correlate with disease progression and with survival [8].

On the other hand, ICF, which is thought to represent a net facilitation most likely mediated by glutamatergic NMDA receptors, and thus possibly an indirect marker of excessive glutamate activity, has been shown to be increased in ALS [9,10].

Taken together, our findings provide first-time evidence of symptom improvement in patients with ALS by restoration of intracortical circuits measures after cortico-spinal tDCS treatment.

In the light of limited treatment options for patients with ALS, based on the results of this study, a two-weeks' treatment with cortico-spinal tDCS could be considered a potentially promising tool for future therapeutic approaches. Future studies on larger number of patients and in multicenter cohorts, evaluating whether the repetition of multiple tDCS sessions might further outlast clinical improvement, and assessing the predictors of clinical response, are warranted.

Author contributions

AB, AA and BB made substantial contributions to the conception and design of the study. AB and BB did the literature searches. AB and BB did the statistical analysis and drafted the figures. AB and BB drafted the initial version of the manuscript. All the authors contributed to data acquisition and data interpretation, revised the manuscript critically for important intellectual content, approved the final, submitted version of the manuscript, and agreed to be accountable for all aspects of the work.

Disclosure statement

A. Benussi, A. Alberici, M. S. Cotelli, V. Dell'Era, V. Cantoni, E. Bonetta, R. Manenti, M. Filosto, R. Morini, A. Datta, C. Thomas report no disclosures relevant to the manuscript. A. Padovani is consultant

and served on the scientific advisory board of GE Healthcare, Eli-Lilly and Actelion Ltd Pharmaceuticals, received speaker honoraria from Nutricia, PIAM, Lansgstone Technology, GE Healthcare, Lilly, UCB Pharma and Chiesi Pharmaceuticals. B. Borroni reports no disclosures relevant to the manuscript.

Acknowledgements

The authors are indebted to the patients and their families for taking part in this study. A particular thanks goes to Prof. Steve Vucic from the Westmead Institute, University of Sydney, for his exceptional suggestions and advice concerning the drafting of the manuscript.

This study was supported by AIRAlzh Onlus-COOP Italia (V. Cantoni).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2019.06.011.

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22 May 2019
Available online 8 June 2019