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LETTER TO THE EDITOR

COMMENTARY ON: "COMBINED TRANSCRANIAL DIRECT CURRENT STIMULATION AND BREATHING-CONTROLLED ELECTRICAL STIMULATION FOR MANAGEMENT OF NEUROPATHIC PAIN AFTER SPINAL CORD INJURY"

We read with interest the article by Li et al. on the use of combined transcranial direct current stimulation (tDCS) and breathing-controlled electrical stimulation (Bre-Estim) for management of neuropathic pain after spinal cord injury (1, 2).

The authors present a well-designed study with interesting findings, which concludes that Bre-Estim has an immediate analgesic effect in comparison with active tDCS. In addition, they concluded that there was no additive effect of a combined tDCS and BreEstim intervention for neuropathic pain after SCI. However, we have some difficulty in interpreting their findings (3).

First, the methodology is unclear. The treatment protocol states that an intervention comprising 20 min active tDCS followed by 20 min BreEstim was given, and, to assess pain, a visual analogue scale (VAS) was used as outcome measure after 10 min tDCS and 10 min BreEstim. The authors did not specify the time interval between interventions, and why the pain level was assessed after 10 mins. In order to check the immediate effect the pain level should have been assessed immediately after the intervention (1).

Secondly, we have some doubts about the study design. The methodology section reports that this is a single-blinded, single-centre, sham-controlled cross-over design. However, if this is a sham-controlled design why did the study deviate towards an experimental design? A pre-post control group design should have been used.

The authors stated in the clinical trial registry that they hypothesized that a single session of combined BreEstim and tDCS would produce an analgesic effect; however, in the main article it was stated that the intervention was given for at least 3 days. In the trial registration, they stated that participants would be randomized, but the authors did not mention randomization in the study (2).

The outcome measures used are not clear; secondary outcome measures are not explained in the study, but they are mentioned in the trial registration. It is not stated how the authors conformed the neuropathic pain in patients with SCI. The primary outcome measure, VAS, cannot measure the quality of pain. Rather than a VAS, a neuropathic pain scale (NPS), which can measure treatment outcome and pain descriptors and can differentiate between neuropathic and chronic pain should have been used (4).

The characteristics of participants and neuropathic pain mentioned in Table I are not clear. Neuropathic pain characteristics are mentioned among 12 participants, of which 5 have neuropathic pain in the lower limbs, 6 have neuropathic pain in the upper limbs, and in 1 patient the region of pain is not mentioned. In addition, the level of injury is not stated. The participants should have had neuropathic pain symptoms in the upper limb, since BreEstim is used specifically for median nerve stimulation in the upper limb (4); it is not clear why the author recruited patients with neuropathic pain in the lower limb.

The methodology states that the total number of electrical stimuli given during the BreEstim intervention was 160, with sufficient rest during treatment and a duration of approximately 20 min. It is not clear why the term "approximately" was used for treatment duration; the duration of treatment should be specific (1).

The statistical analysis section does not explain why the non-parametric test was not performed, as the primary outcome measure is an ordinal scale. Finally, it is not explained why repeated measure analysis of variance (ANOVA) was used instead of a Friedman test for data analysis (5).

We would be interested in the authors' thoughts on these comments.

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RESPONSE TO LETTER TO THE EDITOR FROM SRIVASTAV ET AL.

We thank the authors for their sincere interest in our study. Point-by-point clarification is provided here regarding their concerns about the study design and methodology.

The treatment protocol was illustrated in Fig. 1. The protocol included a 20-min tDCS (active or sham), followed by a 20-min BreEStim. As shown in Fig. 1, the interval between tDCS and BreEStim was 10 min.

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The "immediate" effect is a relative term. Assessment at "10 min" after an intervention could be reasonably called "immediate" with reference to the delayed analgesic effect observed at the 4-week follow-up visit after a 5-day tDCS intervention (6).

In this study, each subject received a "sham" or "active" tDCS conditioning intervention prior to the BreEStim treatment, but on different days. Therefore, this is a sham-controlled study. As shown in Fig. 1, we compared measures before and after each intervention. It is also a pre-post sham-controlled study.

The authors questioned "the intervention was given for at least 3 days" and randomization. To clarify, we explicitly mentioned in the study that "each combined intervention was given at least 3 days apart and in a randomized order." This means that the order of each combined intervention was randomized. Each subject received only one session of each combined intervention. Two combined interventions were at least 3 days apart.

In addition to VAS assessment, we performed secondary outcome measures, including electrical sensation threshold and electrical pain threshold. As reported in Clinicaltrials.gov, there were great variations in both measures. Given the impaired sensation in subjects with SCI, we were not sure how informative this set of data was. It was reported on Clinicaltrials.gov, but not in the article. The primary goal was whether combined tDCS and BreEStim could yield additive analgesic effects. VAS was appropriate for this goal.

BreEStim was applied to the median nerve in this study. However, we do not agree with the authors that BreEStim produces analgesic effects only for the arm. Our recent series of experiments has provided evidence that BreEStim has central analgesic effects in pain-free healthy subjects (7–9) and in subjects with SCI (10, 11). This study provided further evidence for this central analgesic effect.

The authors questioned the use of the term "approximately" to describe the duration of BreEStim treatment. In contrast to tDCS treatment, the duration of which was pre-set by the experimenter, electrical stimulation was triggered by voluntary breathing of the subjects in the BreEStim treatment. Subjects performed BreEStim at their own pace. As explicitly described, sufficient rest was allowed during the BreEStim treatment. Due to this methodology, the best way to standardize the dose or "duration" of the BreEStim treatment was to control the number of electrical stimuli, rather than the duration. In this study, every subject received 160 electrical stimuli during BreEStim; approximately 20 min with rest.

With regard to the statistical analysis, we were aware that VAS is an ordinal scale. We provided the rationale for this, with literature support, in the study.

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