Author’s response to reviews

Title: Photobiomodulation using Low-Level Laser Therapy (LLLT) for patients with chronic Traumatic Brain Injury: a randomized controlled trial study protocol

Authors:

Guilherme Poiani (comporta.saude@gmail.com)
Ana Luiza Zaninotto (ana.zaninotto@yahoo.com.br)
Ana Maria Carneiro (amcostac@bol.com.br)
Renato Zangaro (razangaro@gmail.com)
Afonso Salgado (afonsosisalgado@yahoo.com.br)
Rodolfo Parreira (dolfo23@yahoo.com)
Almir de Andrade (alandrade.psnc@gmail.com)
Wellingson Paiva (wellingsonpaiva@yahoo.com.br)
Manoel Teixeira (manoeljacobsen@gmail.com)

Version: 1 Date: 07 Dec 2017

Author’s response to reviews:

Dear Editor

Trials Journal of BioMed Central

The corrections have been done in the present manuscript according to the manuscript revised with regards to the peer reviewer’s comments and editorial comments.

MANUSCRIPT ID TRLS-D-17-00457 entitle “Transcranial Light Therapy for traumatic brain injury patients: stydy protocol for a randomized controlled trial”

Reviewer #1

1. "stydy protocol for a randomized controlled trial"? study protocol?

R: Yes. We typed wrong. We changed the title as:
Photobiomodulation using Low-Level Laser Therapy (LLLT) for patients with chronic Traumatic Brain Injury: a randomized controlled trial study protocol.

2. Background

(1) The authors reported, "It is also a global health problem, exerting great socio economic impact worldwide with annual expenditures involving billions of dollars." However, the cited publication was incidence and lifetime costs of injuries in the United States. Publications of epidemiology and disease burden on TBI worldwide are necessary. (Page 3)

R: Right, we made the correction in the paragraph. We added an epidemiology paragraph:

Epidemiology

Traumatic brain injury (TBI) is one of the main problems in the public health system due to its magnitude, clinical and social consequences1. It is the main cause of disability in young adults with an estimation of 2 million visits to emergency services in the United States in 2009 2. In low-income countries, the rate of TBI related especially due to motor vehicle are higher than 80% of all the cases, dealing to higher costs and disabilities3, 4. In Brazil, the incidence of TBI is 65.6/100,000 inhabitants per year, however this incidence appears to be underestimated due the lack of methodology or inadequate medical records documentations5.

(2) Is there any previous study focus on transcranial light therapy for TBI such as preclinical research, case report, and case series study?

R: yes, there are studies already done. We included those references in the introduction and safety.

Page 4: In animal models, LLLT has been investigated as an alternative treatment for brain injury, increasing neurogenesis after TBI6

Page 9: Phase 1 trials and animal studies showed evidence related to the safety of the LLLT 7-9

3. Method

What are the primary and secondary outcomes in this study?

R: Dear reviewer, thank you for your point. We added it clearly and purposefully our primary and secondary outcomes.

Pages 8 and 9
Primary outcome

- Inhibitory attentional control (time score) measured by Stroop test. The Stroop test is known to be an accurate assessment of executive function in mild to moderate TBI.

Secondary outcomes

- Verbal and visuospatial episodic memory
- Executive functions (working memory, verbal and visuospatial fluency, attentional processes)
- Anxiety and depressive symptoms.

4. Patients

The authors reported, "Will be asked 36 patients [28], of both sexes which entered the Neuro Traumatic Clinic of the Hospital das Clínicas (USP). After thorough screening, ambulatory patients will be divided into 2 groups (1: 1) or placebo optical active device in accordance with the randomization list." These sentences are in confusion. And the cited article (28) is a randomized trial of low-frequency rTMS in chronic stroke. Why did you cited such article in this section? (Page 4)

R: Dear reviewer, thank you. We rewrote the paragraph and corrected the reference.

5. Inclusion criteria

What does it mean that "with time of TBI from 3 months"? Do you mean patients of TBI within 3 months after trauma? (Page 5)

R: Dear reviewer, we rewrote the sentence to better comprehension.

Inclusion criteria

- Patients of both genders;
- Age between 18 and 60 years;
- Glasgow Coma Scale (GCS) ≤ 12 at admission in the emergency room;
• Computer Tomography (CT) or Magnetic Resonance Imaging (MRI) consistent with closed TBI, including intracranial hematoma, subdural hematoma, epidural hematoma, diffuse axonal injury, hemorrhagic contusion and subarachnoid hemorrhage;

• Loss com consciousness of 30 minutes or more;

• Post-traumatic amnesia of 24 hours or more;

• Outpatients with more than 6 months TBI.

6. Randomization and blinding

(1) What is the method of generating the allocation sequence?

R: Dear reviewer, thank you for your report. We added the paragraph on page 8.

Randomization

All eligible recruited patients will be randomly divided into two groups with 1:1 ration and blocks of 4 and 6 performed by the co-investigator through the randomization list (randomization.com). The randomization list will be keep in a safe storage with the co-investigator responsible for the stimulation sessions. She will provide the allocation concealment assignment for the patients. No information about the assigned group will be given for the patient nor the research assessor.

(2) The authors reported this study as a double-blind trial, why the researchers involved with TBI sessions assign participants to the intervention group? Is it a single blinded trial? (Page 5)

R: Dear reviewer, we rewote the paragraph on page 8

Blinding and allocation concealment

Both helmets, the active and the sham, are identical on size, color, and weight. The active helmet activates red light when plugged, however, the sham helmet cannot provide visible light (Figure 1). The patient is not able to see the light and there is no hit during the active stimulation that can suggest the type of intervention. The unblinded investigator is the person in charge to perform the stimulation. Both assessor researcher and patient will be blind for the type of intervention.

During the study, telephone contact can be used maintain patient adherence in the trial. This study involves the participation of a research committee not directly related to the allocation of the patients. They can remove the blinding if any relevant situation may rise involving any clinical condition, adverse event or even abandonment of the patient.
(3) The randomization (sequence generation, allocation concealment, and implementation) as well as blinding sections are in confusion. Please improve them according to SPIRIT statement [1].

R: Dear reviewer, we added this information on page 8:

The randomization list will be keep in a safe storage with the co-investigator responsible for the stimulation sessions. She will provide the allocation concealment assignment for the patients. No information about the assigned group will be given for the patient nor the research assessor.

Both helmets, the active and the sham, are identical on size, color, and weight. The active helmet activates red light when plugged, however, the sham helmet cannot provide visible light (Figure 1). The patient is not able to see the light and there is no hit during the active stimulation that can suggest the type of intervention.

(4) Is there a SPIRIT Checklist for this protocol?


R: Dear reviewer, sure, we fixed that.

7. Data collection and management

Any plans for data collection and management?

R: Yes, we have a plan for collecting and managing data. We added the enrollment and chronogram table as Table 1.

8. Data analysis

For primary and secondary outcomes, the relevant statistic methods should be declared in detail. (Page 6)

R: Ok. The Statistical methods was rewritten.

Pages 9 and 10:

Statistical analysis

Intention-to-treat and per-protocol analyses will be performed for the primary and secondary outcomes. Missing data will be analyzed with regression imputation, considering the confounders (months of the trauma, years of age, schooling years, depressive symptoms).
Patients that did not receive 60% of the total stimulation, will be considered non-adherent and analyzed as per-protocol.

Means and standard deviation will be used to represent data with normal distribution and medians and quartiles to describe non-normally distributed data. Two-way ANOVA (2 GROUPS X 3 TIMES) with repeated measures (for parametric variables) or the Kruskal-Wallis test (for nonparametric variables) will be used for the analysis of the LLLT effects obtained in the three timelines: baseline, 1 week and 3 week after the intervention. The Bonferroni correction for multiple comparisons will be employed as a post-hoc test. The effect size will be calculated based on the difference between means of the pre-intervention and post-intervention evaluations and will be expressed with respective 95% confidence intervals. Parametric Student’s t-test or a Mann-Whitney U test for non-parametric data will be employed to assess between-group (active and sham helmet) differences in age, height, weight, and body mass index (BMI), time of TBI injury, level of education, and Glasgow Coma Scale at admission on the emergency room. For all effects, a p-value < 0.05 will be considered indicative of statistical significance. The data will be organized and tabulated using the Statistical Package for the Social Sciences (SPSSv.19.0).

9. Sample size

The cited article (29) is a randomized, double-blind trial of low-frequency rTMS on naming abilities in early aphasic stroke patients. Why did you cited such article about rTMS in this section? (Page 7)

R: Dear reviewer, you are right. We rewrote the paragraph on page 8.

Sample size

Based on the previous pilot study11 that analyzed the cognitive function of patients with TBI after repetitive sessions of RED/ Near-infrared Light-Emitting Diode Treatment. Considering the improvement on Stroop test of 1 standard deviation (SD) related to the baseline, the level of significance of 0.05 and the power of 80%, it was estimated 16 patients per group. Considering the rate of 15% of drop-outs, we added 2 participants per group, a total sample of 36.

10. Quality of written English

The English of this manuscript is poor. The following but not limited to sentences are necessary to be improved.

R: Dear reviewer, we agree and rewrote all the manuscript.

Reviewer #2
1. Please, rewrite the protocol following the SPIRIT advice and add a sentence specifying that the final report will following the CONSORT 2010 guideline.

R: Dear reviewer, thank you for your point. We rewrote the manuscript following the CONSORT SPIRIT guidelines. We changed the figures, fluxogram and table accordingly.

2. The sample size is not enough, and in the sample size calculation part, too little data was provided to figure out the sample size, please explain your pilot study in detail.

Dear editor, we provided a sample size calculation, in which were included in the text on page 8.

Sample size

Based on the previous pilot study11 that analyzed the cognitive function of patients with TBI after repetitive sessions of RED/ Near-infrared Light-Emitting Diode Treatment. Considering the improvement on Stroop test of 1 standard deviation (SD) related to the baseline, the level of significance of 0.05 and the power of 80%, it was estimated 16 patients per group. Considering the rate of 15% of drop-outs, we added 2 participants per group, a total sample of 36.

3. Patients inclusion/exclusion criteria and Blind is also unclear. Especially in the inclusion section, only used Glasgow Coma Scale as criteria. It is too premature. Which type of TBI involved in the trial should clear? Open or close? The cognitive status should also considerate.

Dear reviewer, we agree with your point and rewote the method section.

Method

Study design

This is a prospective, multicenter, randomized, parallel placebo-controlled trial that will be conduct at the Clinics Hospital, University of São Paulo (HC-FMUSP) and Salgado Institute, Londrina, Brazil. The protocol is registered on clinicaltrials.org number NCT02393079. The trial will follow the main CONSORT (Consolidated Standards of Reporting Trials) guidelines as well as SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines.

Eligible participants

Inclusion criteria

• Patients of both genders;
· Age between 18 and 60 years;

· Glasgow Coma Scale (GCS) \( \leq 12 \) at admission in the emergency room;

· Computer Tomography (CT) or Magnetic Resonance Imaging (MRI) consistent with closed TBI, including intracranial hematoma, subdural hematoma, epidural hematoma, diffuse axonal injury, hemorrhagic contusion and subarachnoid hemorrhage;

· Loss of consciousness of 30 minutes or more;

· Post-traumatic amnesia of 24 hours or more;

· Outpatients with more than 6 months TBI.

Exclusion criteria

· Metal implant or device in the brain or scalp;

· Uncontrolled epilepsy;

· Non-consent sign;

· Portuguese as not first language;

· Non-comprehension and/or no able to follow instructions.

Recruitment

The patients will be contacted and invited to participate before or after their regular appointment at the Neurotrauma Outpatient Clinics at the HC-FMUSP or by a contact list of provided by the acute Neurotrauma Inpatient Section at the HC-FMUSP. The patients will give a verbal consent before joining for the first consent visit.

Study intervention

Standard care

All patients will keep their clinical follow-up at the Neurotrauma Outpatient Clinics at HC-FMUSP or at Salgado Institute, Brazil, independently of the study group assignment or decision of dropping-out.
Discussion

The present study is designated to evaluate the effects of 18 sessions of LLLT over the cognition, in patients with chronic moderate and severe TBI. Our primary hypothesis is that the sessions of active LLLT will improve attention (at least 1 standard deviation) measured by Stroop test compared to placebo group (sham LLLT). And our secondary hypothesis is that the active group will improve in all domains assessed by the neuropsychological battery, including cognition and mood, compared to placebo group.

LLLT can modulate many biological penetrating the scalp into the brain, playing a role improving the outcome of the patients in two different ways, depending on the stage of the trauma. In the acute phase after the TBI, the initial neuronal injury occurs instantly and oftentimes causes irreversible damage to the central nervous system, due to impairment of neuronal cell functions, including mitochondria, and glia cells. The disruption of neuronal circuitry causes loss of connectivity between different areas of the brain, and can negatively impact neural regeneration, leading to dysfunctional interactions. In the secondary stage after the trauma, other changes may occur, including release of neurotransmitters, decreased glucose utilization, lactic acid accumulation, reduced activity of ATP-reliant ion pumps, increased release of glutamate, Ca2+-induced depolarization, and excitotoxicity.

Previous studies showed that improvement on cognition, including attentional process and episodic memory after repetitive sessions of LLLT in patients with TBI. It seems that the LLLT decrease the inflammatory response, helping the neuroprotection after the TBI. This process leads to increases on the ATP and cellular energy, blood flow and decreasing some metabolic process. In sum, the LLT seems to increase of the intercellular synapses, acting as a possible treatment after acute and chronic TBI.

Other studies reported the effects of the LLLT in another sample. Lampl et al used the LLLT in patients with ischemic stroke and showed that infrared wavelength therapy was safety and efficacy in the experimental group when compared to control when treatment was started 24 hours after the onset of stroke. Another study with psychiatric patients showed that 7 (out of 10) patients with severe cases of depression and anxiety presented symptom remission after two weeks elapsed with four LLLT applications in the prefrontal region, which did not occur with the control group. Likewise, LLLT has been demonstrated as a safe and effective technique in significantly improving the memory, attention and mood performance of healthy people.

Overall, we expect that our trial can complement previous finds, as an effective low-cost therapy to improve cognitive sequel in patients with chronic TBI.


