Journal of Lasers in Medical Sciences

J Lasers Med Sci 2022;13:e65

Case Series

http://journals.sbmu.ac.ir/jlms

doi 10.34172/jlms.2022.65

Transcranial Infrared Laser Stimulation for the Treatment of Traumatic Brain Injury: A Case Series

Elisabeth S. Rindner[1*], Jonathan M. Haroon[1], Kaya G. Jordan[1], Kennedy D. Mahdavi[1], Jean R. Surya[1], Margaret A. Zielinski[1], Barshen Habelhah[1], Victoria Venkatraman[1], Sergio A. Becerra[2], Lider Chan[3], Taylor P. Kuhn[4], Sheldon E. Jordan[1,5]

[1]The Regenesis Project, Los Angeles, CA, USA
[2]Synaptec Network, Los Angeles, CA, USA
[3]Orthopedic Physical Therapy Associates, Los Angeles, CA, USA
[4]Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles, CA, USA
[5]Department of Neurology, University of California, Los Angeles, CA, USA

***Correspondence to**
Elisabeth S. Rindner,
Email: erindner@theneuroassociates.com

Received: October 12, 2022
Accepted: December 10, 2022
Published online December 13, 2022

Abstract

Introduction: This study intended to evaluate the safety and possible therapeutic effect of transcranial infrared laser stimulation (TILS) based on photobiomodulation (PBM) among patients with traumatic brain injury (TBI).

Methods: Eleven participants who were diagnosed with TBI after full neurological examination and MRI evaluation by a board-certified neurologist completed five to eight 20-minute TILS sessions using the Cytonsys CytonPro-5000 apparatus (pilot laser control, focused wavelength of 1064 nm, maximum output power of 10W, maximum optical power density of 500 mW/cm^2, effective area 4.5 cm^2 in diameter). Per TILS session, participants underwent a laser dose of 250 mW/cm^2 continuous laser wave to each hemisphere using predetermined patient-specific coordinates. Structural imaging was used to neuronavigate individual treatment targets in the frontal cortex (Brodmann area 10). The primary safety measure for this study was the occurrence of adverse events (AEs) or serious adverse events (SAEs). The primary efficacy outcome measure was the participant-rated global rating of change (GRC) post-intervention. Secondary outcome measures included a battery of neuropsychological testing and mood questionnaires done both pre- and post-intervention.

Results: All patients enrolled in this study protocol were able to tolerate the study procedures without any AEs or SAEs. Nine out of eleven participants had clinically significant improvements in GRC score (≥ +2). Neuropsychological testing and mood questionnaire outcomes also suggested a positive therapeutic effect.

Conclusion: This study provides preliminary evidence supporting the safety and potential efficacy of TILS as a non-invasive clinical intervention for individuals with TBI.

Keywords: Traumatic brain injury; Transcranial infrared laser stimulation; Near infrared light therapy; Brain stimulation.

Introduction

Traumatic brain injury (TBI) is the leading cause of trauma-related death in individuals under the age of 45, with TBIs responsible for 50 000 deaths per year in the United States alone.[1] TBI has been shown to be a risk factor for the development of mood disorders, and individuals who have sustained even a single TBI event are approximately four times more likely to develop dementia later in life than people without TBI.[2-4] TBI pathogenesis is rather complex, resulting from both primary and secondary injuries that lead to temporary or permanent neurological deficits due to dysregulated cerebral oxygenation.[5]

The currently available immediate therapies for TBI have mixed results and include head elevation, hyperventilation, prophylactic antiepileptics, and therapeutic cooling.[6] There is a need for more non-invasive and effective techniques to prevent TBI from progressing to permanent neurological deficits.[7-9]

Recent research suggests transcranial infrared laser stimulation (TILS) using low-level light/laser therapy (LLLT) in the near infrared (NIR) wavelengths is a safe and non-invasive method to treat TBI.[10,11] In a recent randomized clinical trial using human participants, LLLT was shown to be safe and demonstrated an engagement of neural substrates that may be disturbed in patients with moderate TBI.[11] By utilizing lasers in the red-to-near-infrared wavelengths, TILS penetrates the skull and

Please cite this article as follows: Rindner ES, Haroon JM, Jordan KG, Mahdavi KD, Surya JR, Zielinski MA, et al. Transcranial infrared laser stimulation for the treatment of traumatic brain injury: A case series. *J Lasers Med Sci.* 2022;13:e65. doi:10.34172/jlms.2022.65.

facilitates the healing of tissue underneath through the process of photobiomodulation (PBM)[12] which promotes mitochondrial respiration and enhances neurocognitive function.[13]

In rat models, it has been demonstrated that TILS can improve frontal cortex oxygen consumption and metabolism, thereby increasing frontal cortex-based attention and memory functions[14] which may be impaired in individuals with TBI.[7,8,15,16] In humans, TILS with a wavelength of 1064 nm increases the levels of oxidized cytochrome C oxidase (CCO) improving cerebral oxygenation and energy metabolism.[14,17]

Based on the above literature, we hypothesize that TILS based on PBM targeted at the frontal lobes may be a safe and potentially therapeutic treatment for individuals who have negative cognitive effects due to TBI.

Methods

This study (PRO #20192916, NCT #04489082) was reviewed and approved by WIRB-Copernicus Group (WCG) Institutional Review Board. Participants were recruited from Los Angeles, California neurology and psychiatry clinics. All participants provided written, signed informed consent, and they were given a copy of their signed consent.

Participants

This article reports on eleven participants who were diagnosed with TBI after full neurological examination and MRI evaluation by a board-certified neurologist and who have completed the protocol. Of the eleven participants (M_{age} = 35.5 years old, SD_{age} = 12.4 years), nine were identified as male and two as female (Table 1). Since this was an open-label study for the safety and feasibility of TILS as an intervention, we permitted comorbidity with mood-related disorders. However, TBI was considered the primary diagnosis at the time of enrollment for all participants. Concurrent interventions and therapies were not considered exclusionary.

Magnetic Resonance Imaging

Prior to the first TILS session, participants obtained a high-resolution structural T1 magnetic resonance imaging (MRI). Using the structural T1 images, patient-specific targets of the frontal lobes (Brodmann area 10) were determined through neuronavigation by a board-certified neurologist. Using the OsiriX Pro display program, the determined target can be localized in three-dimensional space and projected onto the scalp surface by generating an orthogonal line (with calculated measurements) to fiducial landmarks on the surface (e.g. nasion, inion) on a computer display. These same measurements are then used on the patient's real head, working back from the fiducial markers to the projected target on the patient's scalp.

Transcranial Infrared Laser Stimulation

The Cytonsys CytonPro-5000 apparatus was used for the TILS sessions. CytonPro-5000 has pilot laser control, with a focused wavelength of 1064 nm and a maximum optical (output) power of 10W. The maximum optical power density of CytonPro-5000 is 500 mW/cm^2, with an effective area of 4.5 cm^2 in diameter.

On the days of each TILS session, participants underwent an irradiance of 250 mW/cm^2 continuous laser wave to each hemisphere using predetermined patient-specific coordinates targeting Brodmann area 10. The delivered photon energy density was 120 J/cm^2 (0.25

Table 1. Summary of the Patients' Basic Clinical Information and Self-reported Global Rating of Change (GRC) Following Completion of the Study Protocol

Participant ID	Age	Time Post-TBI	Event Causing Head Injury	Clinical Presentation	GRC
P1	53	10+years	History of 10+concussions, some with LOC.	Memory loss, forgetfulness, problems with attention	(+1)
P2	52	2 months	Concussion sustained during a sports accident, history of past concussions.	Headache, dizziness, insomnia, fatigue, memory loss	0
P3	42	2 months	Multiple car accidents, LOC. Prior history of two concussions.	Impaired memory, poor attention, depression, back pain, dizziness	(+4)
P4	46	2 years	Motor vehicle accident with LOC. Prior history of two concussions.	Sleep dysfunction, poor memory, slow processing speed, difficulty following conversations	(+5)
P5	17	3 months	Concussion sustained during a basketball game with LOC.	Orbital fracture, problems with concentration and memory, migraines	(+3)
P6	19	4 years, 9 months	Concussion sustained from weight falling on the head.	Slower processing, migraines, attention deficit	(+2)
P7	34	3 years, 4 months	Concussion sustained from assault to head with LOC.	Impaired memory, poor concentration, mood instability, back pain	(+3)
P8	41	8 months	Concussion sustained during a surfing accident with LOC, prior history of two concussions.	Headaches, problems with concentration and memory	(+3)
P9	25	9 days	Motor vehicle accident.	Headache, problems with concentration, attention, and memory	(+4)
P10	31	3 years	Motor vehicle accident.	Memory loss, headaches, neck pain, back pain, depressed mood, irritability	(+3)
P11	31	6 years	Concussion sustained during sports accident. History of prior concussions.	Headaches, fatigue, dizziness, depressed mood	(+2)

W/cm $^2 \times 10$ minutes $\times 60$ s/min) = 120 J/cm^2 per site), with an estimated 2% reaching the cortical surface at 1064 nm.[18] To ensure safety, both the patient and the near-infrared light administrators wore protective eyewear; the administrators of the TILS were careful not to shine the light in or near the eyes, and the patient's eyes remained closed during the laser application. All participants received 10 minutes of treatment to each frontal lobe, for a total treatment duration of 20 minutes per session. Eight sessions completed within 8 weeks were prescribed to each participant. Due to individual circumstances, two were unable to attend all 8 sessions, with one completing 5 sessions and one completing 6.

Outcome measures

The primary safety measure for this study was the occurrence of adverse events (AEs) or serious adverse events (SAEs). The primary efficacy outcome measure for this study was the participant-rated GRC. The GRC consists of a single Likert scale ranging from "-5" (very much worse) to "0" (neutral/no change) to "5" (very much better). The GRC was obtained in an interview format to assess the patient's perceived change in overall status following their treatment. A score that is at least 2 or greater is considered to indicate clinically significant change.[19]

At baseline and completion of the study, participants also completed a comprehensive neuropsychological test battery to assess neurocognitive function at multiple domains. These included Rey Auditory Verbal Learning Task (RAVLT) trial A1 and the color-word interference (CWI) module from the Delis-Kaplan Executive Function System (D-KEFS).[20] The CWI inhibition task (trial 3) and RAVLT trial A1 are of particular interest due to their sensitivity in evaluating executive functioning[20] and attention,[21] respectively. For CWI, tests were conducted for normality and to assure other assumptions of the general linear model were met. Raw scores were converted to scaled scores using normalized data from age- and education-adjusted norms. Statistical significance was determined by paired-samples t-test conducted on the RAVLT trial A1 and CWI trial 3 scores pre- and post-intervention. The Beck Anxiety Inventory (BAI) and Beck Depression Inventory (BDI-II) are self-report scales that were used to assess mood at baseline and completion.

Results

All patients enrolled in this study protocol were able to tolerate the study procedures without any AEs or SAEs, supporting the safety of PBM utilizing TILS as a clinical intervention for the treatment of TBI. The individual circumstances which prevented two participants (P7 and P9) from completing all 8 sessions were related to travel restrictions.

The GRC reflects clinically meaningful changes in patient well-being and was used as the primary efficacy outcome for this study. Seven out of the nine participants who completed the protocol had improvements in scores that were clinically significant (as defined as $\geq +2$). The time constraints of participants P7 and P9 did not allow for the completion of all 8 treatments; however, the GRCs reported by these two participants based on the treatments they did complete were +3 and +4, respectively.

Neurocognitive Testing Outcomes

In the RAVLT trial A1, by raw scores, 8 out of 11 improved by at least 1 point and 3 stayed the same ($P < 0.01$). In the CWI inhibition task (trial 3), 6 out of 11 improved and 2 stayed the same in scaled scores. This change was not statistically significant (Table 2).

Mood Outcomes

For the BAI, 5 out of 11 patients improved by ≥ 3 points. All three patients who were above the clinically significant cutoff score for anxiety (BAI ≥ 15)[22] at baseline changed to below the cutoff score post-treatment. For the BDI-II, 8 out of 11 patients improved by ≥ 3 points. Three of the six patients who were above the clinically significant cutoff score for depression (BDI-II ≥ 16)[23] at baseline changed to below the cutoff score post-treatment (Table 2).

Discussion

This study suggests the safety of PBM utilizing TILS and indicates that it should continue to be evaluated as a non-invasive therapy for the management and treatment of TBI. Improvements (by the GRC, neuropsychological testing, and mood questionnaires) provide preliminary evidence supporting the ability of TILS to modulate frontal cortex activity. Additionally, TILS appears to induce positive cognitive and emotional changes in patients with TBI in a clinical setting.

Literature has suggested that impaired cerebral blood flow (CBF) regulation in the frontal lobe may be responsible for the neurological deficits seen in TBI patients.[5] Arterial spin labeling (ASL), a non-invasive imaging method that quantifies CBF, demonstrates that individuals with TBI tend to show hypoperfusion bilaterally in the frontal and temporal lobes despite no significant abnormality detected on standard MRI studies.[16] In a recent case study, the use of TILS was shown to improve CBF regulation indicated by a return of ASL signal to the bilateral frontal lobes at the site of treatment.[24] Further, the neuroreactivity of PBM through TILS was demonstrated in a randomized human clinical trial which showed statistically significant diffusion tensor imaging differences in white matter tracts between sham and LLLT-treated groups.[11] Therefore, this is a possible systems-level mechanism of action for the TILS-related improvement in frontally-mediated cognitive and psychiatric functioning in our study. Future studies

Table 2. Summary of Pre-treatment, Post-treatment, and Change in Neuropsychological Test Scores and Mood Questionnaires for Each Patient

Participant ID	RAVLT (trial A1)			CWI (trial 3)			BAI			BDI-II		
	Pre	Post	Change	Pre-scaled	Post-scaled	Change	Pre	Post	Change	Pre	Post	Post
P1	6	6	0	15	11	-4	6	0	-6	8	0	-8
P2	4	9	5	15	15	0	16	15	-1	17	12	-5
P3	5	6	1	8	9	1	44	16	-28	27	24	-3
P4	5	6	1	11	10	-1	11	6	-5	22	7	-15
P5	6	12	6	10	15	5	10	x	x	14	x	x
P6	7	12	5	7	9	2	11	9	-2	22	18	-4
P7	5	7	2	11	14	3	7	3	-4	13	12	-1
P8	4	4	0	5	12	7	5	3	-2	26	13	-13
P9	10	13	3	14	15	1	6	2	-4	3	5	2
P10	4	7	3	1	1	0	15	13	-2	49	45	-4
P11	7	7	0	17	16	-1	0	0	0	5	0	-5

Note: Scores are reported as raw scores (RAVLT, BAI, BDI-II) or scaled scores (CWI).

should utilize functional imaging techniques as a post-intervention measure of change to help elucidate the mechanism of TILS on CBF.

This study was limited by several confounding variables, including (1) the duration of time between the occurrence of the TBI and initiation of the study protocol; (2) small sample size; (3) variance in participant willingness and ability to complete some outcome measures. In this study, we intended to schedule treatments once a week for 8 weeks, but due to travel and logistical concerns surrounding the COVID-19 pandemic, participants completed the treatments according to different schedules. The greatest frequency was every other day for 3 weeks for 8 treatment sessions. The least common frequency was once a week for 11 weeks for 8 treatment sessions. Everyone else falls within the range and completed 8 total treatments, except for two participants who, due to personal reasons, only completed 5 or 6 sessions. Future studies should focus on examining the optimal treatment frequency necessary to prevent long-lasting TBI-related neurochemical changes and maximize potential therapeutic benefits. Similarly, future studies evaluating the optimal temporal relationship between the TBI itself and the treatment are warranted, as previous animal research has indicated that time since injury may play a role in the efficacy of the treatment.[9,25]

Conclusion

Our findings suggest that PBM utilizing TILS is safe and well-tolerated and may have the ability to produce positive cognitive and emotional benefits for individuals with TBI. These preliminary results warrant further investigation of TILS as a non-invasive treatment for TBI and other psychiatric, cognitive, and neurological disorders.

Conflict of Interests

We have no conflict of interest to disclose.

Ethical Considerations

The study was approved by the WIRB-Copernicus Group (WCG) Institutional Review Board.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

1. Vella MA, Crandall ML, Patel MB. Acute management of traumatic brain injury. Surg Clin North Am. 2017;97(5):1015-30. doi: 10.1016/j.suc.2017.06.003.
2. Ozga JE, Povroznik JM, Engler-Chiurazzi EB, Vonder Haar C. Executive (dys)function after traumatic brain injury: special considerations for behavioral pharmacology. Behav Pharmacol. 2018;29(7):617-37. doi: 10.1097/fbp.0000000000000430.
3. Edwards G 3rd, Zhao J, Dash PK, Soto C, Moreno-Gonzalez I. Traumatic brain injury induces tau aggregation and spreading. J Neurotrauma. 2020;37(1):80-92. doi: 10.1089/neu.2018.6348.
4. Chauhan NB. Chronic neurodegenerative consequences of traumatic brain injury. Restor Neurol Neurosci. 2014;32(2):337-65. doi: 10.3233/rnn-130354.
5. McKee AC, Daneshvar DH. The neuropathology of traumatic brain injury. Handb Clin Neurol. 2015;127:45-66. doi: 10.1016/b978-0-444-52892-6.00004-0.
6. Galgano M, Toshkezi G, Qiu X, Russell T, Chin L, Zhao LR. Traumatic brain injury: current treatment strategies and future endeavors. Cell Transplant. 2017;26(7):1118-30. doi: 10.1177/0963689717714102.
7. Morries LD, Cassano P, Henderson TA. Treatments for traumatic brain injury with emphasis on transcranial near-infrared laser phototherapy. Neuropsychiatr Dis Treat. 2015;11:2159-75. doi: 10.2147/ndt.s65809.
8. Chao LL, Barlow C, Karimpoor M, Lim L. Changes in brain function and structure after self-administered home photobiomodulation treatment in a concussion case. Front Neurol. 2020;11:952. doi: 10.3389/fneur.2020.00952.
9. Hamblin MR. Photobiomodulation for traumatic brain injury and stroke. J Neurosci Res. 2018;96(4):731-43. doi: 10.1002/jnr.24190.
10. Hamblin MR. Shining light on the head: photobiomodulation for brain disorders. BBA Clin. 2016;6:113-24. doi: 10.1016/j.

bbacli.2016.09.002.
11. Figueiro Longo MG, Tan CO, Chan ST, Welt J, Avesta A, Ratai E, et al. Effect of transcranial low-level light therapy vs sham therapy among patients with moderate traumatic brain injury: a randomized clinical trial. JAMA Netw Open. 2020;3(9):e2017337. doi: 10.1001/jamanetworkopen.2020.17337.
12. Huang LD, Kao TC, Sung KB, Abraham JA. Simulation study on the optimization of photon energy delivered to the prefrontal cortex in low-level-light therapy using red to near-infrared light. IEEE J Sel Top Quantum Electron. 2021;27(4):1-10. doi: 10.1109/jstqe.2021.3051671.
13. Saucedo CL, Courtois EC, Wade ZS, Kelley MN, Kheradbin N, Barrett DW, et al. Transcranial laser stimulation: Mitochondrial and cerebrovascular effects in younger and older healthy adults. Brain Stimul. 2021;14(2):440-9. doi: 10.1016/j.brs.2021.02.011.
14. Rojas JC, Gonzalez-Lima F. Neurological and psychological applications of transcranial lasers and LEDs. Biochem Pharmacol. 2013;86(4):447-57. doi: 10.1016/j.bcp.2013.06.012.
15. Naeser MA, Saltmarche A, Krengel MH, Hamblin MR, Knight JA. Improved cognitive function after transcranial, light-emitting diode treatments in chronic, traumatic brain injury: two case reports. Photomed Laser Surg. 2011;29(5):351-8. doi: 10.1089/pho.2010.2814.
16. Lin CM, Tseng YC, Hsu HL, Chen CJ, Chen DY, Yan FX, et al. Arterial spin labeling perfusion study in the patients with subacute mild traumatic brain injury. PLoS One. 2016;11(2):e0149109. doi: 10.1371/journal.pone.0149109.
17. Gutiérrez-Menéndez A, Marcos-Nistal M, Méndez M, Arias JL. Photobiomodulation as a promising new tool in the management of psychological disorders: a systematic review. Neurosci Biobehav Rev. 2020;119:242-54. doi: 10.1016/j.neubiorev.2020.10.002.
18. Salehpour F, Majdi A, Pazhuhi M, Ghasemi F, Khademi M, Pashazadeh F, et al. Transcranial photobiomodulation improves cognitive performance in young healthy adults: a systematic review and meta-analysis. Photobiomodul Photomed Laser Surg. 2019;37(10):635-43. doi: 10.1089/photob.2019.4673.
19. Kamper SJ, Maher CG, Mackay G. Global rating of change scales: a review of strengths and weaknesses and considerations for design. J Man Manip Ther. 2009;17(3):163-70. doi: 10.1179/jmt.2009.17.3.163.
20. Delis DC, Kaplan E, Kramer JH. Delis-Kaplan Executive Function System. San Antonio, TX: Psychological Corporation; 2001. doi: 10.1037/t15082-000.
21. Ferreira Correia A, Campagna Osorio I. The Rey Auditory Verbal Learning Test: normative data developed for the Venezuelan population. Arch Clin Neuropsychol. 2014;29(2):206-15. doi: 10.1093/arclin/act070.
22. Gillis MM, Haaga DA, Ford GT. Normative values for the beck anxiety inventory, fear questionnaire, Penn state worry questionnaire, and social phobia and anxiety inventory. Psychol Assess. 1995;7(4):450-5. doi: 10.1037/1040-3590.7.4.450.
23. Beck A, Steer R, Brown G. Beck Depression Inventory Manual. 2nd ed. San Antonio, TX: Psychological Corporation; 1996. doi: 10.1037/t00742-000.
24. Haroon J, Mahdavi K, Zielinski MA, Habelhah B, Chan L, Bystritsky A, et al. A case of COVID-encephalopathy imaged with fMRI and treated with near infrared light. Brain Stimul. 2021;14(6):1444-6. doi: 10.1016/j.brs.2021.09.005.
25. Oron A, Oron U, Chen J, Eilam A, Zhang C, Sadeh M, et al. Low-level laser therapy applied transcranially to rats after induction of stroke significantly reduces long-term neurological deficits. Stroke. 2006;37(10):2620-4. doi: 10.1161/01.STR.0000242775.14642.b8.