



Photobiomodulation in Parkinson's disease: A randomized controlled trial

To the Editor

Photobiomodulation, which uses non-thermal and non-ionizing light in the visible and infrared spectrum, has been proposed as a potential strategy for improving the symptoms of patients with Parkinson's disease (PD) [1], but this has not been tested in a randomized controlled trial (RCT). We thus sought to assess whether photobiomodulation can ameliorate the cardinal motor symptoms of PD using an RCT design.

The present RCT (NCT03811613) was conducted from January 29th–April 6th, 2018. Patients were randomly assigned (<http://www.graphpad.com/quickcalcs/randomize1.cfm>) to a photobiomodulation or sham (control) group. Researchers in charge of the sessions and endpoint assessment were blinded to participants' allocation. The study complied with the Consolidated Standards of Reporting Trials (CONSORT) statement and was approved by the local Ethics Committee (reference #08/18).

All participants gave their written informed consent to take part in the study. They were recruited from a local PD patients association (Asturias, Spain), where all study procedures were performed. Eligibility criteria were: diagnosis of idiopathic PD; stage 1–2 on the Hoehn and Yahr Scale; no neurological condition other than PD; able to stand for 2min and walk 10 m without assistance; and no severe dyskinesias or “ON-OFF” phases. Participants were instructed to maintain their medication and usual activity routine during the study. They received 18 photobiomodulation or sham sessions for 9wks. During the sessions they were blindfolded, so that the light signal was not perceivable (the device emits no sound). Sessions lasted 9min and were administered twice weekly on non-consecutive days.

Photobiomodulation was administered using red light-emitting diodes (LEDs) with a wavelength of 670nm (which has been proven to penetrate the skull) [2] in six 1-min blocks, alternating the LEDs between the right and left temples and with a 30-sec rest between blocks. This LED location aimed to reach one of the *substantia nigra pars compacta*, with death of dopamine-producing neurons in this area being a proposed major pathological substrate associated with PD motor symptom [1,3].

The LED unit we used (WARP 10, Quantum Devices; Barneveld, WI) produces J/cm^2 of energy at its highest intensity ($60mW/cm^2$). When $8J/cm^2$ of energy are applied to the head, approximately 2–3% of the near-infrared photons reach the brain cortex at depths of 1cm from the skin or scalp surface, and 0.2–0.3% are estimated to reach depths of 2cm (and thus to reach the white matter) [3]. Accordingly, transcranial application of J/cm^2 is estimated to

deliver $0.09375 J/cm^2$ (1.9%) and $0.009375J/cm^2$ (0.19%) to the brain cortex and white matter, respectively. Based on these considerations, we estimated that $0.009375J/cm^2$ of LED (0.19%) could be delivered to the *substantia nigra pars compacta*. The laser wave was continuous with a uniform circular beam area during all the sessions. Procedures for the sham group were identical except that patients received photobiomodulation for only 5sec followed by 55sec with no treatment (=1/12th of the energy used for the intervention group). Although there are no prior studies using this sham protocol in PD, it has proven ineffective for cognitive improvement in healthy adults [4]. Thus, we considered it might be used as a control in the present patient population as it could equate to a subjective experience (e.g., feeling a brief sensation of heat at the start of a treatment session) without producing benefits.

Endpoint assessment was conducted by the same researchers the week prior to (i.e., baseline) and after the 9wk intervention. Post-intervention tests were performed 72–96h after the last therapy session. Baseline and post-intervention tests were conducted while patients were in the medication ON-state (i.e., 1–2h hours after taking their morning or evening dose). The primary endpoint was assessment of movement alterations with the Spanish-validated version of the motor portion of the Movement Disorders Society-Unified PD Rating Scale (MDS-UPDRS) [5]. Secondary endpoints were: motor function (Spanish-validated version of the Short Parkinson's Evaluation Scale/Scales for Outcomes in PD) [6]; static posturography [7]; walking speed, assessed with the ten-meter walk test (TMWT), which was performed at two different rhythms, the preferred and fastest-possible rhythm, respectively [8]; and the timed up and go (TUG) test [9].

We used the intention-to-treat approach (missing individual data imputed with the baseline-observation-carried forward approach). Data normality and homoscedasticity were evaluated using Shapiro-Wilks and Levene's tests, respectively. Paired Student's *t*-test was used to determine the endpoint changes within each group during the intervention. The mean difference (post-intervention minus baseline) was compared between groups with unpaired Student's *t*-test. The magnitude of the differences was assessed with standardized effect sizes (ES, Hedges' *g*). The α as set 0.05.

Seventeen and 18 patients were randomly assigned to the intervention and sham group, respectively (age 72 ± 7 yrs and 70 ± 8 yrs, respectively; 7 and 8 women; time since diagnosis 9 ± 4 yrs and 8 ± 4 yrs; Hoehn and Yahr stage 1.5 ± 0.6 and 1.5 ± 0.5 ; MDS-UPDRS score [motor part] 11 ± 6 and 9 ± 5 ; levodopa dosage 644 ± 160 mg/day and 596 ± 162 mg/day) (Supplementary file 1).

Table 1
Effects of photobiomodulation or sham therapy on study endpoints.

Endpoint	Group	Baseline	Post-intervention	Post minus baseline (mean [95% CI])	P-value within groups	P-value between groups
MDS-UPDRS, motor part	PBM	11 ± 5	10 ± 4	-1 (-2, 4)	0.571	0.470
	Sham	9 ± 5	9 ± 4	0 (-3, 3)	0.973	
SPES/SCOPA	PBM	11 ± 10	10 ± 8	-1 (-6, 8)	0.787	0.188
	Sham	9 ± 5	9 ± 5	0 (-4, 4)	0.930	
CoP Length (mm)	PBM	108 ± 37	116 ± 46	8 (-42, 15)	0.351	0.721
	Sham	107 ± 24	112 ± 26	5 (-23, 12)	0.531	
CoP Area (mm²)	PBM	230 ± 110	278 ± 112	48 (-136, 30)	0.203	0.540
	Sham	216 ± 110	234 ± 116	18 (-94, 59)	0.647	
CoP Speed (mm/s)	PBM	3.3 ± 1	3.7 ± 1.1	0.4 (-1, 0.2)	0.212	0.362
	Sham	3.0 ± 0.7	3.2 ± 0.9	0.2 (-1, 0.4)	0.513	
TMWT (preferred rhythm) (s)	PBM	6.0 ± 1.1	6.1 ± 1.0	0.0 (-1.0, 0.8)	0.915	0.215
	Sham	6.5 ± 1.0	6.4 ± 1.0	-0.1 (-7.9, 2.9)	0.349	
TMWT (fast rhythm) (s)	PBM	4.9 ± 0.9	4.3 ± 0.7	-0.6 (0.0, 1.1)	0.045*	0.001*
	Sham	5.0 ± 1.03	5.0 ± 1.0	-0.0 (-0.7, 0.7)	0.891	
TUG test (s)	PBM	11.0 ± 2.6	10.6 ± 2.5	-0.4 (-3.2, 10.3)	0.298	0.094
	Sham	12.6 ± 5.1	12.8 ± 5.4	0.2 (-3.7, 3.4)	0.920	

Values are presented as mean ± standard deviation. Differences between groups correspond to the comparison of the change (post-intervention minus baseline) observed in each group. Abbreviations: CI, confidence interval; CoP, center of pressure (static posturography); MDS-UPDRS, motor part of the Movement Disorders Society-Unified Parkinson's Disease Rating Scale; PBM, photobiomodulation; SPES/SCOPA, Short Parkinson's Evaluation Scale/Scales for Outcomes in Parkinson's Disease; TMWT, ten-meter walk test; TUG, timed up and go.

Baseline scores were used for two (intervention group) and three patients (sham) who were not available for post-intervention assessment. No adverse events were noted.

We found no changes over the 9-wk period in the sham group (all $p > 0.1$). Yet, the photobiomodulation group showed gait improvements (*i.e.*, TMWT, fast rhythm; $p = 0.045$, $ES = 0.73$), and a significant between-group difference was found for the mean change (post-intervention minus baseline) in this endpoint ($p = 0.001$, $ES = 1.17$, Table 1). No other intervention effect was noted, although there was trend towards greater benefits in the TUG test after photobiomodulation ($p = 0.094$, $ES = 0.54$).

Photobiomodulation improved gait speed in the fast rhythm of the TMWT by 0.33 m/second on average, which is of potential clinical relevance as 0.23 m/second has been identified as the minimal detectable change [8]. Our findings are in agreement with those of a previous study that reported gait improvements in PD patients after transcranial photobiomodulation [10], as well as with other pre-clinical studies that suggest that photobiomodulation could be a potential strategy against neurodegenerative diseases [1].

The present study is preliminary in essence and further corroboration is needed in larger cohorts. Yet, our findings are encouraging and might provide useful information for PD management.

Declarations of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.brs.2019.02.009>.

References

- [1] Johnstone DM, Moro C, Stone J, Benabid AL, Mitrofanis J. Turning on lights to stop neurodegeneration: the potential of near infrared light therapy in Alzheimer's and Parkinson's Disease. *Front Neurosci* 2016;9:1–15. <https://doi.org/10.3389/fnins.2015.00500>.
- [2] Naeser MA, Saltmarche A, Kregel 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;29:351–8. <https://doi.org/10.1089/pho.2010.2814>.
- [3] Braak H, Braak E. Pathoanatomy of Parkinson's disease. *J Neurol* 2000;247:113–10.
- [4] Barrett D, González-Lima F. Transcranial infrared laser stimulation produces beneficial cognitive and emotional effects in humans. *Neuroscience* 2013;230:13–23.
- [5] Rodríguez-Violante M, Cervantes-Arriaga A. La escala unificada de la enfermedad de Parkinson modificada por la Sociedad de Trastornos del Movimiento (MDS-UPDRS): aplicación clínica e investigación. *Arch Neurocienc* 2014;19:157–63.
- [6] Martínez-Martín P, Benito-León J, Burguera J, Castro A, Linazasoro G, Martínez-Castrillo, JC Valdeoriola F, et al. The SCOPA-Motor Scale for assessment of Parkinson's disease is a consistent and valid measure. *J Clin Epidemiol* 2005;58:674–9.
- [7] Ruhe A, Fejer R, Walker B. The test-retest reliability of centre of pressure measures in bipedal static task conditions – a systematic review of the literature. *Gait Posture* 2010;32:436–45.
- [8] Lang JT, Kassin TO, Devaney LL, Colon-Semenza C, Joseph MF. Test-retest reliability and minimal detectable change for the 10-meter walk test in older adults with Parkinson's disease. *J Geriatr Phys Ther* 2016;39:165–70. <https://doi.org/10.1519/JPT.0000000000000068>.
- [9] Podsiadlo D, Richardson S. The timed "up & go": a test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc* 1991;39:142–8. <https://doi.org/10.1111/j.1532-5415.1991.tb01616.x>.
- [10] Maloney R, Shanks S, Maloney J. The application of low-level laser therapy for the symptomatic care of late stage Parkinson's disease: a non-controlled, non-randomized study. *Laser Surg Med* 2010;185:61.

Luis Santos*

Department of Physical Education and Sport, University of León, León, Spain

Performance and Health Group, Department of Physical Education and Sport, University of A Coruña, A Coruña, Spain

Susana del Olmo-Aguado

Ophthalmological Research Foundation, Fernández-Vega University Institute, Oviedo, Spain

Pedro L. Valenzuela

Department of Systems Biology, University of Alcalá, Alcalá de Henares, Spain

Kristian Winge

Department of Neurology, Zealand University Hospital, Roskilde, Denmark

Eliseo Iglesias-Soler

Performance and Health Group, Department of Physical Education and Sport, University of A Coruña, A Coruña, Spain

Juan Argüelles-Luis

Department of Functional Biology, University of Oviedo, Oviedo, Spain

Samuel Álvarez-Valle

Spanish Confederation of Persons with Physical and Organic Disability (COCEMFE), Asturias, Spain

Guillermo J. Parceros-Iglesias

Asturias Parkinson Association, Asturias, Spain

Ana Fernández-Martínez

Asturias Parkinson Association, Asturias, Spain

Alejandro Lucia

European University of Madrid (Faculty of Sport Sciences) and Research Institute Hospital 12 de Octubre ('i+12'), Madrid, Spain

* Corresponding author. Department of Physical Education and Sport, University of León, Campus de Vegazana S/N, 24007, León, Spain.

E-mail address: lsanr@unileon.es (L. Santos).

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