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Research Article

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If Light Could Help: The Use of Transcranial Photobiomodulation in Parkinson's Disease. A Controlled Clinical Study.

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Abstract

Objective: The aim of this study is to investigate whether a 4-week physiotherapeutic rehabilitation combined with transcranial photobiomodulation (tPBM) treatment is more effective than the only motor rehabilitation and if the improvement persists at 1-month follow-up.

Methods: We investigated 40 Parkinson's disease (PD) patients, divided into two different groups: a control group that underwent only physiotherapeutic rehabilitation and the experimental one that underwent physiotherapeutic rehabilitation combined with PBM treatment. Outcome measures were UPDRS Part I, Part II and Part III. Patients were evaluated at admission, at the end of 4-week treatment and at 1 month follow up.

Results: All outcome measures improved for each group, but significantly improved at the end of treatment for the experimental group not only related to motor symptoms but also to everyday struggle.

Conclusion: Our results demonstrate that the combination of PBM treatment with physiotherapeutic rehabilitation was effective in improving motor symptoms in PD patients and the improvement in balance, gait and tremor were partially maintained after 1 month.

Keywords

Parkinson's disease, Photobiomodulation, Rehabilitation, Physiotherapy

Introduction

Overview of Parkinson's disease

Nowadays, one of the most widespread neurodegenerative disease is PD, with one case for every 50 people over 80 who are diagnosed with this pathology. The number of PD patients is constantly growing bringing the scientific community to assume that by 2040 this number will hit 12 million [1].

Main feature of PD is the dysregulation of neural circuits in basal ganglia, which are responsible for movement control. Moreover, a selective degeneration of dopaminergic neurons located in Substantia Nigra Pars Compacta is prominent and determines the weakens of muscular tone, gait, and limb movement due to the effect on the basal ganglia motor loop.

PD patients end up in a hypo-dopaminergic states that promotes, at a clinical level, limb rigidity, a generalized slow movement (bradykinesia), and a typical proximal tremor (from 4 - 6 Hz) of the upper extremity that progressively expands to the contralateral side.

Histologically, damaged neurons show an overproduction of intra-plasmatic inclusions that contain misfolded alpha-sinuclein protein fibrils. These fibrils are known as Lewy Body and are a PD hallmark [2].

Although the exact cause of PD remains unknown, several studies show that PD is associated with genetic mutation, neurotoxicity, and vascular dysfunctions that initiate neural death [3-5]. Moreover, mitochondrial dysfunction resulting from the aforementioned factors play a crucial role in PD pathogenesis.

The first clinical approach for PD patient is the prescription of a drug that increases dopamine levels providing a precursor, L-dopa that replaces dopamine unable to pass through blood-brain barrier. This treatment seems to be useful in managing motor symptoms in the initial phase of PD, but its effectiveness decreases with a long-term use, causing often side effects such as dyskinesia [6, 7].

Epidemiological data estimate that the annual cost of a PD patient wander around 5,800 - 10,300 USD. In fact, the natural course of this disease is progressively slow causing a constant need to rely on public facilities and caregivers. Because of this epidemiological data and PD occurrence, several research groups tried to find a new way to help patients and to slow down the arising of some of the motor/cognitive symptoms of PD by finding new technologies based on non-invasive brain stimulation. One of these new approaches, covered in this paper, is tPBM.

What is photobiomodulation (PBM)?

MThis term describes the use of Red and Near Infrared (NIR) light to relieve inflammation and pain and tissue death. The neural tissues are exposed to Low Flow Light with wavelengths that range from 600 to 1100 nanometres (nm) depending in which therapeutic method is used [8]. Over 50 years ago, Endre Mester discovered this technique while he was working on hair growth and wound healing in mice [9]; since then, PBM started being accepted in clinical practice and physiotherapy thanks to the availability of Light Emitting Diodes (LEDs) known to be safer, lower cost and better compatible with everyday life than Lasers [8, 9].

Many preclinical studies have been conducted to evaluate safety and optimal treatment parameters of Brain PBM [10-12]. It has been shown the neuroprotective effect of NIR LEDs in a variety of neurological conditions such as ischemic stroke [13], PD [14], traumatic brain injury [15], Alzheimer's disease, and psychological disorders such as depression and anxiety [16].

PBM is described as beneficial since it targets organs without causing aversive effects [16, 17] and increases Cerebral Blood Flow improving the brain energy metabolism [17, 18]. PBM can promote neuronal protection and survival through the mediation of anti-apoptotic and pro-apoptotic mediators [19, 20], inflammatory signalling molecules [21, 22], and stimulating neurotrophic factors [12-23]. PBM is demonstrated to have beneficial effects at behavioural level such as antidepressant effects, cognitive enhancement, and sleep improvement [15, 24-27].

PBM involves the use of light in a non-invasive and non-thermal way. The light from the visible and NIR spectrum produces cellular reactions triggering neuroprotective responses, improvement in metabolism, neurogenesis, improvement in blood flow, and decrease in oxidative stress and inflammation [16, 28].

The excitation of the mitochondrial Cytochrome-C Oxidase (CCO) is crucial for the effect of PBM since it is a major photoacceptor in the red to NIR light spectrum [29]. When exposed to this type of light, CCO undergoes an increase in the availability of electrons for the reduction of molecular oxygen with an increase in the mitochondrial membrane potential, increasing levels of adenosine triphosphate (ATP), cyclic adenosine monophosphate, and reactive oxygen species which point out an improvement in mitochondrial functioning in cellular metabolism [16, 28-32].

It is established that CCO itself is not the only photoacceptor capable of triggering cellular processes after being light stimulated. A review by Freitas and Hamblin shows that there are no less than fourteen different transcription factors and signalling mediators activated by light exposure [28]. From the initial photon absorption to the last behavioural effect on neurological disorders, a variety of processes occur that can be beneficial for brain disorders. These processes can be divided into short-term stimulation (ATP, blood flow, lymphatic flow, cerebral oxygenations, less edema); neuroprotection (upregulation of anti-apoptotic proteins, less excitotoxicity, more antioxidant, less inflammation); neurotrophins, neurogenesis and synaptogenesis [16, 34].

tPBM in PD

In the attempt to overcome the limits in daily practice management of PD, PBM has been included as an innovative technology for the treatment of motor and cognitive symptoms, especially in early stage of PD.

Initially, through *in vitro* studies, it has been observed that PBM reduces cellular apoptosis and oxidative stress, increasing neuronal production of ATP [35-37]. Studies demonstrate that the application of PBM on human cells enhances mitochondrial dysfunction and reduces oxidative stress [38-40].

The idea of using PBM as a therapeutic approach in PD comes from the strong belief that this disease is caused by a bioenergetics damage; since PBM is specific for the improvement of cell energy production it is one of the most innovative approaches of the last decade for PD treatment.

In addition, neuroinflammation is underlying PD and PBM offers immunomodulatory effects both at local and systemic level [41].

Long-term administration of PBM showed an astrogliosis reduction (a consequence of neuroinflammation) and a reduction in immunogenic cytokine; this results, combined with the absence of side effects of its use [42, 43], lend this technology more attractive for the treatment of this pathology.

At the present day, tPBM is a treatment that produces positive effects in different clinical conditions such as Traumatic Brain Injury, stroke, and depression since the target

brain areas are at a cortical level. On the other hand, the brain structures involved in PD are localized at 80 - 100 nm deep from the cranial suture and underneath the dura mater. Several studies show that the NIR light does not penetrate more than 20 mm deep from the cortex. This could surely be a limit to this technology applied to PD, if we consider PD as an involvement of only subcortical regions. Starting from a study conducted by Maloney et al., on PD patients showing that there is improvement in cognitive and motor symptoms after treatment with tPBM and the maintenance of enhancements until 2-weeks follow up [44], our research group tried to figure out the reason why such a near infrared light treatment at a cortical level is worthy in PD treatment.

Hypothesis

Our research hypothesis is that 810 nm tPBM allows motor cortical neurons to reinforce their metabolic mechanism [17, 18] that is impaired due to the damage set out to the subcortical structures [45]. According to a clinical point of view, if we combine a tPBM treatment (that activates motor cortical areas) with a physiotherapeutic rehabilitation treatment (that activates sensory-motor cortical areas) this will cause a bottom-up and top-down integration of sensory-motor information resulting in an improvement of motor and cognitive aspects. Obviously, combined with this evidence of sensory-motor integration is the ability of NIR light to reduce oxidative stress [16, 28] and to modulate neurotransmitters production.

The aim of this study is to investigate whether a 4-week physiotherapeutic rehabilitation combined with tPBM treatment is more effective than the only motor rehabilitation and if the improvement persists at 1-month follow-up.

Materials and Methods

The study was conducted in Milan, Italy. All participants gave written informed consent prior to taking part and all protocols were conducted in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. The Consolidated Standards of Reporting Trials (CONSORT) guidelines were followed for this trial and a CONSORT flowchart (Figure 1a). The study is an experimental study with a randomized controlled trial (Figure 1b).

Participants

Patients enrolled were 38 diagnosed with PD aged between 60 and 75. Patients were divided into two different groups: 26 in the control group (18 men and 8 women), who performed only physiotherapeutic rehabilitation, and 12 in the experimental group (7 men and 5 women), who underwent physiotherapeutic rehabilitation combined with the treatment of PBM. Patients were randomly allocated either in the control or in the experimental group.

Most patients were currently treated with Levodopa and continued their intake during this study.

Exclusion criteria

- Use of illegal substances and drugs.
- Associated psychotic and psychiatric disorder.
- Epilepsy or other seizure disorder.
- Magnetic Resonance positive to neoplasm.

Experimental device and procedure of PBM

The experimental device, used for the PBM treatment, is Cerebro® NIR Infrared [16]. This device uses 256 LED set in 4 arrays of 64 LEDs/array all matched to 810 nm (Table 1).

NIR Infrared is calibrated to act on two channels: Channel 1 acts on the motor, premotor and visual cortex, Channel 2 acts on the executive, sensory and linguistic brain areas. The intensity of the two channels was modifiable, so Channel 1 was used at 100% intensity and Channel 2 at 75% intensity. NIR treatment was administrated for 18 minutes twice a week for one month.

Test and questionnaire

Both the control and the experimental group underwent Mini Mental State Examination (MMSE) test to assess possible cognitive impairment at admission [46]. The MMSE investigates different cognitive domains: temporal and spatial orientation, repetition, attention and calculation skills, memory recall and language. The total score on the test was 30. No patients showed cognitive impairment (Table 2).

To assess the treatment outcome of Parkinson's signs, patients were evaluated through the questionnaire MDS-UPDRS Part I, Part II e Part III [47]. Part I and Part II are completed by patient and caregiver, while Part III is evaluated by the operator. For each part, the scores showed 5 ranges: no impairment, slight, mild, moderate, and severe impairment (Table 2). Patients in both groups started from a moderate impairment score.

Table 1: Device technical data.

Led Number	**256**	Power	**50 mw**
Output Power	**15 W**	Total Power	**15 W**
Input Voltage	**100 - 240V**	Optical Power	**24 mw/cm²**
Input Current	**0.8 (0.8a)**	Work Voltage	**5V --- 6A**
Wavelength	**810 nm**	Power Frequency	**50 - 60 Hz**

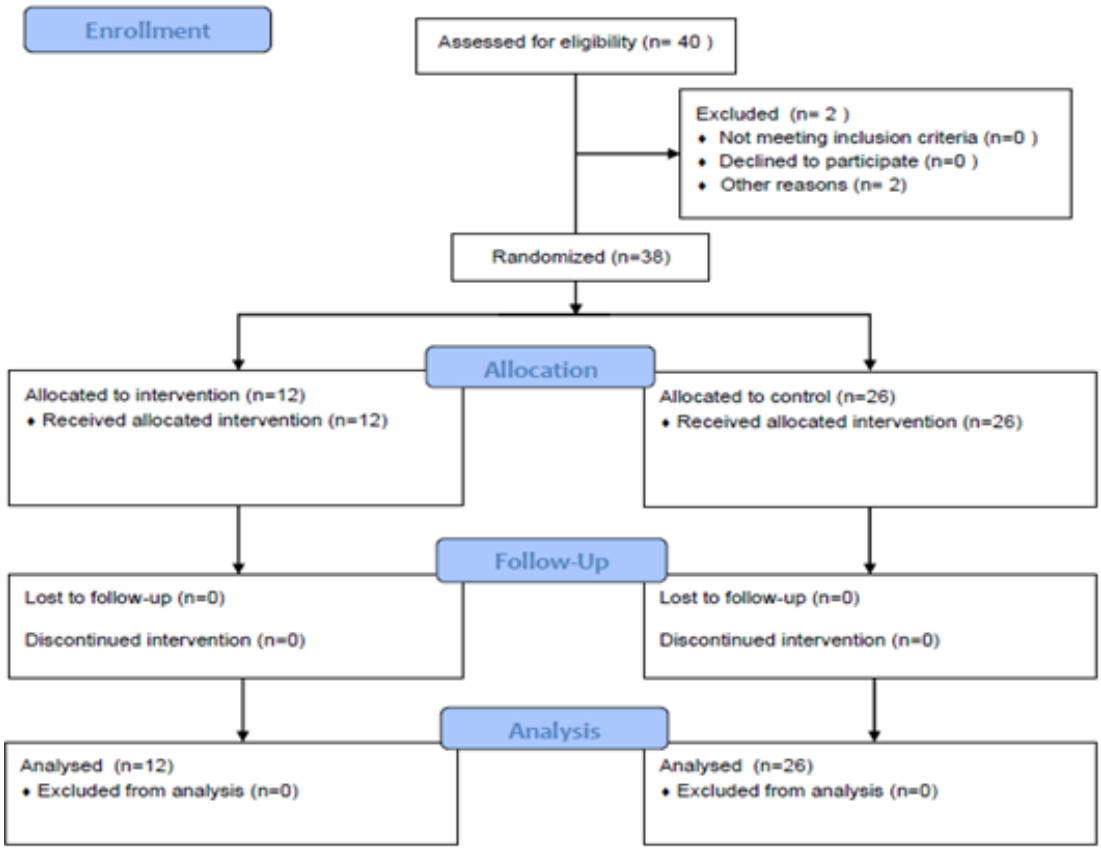
Table 2: Questionnaires and test used to evaluate patients: MMSE Score (as an inclusion/exclusion criteria) and MDS-UPDRS Parts and Score.

MMSE: ≥ 26	
MDS-UPDRS	**MDS-UPDRS SCORE**
Part I: Non-Motor Aspects of Experiences of Daily Living (nM-EDL) Part II: Motor Aspects of Experiences of Daily Living (M-EDL) Part III: Motor Examination	0 = Normal 1 = Slight 2= Mild 3= Moderate 4= Severe

(a)

CONSORT
TRANSPARENT REPORTING of TRIALS

CONSORT Flow Diagram



(b)

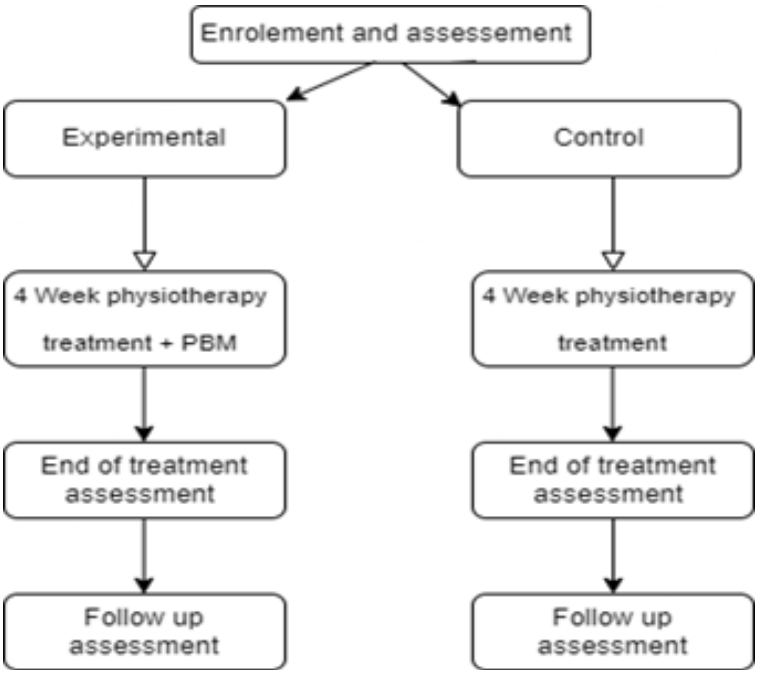


Figure 1: (a) CONSORT flow chart and **(b)** Study design.

Patients were evaluated at admission, at the end of the 4-weeks treatment and at 1-month follow-up.

Data analysis

Data is collected and statistically analyzed using Office Excel and Jamovi version 2.2.5.0 using tables and graphs according to the group and the period of analysis.

Results

We investigated 38 patients diagnosed with PD, divided into two different groups: a control group that underwent only physiotherapeutic rehabilitation and the experimental one that underwent physiotherapeutic rehabilitation combined with PBM treatment. Outcome measures were UPDRS Part I, Part II and Part III.

Patients were evaluated at admission (T1), at the end of 4-week treatment (T2) and at 1-month follow up (T3). All patients at admission showed the same level of impairment (moderate).

Data obtained in the analysis of MDS-UPDRS Part I, which evaluates the non-Motor Aspects of Experiences of Daily Living (nM-EDL), show a clear improvement in the experimental group already at the second analysis, carried out after 4 weeks of treatment (T2) (Figure 2).

The control group showed a "moderate" score of impairment, detected in the first time of evaluation (t1) and a "mild" score in the second analysis (t2); at 1-month follow-up (T3) patients returned to a "moderate" score. The experimental group had a different reaction to the treatments: they started from a "moderate" score of impairments and after 4-week combined treatments (T2) reduced the impairment level into a "slight" score. The experimental group maintained a part of improvement acquired during treatment and at 1-month follow-up (T3) impairment levels were in a "mild" range.

The same analysis was carried out with a focus on the Motor Aspects of Experiences of Daily Living (MDS-UPDRS Part II: M-EDL) and Motor Examination (MDS-UPDRS Part III).

In Part II of the MDS-UPDRS, both the experimental and the control groups started with a score of 3.4 points at admission (T1). After a 4-week treatment (t"), the control group had a minimal improvement, with an average score of 2.4. A significant improvement was found in the experimental group, with an average score of 1.3 (Figure 3). At 1-month follow-up (T3), the control group obtained an average score of 3.4, while the experimental group obtained an average score of 2.4, demonstrating the persistence of improvement in time. After a month, patients generally felt a decrease in tremor and an improvement in walking and balance.

Our research team has also achieved important results at the motor level (Figure 4). Patients who underwent physiotherapeutic rehabilitation combined with PBM treatment gained a better improvement in motor symptoms after 4-weeks treatment (T2) with PBM, compared to the control group. After the 1-month follow-up (T3) the progress was

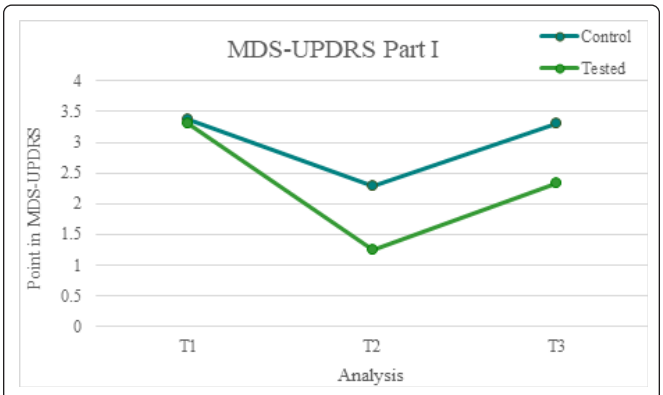


Figure 2: The analysis of MDS-UPDRS Part I shows a clear improvement in the experimental group at the second analysis (T2), carried out after 4 weeks of treatment. Patients in the control group showed a "moderate" score of impairment, detected in the first analysis (T1) and a "mild" score in the second analysis (T2); at 1-month follow-up (T3) patients returned to "moderate". Patients in the experimental group had a different reaction to the treatments: they started to a "moderate" score of impairments and after 4-week combined treatments (T2) reduced the impairment levels into a "slight" score.

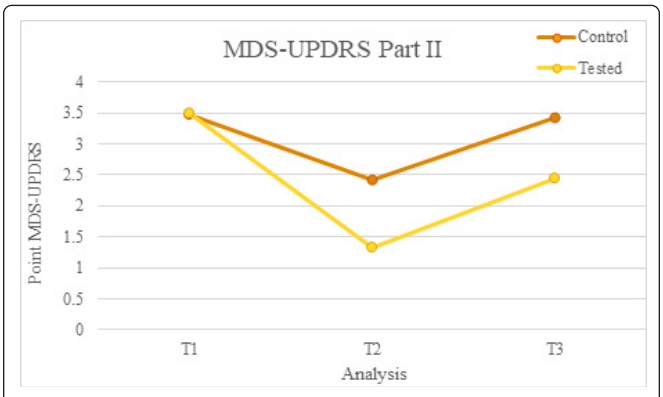


Figure 3: Part II of the MDS-UPDRS, both the experimental and the control groups started with a score of 3.4 points at admission (T1). After a 4-week treatment (T2), the control group had minimal improvement, with an average score of 2.4. A significant improvement was found in the experimental group, with an average score of 1.3. At 1-month follow-up (T3), the control group obtained an average score of 3.4, while the experimental group obtained an average score of 2.4, demonstrating the persistence of improvement in time. After a month, patients generally felt a decrease in tremor and an improvement in walking and balance.

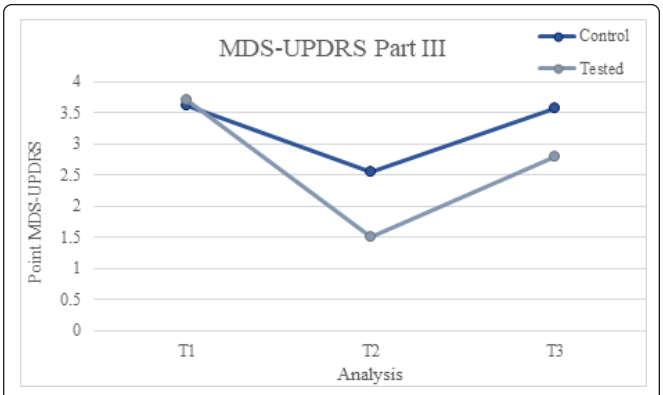


Figure 4: Analysis of MDS-UPDRS Part III shows that the experimental group improved in motor abilities after 4-weeks treatment (T2) with PBM, compared to the control group. After the 1-month follow-up (T3) the progress was partially maintained in the experimental group, while the control group returned to a "moderate" impairment score.

partially maintained in the experimental group, while the control group returned to a "moderate" impairment score.

To analyze motor behavior, in terms of motor signs and motor aspects related to daily life, we compared the results obtained with MDS-UPDRS Part I and Part III, with a focus on the tests at admission (T1) and at follow-up (T3).

The data shows that in the control group, which only performed physiotherapeutic rehabilitation, levels of motor impairment return to a "moderate" score, as in the first analysis (T1). On the other hand, in the experimental group improvements at the motor level persist even one month after the end of the treatments (T3) (Figure 5).

A better result was obtained in the aspects related to daily life. Comparing Part I and Part II in the control and the experimental group, we observed that, while impairment levels in the control group returned to a "moderate" score, the experimental group maintained a "mild" scoring average in both Part I and II (Figure 6).

Data show how effective PBM is not only at the end of treatment, but also the 1-month follow up value is overall better and with a better resistance to the decline of improvements. That confirms the long-term efficacy of this technology. The t-test between the MDS-UPDRS in T1, T2 and T3 of the two groups show a solid significant difference in the T1 and T2 scoring between the two groups. The experimental group shows in fact a lower score, meaning that the symptoms and the impact on everyday life are considerably better than the control groups. The t-test confirmed how significant the improvement of the experimental group is, enhancing our hypotheses (Figure 7).

This test can allow us to show that the baseline of the groups is similar, not reporting any kind of differences in the MDS score at the beginning of the different treatment.

The repeated measures ANOVA analysis showed that the differences between the two groups are significant. The Post-hoc tests comparing the MDS score for each group in T0, T1 and T2 up shown significant differences in terms of scoring at T1 and T2 where the experimental group has a relevant lower score meaning that the symptoms and the impact on everyday life are considerably better than the control groups. Post-hoc confirmed how significant the improvement of the experimental group is, enhancing our hypotheses (Figure 7).

In addition, from interviews with patients and caregivers, the experimental group reported greater balance, safer walking, and an upright position. Above all, patients in the experimental group felt less fatigue and drowsiness, reduced feeling of lack in taking the upright position and improved mood.

Conclusion

The aim of this study is to provide a new clinical approach for patients diagnosed with PD. Different innovative techniques have brought to light in the last decades trying to improve patient's quality of life. One of these is PBM and especially NIR light that has been proven to be effective on many aspects of neuronal metabolic processes. The idea of using PBM as a therapeutic approach in PD comes from the strong belief that this disease is caused by a bioenergetics damage; since PBM is specific for the improvement of cell energy production it is one of the most innovative approaches of the last decade for PD treatment. In addition, neuroinflammation is underlying PD and PBM offers immunomodulatory effects both at local and systemic level [41]. Long-term administration of PBM showed an astrogliosis reduction (a consequence of neuroinflammation) and a reduction in immunogenic cytokine; this results, combined with the absence of side effects of its use [42, 43], lend this technology more attractive for the treatment of this pathology. Maloney et al., [44] provided evidence of PBM being effective on PD symptoms although it is not a disease in which cortical brain areas are primary involved. Based on this evidence, our study focused on determining if a combined 4-week treatment of 810 nm tPBM and physiotherapeutic rehabilitation could improve motor symptoms and extend the acquired improvement to 1-month follow up. It is well known and scientifically shared that PD is characterized by a subcortical damage related to neurons in Substantia Nigra Pars Compact but it is also characterized by many other metabolic dysfunctions that determines neuroinflammation. PD is associated with impairments related to the entire motor domain (such as walking, standing, turning, instability in taking upright position and distal tremor), but it is impossible to firmly assume that there is absolutely no control exerted by the cortical motor areas. If there is a control system coming from above, from the cortical areas, spreading their

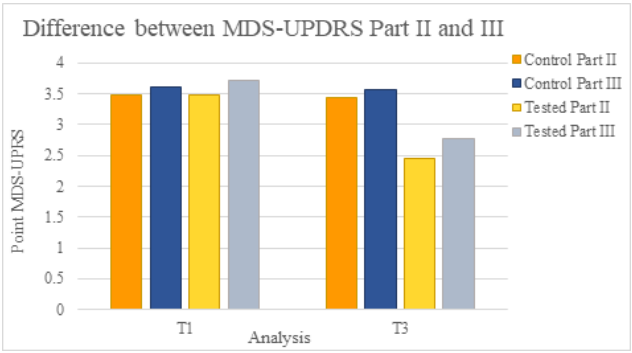


Figure 5: MDS-UPDRS Part II and Part III. Compared to the control group, the experimental group has maintained motor improvements one month after (T3) the end of the treatment.

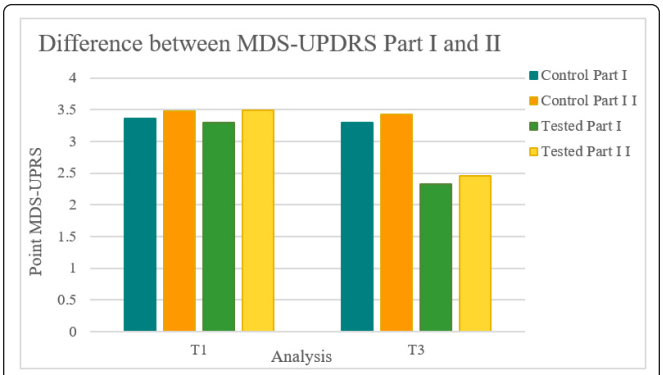


Figure 6: MDS-UPDRS Part I and Part II. Compared to the control group, the experimental group-maintained improvements one month after the end of the treatment (T3).

Between Subjects Effects

	Sum of Squares	df	Mean Square	F	p	η^2_p
Group	93.55	1	93.553	576	< .001	0.941
Residual	5.84	36	0.162			

Note. Type 3 Sums of Squares

Post Hoc Comparisons - MDS tot ✻ Group

Comparison								
MDS tot	**Group**	**MDS tot**	**Group**	**Mean Difference**	**SE**	**df**	**t**	**$p_{bonferroni}$**
pre	Control	pre	Experimental	-0.0563	0.1053	36.0	-0.535	1.000
		post	Control	3.2054	0.0816	36.0	39.304	< .001
		post	Experimental	6.3628	0.1161	36.0	54.825	< .001
		follow up	Control	0.1423	0.0549	36.0	2.591	0.206
		follow up	Experimental	2.8878	0.1042	36.0	27.709	< .001
	Experimental	post	Control	3.2617	0.1104	36.0	29.542	< .001
		post	Experimental	6.4192	0.1200	36.0	53.474	< .001
		follow up	Control	0.1987	0.1048	36.0	1.895	0.992
		follow up	Experimental	2.9442	0.0808	36.0	36.421	< .001
post	Control	post	Experimental	3.1574	0.1207	36.0	26.163	< .001
		follow up	Control	-3.0631	0.0781	36.0	-39.222	< .001
		follow up	Experimental	-0.3176	0.1094	36.0	-2.904	0.094
	Experimental	follow up	Control	-6.2205	0.1156	36.0	-53.814	< .001
		follow up	Experimental	-3.4750	0.1150	36.0	-30.229	< .001
Follow up	Control	follow up	Experimental	2.7455	0.1037	36.0	26.475	< .001

Estimated Marginal Means - MDS tot ✻ Group

				95% Confidence Interval	
Group	MDS tot	Mean	SE	Lower	Upper
Control	pre	10.45	0.0592	10.33	10.57
	post	7.24	0.0678	7.10	7.38
	follow up	10.30	0.0583	10.19	10.42
Experimental	pre	10.50	0.0871	10.33	10.68
	post	4.08	0.0998	3.88	4.29
	follow up	7.56	0.0858	7.38	7.73

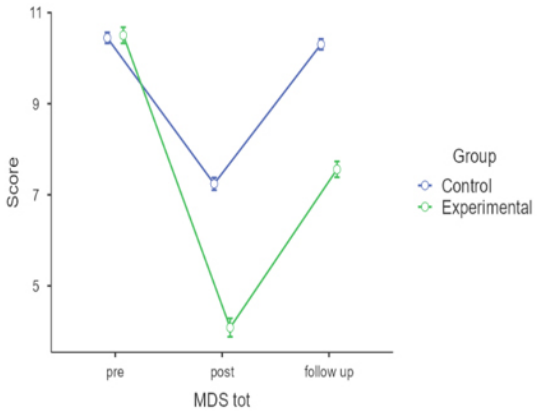


Figure 7: Repeated measures ANOVA between subject and post-hoc comparison and graph. The higher the MDS score is, the worse the Parkinson's signs are.

information top-down to the subcortical ones but, in between, there is a shutdown (whether it is metabolic, electric, chemical, etc.) the information will not be integrated. The same process will happen from a bottom-up point of view: the information, coming from the distal parts of the body, tracing back to the subcortical regions in order to modulate neurotransmitter production (for i.e., muscular tone in order to move the left arm and lift a bag), will not be fully integrated with the cortical motor area because of a shutdown in the exact middle of the information pathway. How is it possible to prevent cortical motor areas from losing their neuronal activity and functionality? A try needs to be addressed to tPBM since it enhances metabolic processes, reduces oxidative stress in cells and promotes neurotransmitters production. In this study, thanks to the PBM device used it was possible to address NIR light to different brain areas (sensory-motor, prefrontal, visual, and cognitive cortical brain areas); this could prove evidence for improvements in sleep quality and mood swings. According to the questionnaire used to evaluate the efficacy of this combined tPBM-physioterapeutic treatment, this combination was more effective than the only and classic physiotherapeutic rehabilitation.

In fact, all outcome measures improved for each group but improved significantly at the end of treatment for the experimental group not only related to motor symptoms but also to everyday struggle.

The experimental group perceived improvement at the motor level, especially tremor reduction, improvement of visuo-spatial orientation, erect posture, and safe walking.

All patients in the experimental group detected improved mood, less drowsiness, and fatigue and reduced feeling of lack in taking the upright position. All these effects also remained at 1-month follow-up.

Results obtained are therefore coherent with our hypothesis about the need to enhance cortical metabolism, especially in primary motor areas, in order to improve neural mitochondrial activity and reduction in inflammatory and oxidative stress derived processes.

Limitation of the Study

The limitation of this study is surely the small sample size. Due to the small sample of PD patients and the device features it was not possible to include a third group treated as a Placebo/Sham Group that could undergo the same rehabilitation program as the experimental one but without the administration of NIR light. Future studies on PD patients and PBM should consider this type of Study Design in order to avoid placebo derived symptom improvements and further control over the PBM efficacy. Moreover, it would be interesting to integrate this data with the evaluation of overall Cognitive Impairments during each assessment time (T1, T2, and T3) in order to assess whether there is an increase also in MMSE scoring.

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Conflict of Interest

Federica Peci declares that she is the CEO of the company, whose *NIR Infrared* helmet was used in this study.

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