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Progress of Photobiomodulation for Parkinson's Disease

Chung Min Tsai*

Social Alternative Service, Ministry of Health and Welfare, Taiwan

Abstract

Parkinson's disease (PD) is a neurodegenerative disease with global burden. The mechanisms and therapeutic effects of photobiomodulation (PBM) correspond to main mechanisms in the pathogenesis of PD. Numerous research results applying PBM for PD were published during the past two decades. Although several systematic review or review articles provided complete introduction, they are either mainly basic research or clinical research, and the year of the article publication is up to 2020. Comprehensive systematic review or review articles containing basic and clinical studies including those articles published in 2021 and 2022 are lacking. Hence, this systematic review aimed to include both basic and clinical studies published up to 2022. Results were obtained by retrieving articles from PubMed with the intersection of the articles derived from the terms of PBM synonyms and Parkinson's disease followed by exclusion. Sixty-nine articles were included ultimately. Among them, 40 original articles were identified, which were composed of 31 basic research and 9 original articles of clinical research. Twenty-one review articles, a systematic review with focused content on PD, and 7 review articles with the term PD under general illustration of PBM were presented. Mechanisms regarding the therapeutic effects of PBM on the in vitro studies were reviewed. Positive outcomes on motor symptoms after PBM treatments were shown in most in vivo and clinical studies. The immunohistochemical examination of in vivo studies reflect the therapeutic effects of PBM on the preservation even reverse of the pathogenic insults of PD on the in vitro studies. The most frequently used wavelength among original articles included was 670nm. Considering the acceptability of PBM for patients with PD, noninvasive transcranial PBM (tPBM) had crucial roles in respect to invasive intracerebral PBM. To match the penetration depth reaching deep brain target, Substantia nigra pars compacta, in human brains of patients with PD, the wavelength 810nm might match the need in the clinical setting of tPBM. More future clinical studies were needed. In conclusion, therapeutic approaches applying PBM for PD are promising. Recent studies revealed positive outcomes. Future clinical practices containing PBM are to be expected.

Keywords: Transcranial, Photobiomodulation, Parkinson's disease

Introduction

Parkinson's disease (PD) is a neurodegenerative disease associated with motor symptoms including tremor, rigidity, slow movement, walking imbalance, as well as non-motor complications. According to the latest global estimates by the World Health Organization, more than 8.5 million individuals lived with PD, and PD caused 329,000 deaths in 2019.[1] The pathogenesis of PD involves dopaminergic neuronal loss in the substantia nigra pars compacta (SNpc)[2] and extra-nigrostriatal systems as well as non-dopaminergic neuronal loss.[3] Mitochondrial dysfunction plays a crucial role in the pathogenesis of PD.[4,5] The dopaminergic neurons in the SNpc are vulnerable to mitochondrial dysfunction in PD,[6] and mitochondrial dysfunction in non-dopaminergic neurons are also reported from human patients with PD and animal models of PD.[4] Impairment or loss of mitochondrial complex I in dopaminergic neurons is a feature of PD.[4,7] The subsequent bioenergetics failure and oxidative stress lead to apoptosis. This pathway along with protein misfolding and aggregation such as α-synnuclein aggregation, ulti-

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***Corresponding author:** Chung Min Tsai, Social Alternative Service, Northern Region Senior Citizen's Home, Ministry of Health and Welfare, Taiwan

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mately result in cell death. The α-synnuclein (the main component of Lewy bodies)[8] aggregation further induces microglial activation which produces proinflammatory mediators and results in progression of PD.[9] Mitochondrial dysfunction of dopaminergic neurons and non-dopaminergic neurons,[10,11] α-synnuclein aggregation,[12] and microglial activation[13] are considered as a potential therapeutic target to ameliorate neurodegeneration in PD.

Photobiomodulation (PBM) therapy, previously termed as low-level laser/light therapy,[14] is the treatments using red to near-infrared (NIR) light with wavelength 600-1100nm[15] which bring out biological alterations in organism secondary to the interactions of photon with molecules in cells or tissues.[16,17] Current generally acknowledged photoreceptor of PBM is cytochrome c oxidase (CcO),[18] the Complex IV of mitochondrial respiratory electron transport chain. After receiving photons of red to NIR light by CcO, ATP production is boosted and mitochondrial biogenesis is promoted.[19] The outcome of PBM in neurons and central nervous system, multiple neuroprotective effects such as reduction of apoptosis, oxidative stress, microgliosis, inflammation, and increase brain-derived neurotrophic factor, glial-derived neurotrophic factor (GDNF),[20-22] etc. Transcranial photobiomodulation (tPBM) is the application of PBM transcranially and noninvasively. tPBM has been applied to dementia including Alzheimer's disease,[23] traumatic brain injury,[24] stroke,[25] epilepsy,[17,21,26,27] PTSD,[28] anxiety and depression.[29]

Corresponding to the two main mechanisms (α-synnuclein aggregation and mitochondrial dysfunction or failure of mitochondrial biogenesis) and a potential therapeutic target (microglial activation) in the pathogenesis of PD, PBM has correlated therapeutic effects against them respectively. PBM improves clearance of misfolding proteins (amyloid-β) in other neurodegenerative diseases (Alzheimer's disease),[30,31] boosts mitochondrial biogenesis,[19] enhances mitochondrial function,[32] and suppresses microglial activation.[30] These along with other therapeutic effects render PBM a potential treatment mean for PD.

Regarding the application of PBM on PD, Li[33] (in Chinese) applied intranasal low energy He-Ne laser for patients with PD, and the results were published in 1999.[34] Xu[35] (in Chinese) and Zhao[36] (in Chinese) also applied intranasal low energy He-Ne laser for patients with PD, and the results were published in 2003.[34] Komel'kova [37] (in Russian) applied laser therapy to PD patients, and the results were published in 2004. Later in the same year, Eells[38] proposed that NIR light-emitting diode (LED) PBM "represents an innovative and non-invasive therapeutic approach for the treatment of" several neurodegenerative diseases including PD. Ever since Liang[39] and Ying[40] (both were led by Professor Margaret T.T. Wong-Riley) revealed that NIR LED attenuated rotenone- and 1-methyl-4-phenylpyridinium ion (MPP+)-induced neurotoxicity in 2008, numerous basic research, clinical studies and review articles regarding the application of PBM to PD had been published.

Salehpour and Hamblin's systematic review carefully included animal studies of PBM for PD (published in 2020), and Hamilton[41] thoroughly reviewed the use of tPBM in PD patients (published in 2018). Foo[32] also reviewed in vitro and in vivo studies accompanied with a clinical study[42] and a clinical trial,[43] yet the article was published in 2020. Nevertheless, comprehensive systematic review containing both basic and clinical research of PBM for PD including articles published on 2021-2022 is lacking. The aim of this systematic review is to go through the basic and clinical/translational researches of PBM for PD and to update the latest progress.

Materials and Methods

Search Strategy

Literature search was performed on PubMed. The search term in the Query box in this study was "((((((((((((((((((low level laser therapy) OR low level laser treatment) OR low level light treatment) OR low level light therapy) OR low energy laser therapy) OR low energy laser treatment) OR low power laser therapy) OR low power light therapy) OR Photobiomodulation) OR near infrared laser therapy) OR near infrared laser treatment) OR near infrared light treatment) OR near infrared light therapy) OR cold laser) OR Near-infrared Laser Stimulation) OR Photoceutical)) NOT (photo thermal OR photodynamic)) AND ((Parkinson's disease OR Parkinson disease) OR Parkinsonism)". Non-English language articles were included. The access date was July 20, 2022, Central Standard Time.

Exclusion Criteria

1. Articles with main context unrelated to PBM or PD.

2. Articles of clinical studies or clinical trials that participants with PD are one of the minor rather than majority subject categories.

Clinical Trials

Further information regarding clinical trials was obtained from the database ClinicalTrials.gov (https://clinicaltrials.gov/).

Results

There were 131 results at initial search (no new result was presented during manuscript preparation), and 62 articles were excluded. Thirty-eight articles were excluded due to being irrelevant to PBM, and 6 articles were excluded due to being irrelevant to PD, and 17 articles were excluded due to being irrelevant to both PBM and PD. A clinical study[44] was further excluded because a PD participant was merely one of the participants selected for balance disorder. Sixty-nine articles on PubMed are relevant to both PBM

and PD up to July 20, 2022.

Among these 69 articles relevant to both PBM and PD, 31 basic researches were identified. Of which, 6 in vitro studies[39,40,45-48] 24 in vivo studies,[49-72] and a Monte Carlo simulation study were included.[73] Nine articles of clinical research including 8 articles of clinical studies[37,42,74-79] and a clinical trial[43] were found. The rest of the articles include 21 review articles[22,25,32,41,80-96] and a systematic review[97] with focused content on PD, and 7 review articles[38,98-103] with the term PD merely mentioned along with other neurodegenerative diseases such as Alzheimer's disease for general description of therapeutic application of PBM.

Regarding the wavelength used for PBM on PD, 635nm,[45] 660nm,[46] 670nm,[39,40,47] and 810nm[48] were used for PBM in vitro study of PD. As for in vivo studies, the wavelength 670nm was used in 21 studies,[49-53,55-58,60,61,63-72] 810nm was used in two studies,[59,62] and in combination use of 670nm and 810nm was noted in a study. In clinical studies, Maksimovich[77] administered intracerebral transcatheter laser with 633nm, Hamilton[42] used tPBM with 670nm, 810nm and 850nm and intranasal PBM with 660nm, Hong[76] chose 940nm, and Liebert[75,79] and Bicknell[74] used 904nm. In regard to the clinical trial, Santos applied 670nm as the wavelength of tPBM.

Regarding the mechanisms of PBM on PD illustrated by in vitro studies, Liang[39] demonstrated in a model of PD induced by the exposure of rotenone and MPP+ that PBM increased cellular ATP production, reduced the expressions of reactive oxygen species, reactive nitrogen species, and neuron numbers with apoptosis. Ying confirmed that those therapeutic effects were also observed in PBM pretreatment manner.[40] Trimmer[48] revealed that PBM restored axonal transport of mitochondria in neurites of human PD cybrid neuronal cells. As for the signal pathway involved in PD, Gu[47] demonstrated that PBM with He-Ne laser protected MPP+ exposed human dopaminergic neuroblastoma cells from MPP+-induced neurotoxicity via upregulation of extracellular signal-regulated kinases/cAMP-response element binding protein/vesicular monoamine transporter 2 pathway. Furthermore, in view of possible application of PBM on stem cell therapy for PD, Yurtsever[46] showed that PBM increased expression of dopaminergic neuron protective protein mRNAs in human dental pulp stem cells. However, no functional characteristic of dopaminergic neurons was developed. In addition to above PBM monotherapy, Mirakabad[45] revealed that combination therapy of PBM and curcumin reduced Bax/Bcl2 ratio (an indicator of apoptosis) and expression of ATG10 and LC3 (indicators of the accumulation of autophagosomes) in PC12 cells pretreated with 6-hydroxydopamine.

As for the mechanisms of PBM on PD illustrated by in vivo studies, Oueslati[59] revealed that PBM suppress α-synnuclein-induced toxicity in a rodent model of PD. Regarding the action on neuronal loss, Purushothuman[65] demonstrated that PBM preserved the survival of tyrosine hydroxylase positive (TH+) cells in striatum in a transgenic mouse model of PD. People,[67] Moro[64,66] and El Massri[61] demonstrated that intracerebral PBM preserved the survival of tyrosine hydroxylase positive (TH+) cells in striatum in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse models of PD, and Darlot[59] observed the similar results in a monkey model of PD. El Massri[53] further revealed that intracerebral PBM increased TH+ cells and GDNF expression in the striatum in MPTP treated monkeys. However, Reinhart[58] revealed that the expression of TH and behavioral improvements were not fully matched. Besides striatum, Shaw[68] also observed the neuroprotection effects of PBM on TH+ cells over other brain regions such as subthalamic nucleus and zona incerta. Regarding the mechanisms involve non-neuronal cells, El Massri demonstrated that intracerebral PBM reduced astrogliosis over caudate-putamen complex in MPTP-treated mice[61] and SNpc and striatum in MPTP-treated monkey.[55]

Eight articles of clinical studies were published from 2004 to 2022. Noninvasive PBM (tPBM, intraoral PBM, and transdermal PBM over neck) were used in 7 articles,[37,42,74-76,78,79] and an invasive approach in the operative setting was used in a study conducted by Maksimovich.[77] As for the study design, except for a randomized double-blind placebo-controlled pilot study,[78] other 7 articles[37,42,74-77,79] are observational studies including an open-labeled, single-arm, phase-I/IIa study.[76]

Bullock-Saxton[78] conducted a randomized double-blind placebo-controlled pilot study which combined tPBM and intra-oral PBM for PD participants in Australia. There were 22 participants with PD enrolled, and they received either tPBM combined with intraoral PBM or sham treatments on 1, 2, or 3 times per week for 4 weeks. A 4-weeks wash-out separated 2 treatment phases. No statistically significant changes regarding physical outcome of upper and lower limbs and Montreal Cognitive Assessments were noted, and a placebo effect was observed.

In addition, Liebert[79] revealed that remote application of PBM over abdomen improved clinical signs of PD patients individually during Coronavirus disease 2019 (COVID-19) pandemic. There were 7 participants in the case series during COVID-19[79] and 12 participants were enrolled according to the later retrospective study[74] and a prospective proof-of-concept study.[75] Participants at the case series received PBM over abdomenand neck (corresponded to C1/C2 region) transdermally,[79] and transcranial and intranasal PBM treatments were also described in the retrospective study[74] and prospective proof-of-concept study.[75] Participants received PBM for 12 weeks (3 times per week for 4 weeks, followed by twice per week for 4 weeks, and once per week for 4 weeks, a total of 24 sessions). After 12 weeks of PBM treatments and 33 weeks follow up, individual improvement of clinical signs of PD patients including mobility, dynamic balance, spiral test, sense of smell, and cog-

nition were shown. Later, Bicknell[74] analyzed the microbiome from the feces of those participants retrospectively. After 12-weeks PBM treatments, a trend toward microbiome changes (increases in some short chain fatty acid-producing bacteria, beneficial genera and decreases in potential pathogens and some bacteria harmful to the microbiome) was noted. These three correlated articles[74,75,79] were counted as a joint clinical study here.

Apart from Hong's study,[76] the rest of above-mentioned clinical studies applied PBM monotherapy for treatments of participants with PD. Patients with PD in Hong's study[76] received combination therapy of transdermal PBM over the neck (pointing to the midbrain) and hydrogen water (H_2 water).

The only-one clinical trial was a double-blinded randomized controlled trial (RCT) of tPBM for PD participants was found, and it was conducted by Santos[43] in Spain, January 29–April 6, 2018. There were 35 participants with PD in actual enrollment. Among them, 17 participants received tPBM treatments and 18 participants received sham treatments.[104] The wavelength used was 670nm, and the LED was placed alternating right and left temples. Six 1-min blocks with a 30-sec rest were performed as a session (total 9 min). tPBM and sham sessions were administered twice weekly on non-consecutive days. After 9-weeks intervention (total 18 sessions), gait improvements evaluated by ten-meter walk test, fast rhythm, were shown in PD participants receiving tPBM.

Discussion

During the exclusion process, Gallamini's clinical observational study[44] was excluded according to the second exclusion criteria. Four female patients with balance disorder received laser acupuncture with the wavelength 635nm. Among them, a patient was diagnosed with PD. She obtained a significant benefit on balance disorder from the laser acupuncture.[44] Walking imbalance is one of the motor symptoms in PD. Though a limited case number, Gallamini's study implied potential therapeutic effects of PBM with laser acupuncture approaches, future studies with more case number are needed.

Among 24 in vivo research[49-72] in the current study, three articles[105-107] which Salephour and Hamblin[97] listed in the systemic review were not included in the current study. On the contrary, an in vivo study which Moro[52] demonstrated that intracranial PBM didn't cause major biosafety concerns, and this study was not included in Salephour and Hamblin's[97] systematic review. As for clinical studies, Maloney's[108] non-controlled, non-randomized study presented in 30th American Society For Laser Medicine & Surgery Conference which was introduced in Hamilton's review article[41] was not included in the current study. Maloney reported that two-week application of tPBM improved speech, cognition, freezing episodes and gait in 8 patients with pakinsonian syndromes.[108]

In Liebert[79] and Bicknell's[74] studies, whether remote PBM treatments over abdomen transdermally really improved clinical signs of PD patients via gut-brain axis need careful examination. Considering that transcranial and intranasal PBM were also applied to PD participants,[74] and these treatments could share the weight of the efficacies of remote PBM treatments regarding the improvement of clinical signs. Chen applied pure remote PBM treatments over abdomen transdermally (gut flora-targeted PBM, gf targeted PBM) without the use of transcranial or intransal PBM, and demonstrated that gf targeted PBM improved senile dementia in an animal model of Alzheimer's disease. Likewise, future clinical studies or trials applying pure remote PBM treatments over abdomen transdermally or gf targeted PBM without the combination use of transdermal PBM over neck or transcranial, intranasal PBM may better illustrate the therapeutic effect of remote PBM treatments for PD patients via gut-brain axis.

Regarding the wavelength used for PBM on PD, 670nm was mostly used overall. One of the possible explanations could be that the preceding in vitro and in vivo studies applied PBM with wavelength 660nm or 670nm most and therapeutic effects were observed, thus, recent researches of PBM for PD stood on the shoulders of the preceding results. However, the in vivo studies with primate subjects[52,53,55,56,60,71] administered invasive approaches, and the application of PBM with the wavelength 670nm in those studies relied on the implantation of the fiber. Close to 670nm, the wavelength 633nm chosen in Maksimovich's clinical study[77] was also administered by invasive approaches with the assistance of optic fiber. Although the invasive approach would guarantee that the PBM reaches SNpc with sufficient intensity, invasive surgery would be a physical-psychological burden to patients with PD. Non-invasive tPBM and intranasal PBM may be more attractive to patients with PD, and tPBM, intranasal PBM, and transdermal PBM (over neck corresponds to C1/C2 region) could be even treated as homecare mode in the future. With this in consideration, a suitable wavelength range of noninvasive PBM for patients with PD is crucial.

According to Pitzschke's[73] human-head Monte-Carlo simulation study, which was noted within the literature search results in current study, the NIR light with wavelength 808nm had deeper penetration than the red light with the wavelength 670nm did, and Pitzschke[73] considered that 808nm is "a better choice for light delivery in the deep brain" with respect to 671nm. Thus, 810nm (808nm) had potential to be more suitable for tPBM with noninvasive approaches targeting SNpc in PD patients. Considering that SNpc is located deep within the human brain. The use of 810nm as the wavelength choice of tPBM would be beneficial to PD. The wavelength 810nm had shown efficacy in an in vitro study[48] 3 in vivo studies.[54,59,62] Furthermore, Reinhart[54] revealed synergistic effects of combined use of the wavelength 670nm and 810nm together

and sequentially use of the wavelength 670nm followed by 810nm yielded better overall outcome in a MTPT mouse model study. Similar to the result of Monte-Carlo simulation of human head, the simulation result performed by Reinhart[54] also revealed that the signal of 810nm was greater than that of the 670nm at the depth of the SNpc.

Conclusion

PBM for PD is established on solid mechanistic basis according to more than 30 basic researches. Clinical studies of PBM for PD showed optimistic outcomes on motor symptoms. A recent double-blinded RCT revealed significant gait improvement after tPBM treatments. Taken together, PBM is beneficial for PD patients in delaying neurodegenerative progression. Clinical trials applying PBM for PD patients in near future and inclusion of PBM as standard clinical therapeutic means in the foreseeable future are to be expected.

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Conflicts of Interests

Author declares that there is no conflict of interest.

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