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Therapeutic Effects of Photobiomodulation Therapy on Multiple Sclerosis by Regulating the Inflammatory Process and Controlling Immune Cell Activity: A Novel Promising Treatment Target

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Abstract

Introduction: Multiple sclerosis (MS) is one of the autoimmune and chronic diseases of the central nervous system; this disease occurs more frequently in young people and women and leads to neurological symptoms. Oxidative stress, inflammatory processes, and oligodendrocyte dysfunction have a pivotal role in the pathophysiology of this disease. Nowadays it is reported that photobiomodulation (PBM) as a non-invasive treatment has neuroprotective potential, but the exact mechanisms are not understood.

Methods: In this study, we reviewed the effects of PBM on MS. In this regard, we used the keywords "Photobiomodulation", "Laser therapy", and "Low-level laser therapy" on MS to find related studies on this subject in PubMed, Google scholar, Elsevier, Medline, and Scopus databases.

Results: PBM has positive effects on MS by regulating the inflammatory process, controlling immune cell activity and mitochondrial functions, as well as inhibiting free radicals production which finally leads to a reduction in neurological defects and an improvement in the functional status of patients.

Conclusion: Overall, researchers have suggested the use of laser therapy in neurodegenerative diseases due to its numerous therapeutic effects.

Keywords: Multiple sclerosis; Photobiomodulation, Myelin, Central nervous system

Introduction

Neurodegeneration disorders, such as Alzheimer's disease (AD), Parkinson's disease (PD) and multiple sclerosis (MS), spinal cord injury (SCI), and COVID 19 are usually progressive diseases that cause structural and cellular changes in the nervous system, eventually leading to symptoms such as cognitive, motor, and memory impairments.[1-5] Today, researchers have used a variety of treatments including drugs and cell therapy to minimize the complications of diseases.[6,7] Since photobiomodulation (PBM) is a non-invasive method, it has received more attention.[8] The pathophysiology of these diseases is often multifactorial and the exact mechanisms are not understood yet. MS is a chronic and inflammatory disease of the central nervous system in which the myelin sheath of the neural cells is damaged through a combination of immune dysregulation and oligodendrocyte dysfunction.[9] Due to its severe and debilitating effects, as well as the imposition of high medical costs, this disease has had wide social and economic effects on the patients.[10] It is well documented that invasion of T helper lymphocytes (CD4+) into neural tissue plays an important role at the onset of this disease.[11,12] Despite many studies in this field, the exact mechanism of the onset and progression of this

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disease is unknown. However, researchers have suggested that the lack of control of immune system cells, as well as the dysfunction of oligodendrocytes, could be the main causes of the disease. Axonal disruption, programmed cell death, and impaired neurotransmitter transmission have also been reported in the disease.[9,11,12] In previous studies, it was well established that in the neuroinflammation condition, the level of production of active oxygen and nitrogen species is significantly increased, which can lead to the disruption of the antioxidant system.[12] Elevated levels of these factors can eventually lead to the widespread destruction of vital cell components such as DNA, lipids, proteins, and mitochondria. Nowadays, there is ample evidence that free radicals play a key role in the progression of MS.[13] Studies have shown that neutrophils and lymphocytes (Th1, Th17, Th22), as well as lymphocytes T CD8, B cells, and macrophages, become activated in this disease, which can lead to the overproduction of inflammatory cytokines, active oxygen and nitrogen species against myelin antigens.[11,14-16] In addition, it has been shown that the activity of regulatory lymphocytes (CD4 + CD25 + Treg) is also impaired in this disease. These factors, in turn, can increase damage to the neural tissue.[17,18] Today, MS treatments focus more on the anti-inflammatory and immune-regulating process. Previous studies have implicated the production of oxidative stress related to mitochondrial dysfunction, which plays an important role in the chronic phase of MS.[10,19,20]

It has been demonstrated that PBM is associated with neuroprotective effects that can mitigate neurological symptoms in neurological disorders through a variety of mechanisms.[21-23] It is well documented that PBM can enhance neuronal regeneration and also induce Schwann cell proliferation and viability of oligodendrocytes in the CNS.[24,25] In the animal model of brain injury, PBM administration could decrease neural cell apoptosis, enhance neural survival, and raise the production of BDNF as a growth factor.[26-28] The beneficial effects of PBM in animal models of SCI have previously been reported.[8,29,30] It was revealed that in the contusion model of SCI, PBM-treated groups showed a significant down-regulation of some oxidant factors such as catalase (CAT), malondialdehyde (MDA), superoxide dismutase (SOD), pro-inflammatory cytokines (TNF-α, IL-1β), and apoptosis-related marker (caspase-3). Furthermore, a considerable increase in glutathione peroxidase (GSH-PX) and anti-inflammatory factors (IL-10) has been reported.[31]

Researchers proposed that PBM could improve functional recovery and decrease neurological impairment by controlling inflammation processes and oxidative stress.[31,32] In addition, it has been shown that PBM can prevent the overproduction of inflammatory factors and free radicals by affecting immune system cells at the site of damage to the nervous system (resident and migrating cells) and regulating their activity which can inhibit the destruction of axonal myelin and neural apoptosis.[33,34] Mitochondrial dysfunction is considered to be one of the main mediators of the pathogenesis and progression of neurodegenerative diseases.[35] In this regard, PBM can also directly affect mitochondrial function (especially cytochrome c), leading to increased ATP production and a reduction in nitric oxide (NO) and oxidative markers at the site of injury.[36-39]

Photobiomodulation Therapy on Multiple Sclerosis

PBM therapy has been used in several experimental animal disease models. Today, the use of PBM to treat many diseases such as osteoporosis, wound healing, muscle problems, inflammatory pain, periodontal diseases, lung inflammation, nervous system injuries and autoimmune diseases is in the spotlight as a non-invasive treatment.[23,27,40-44] PBM have been well documented in previous studies to have beneficial therapeutic effects on neurodegenerative diseases such as SCI, stroke, and traumatic brain injury.[8,21,31] The researchers of these studies have mentioned that PBM is a promising and novel treatment that can reduce neurological complications. Despite many studies in this field, the exact mechanism of the therapeutic effect of PBM on neurodegenerative diseases is still poorly understood. Several studies have shown that PBM has neuroprotective potential.[8,29,30] However, researchers have suggested that the use of PBM in nervous system disorders can reduce apoptosis and autophagy, inhibit free radicals production, decrease inflammatory factors, and ultimately significantly reduce the affected area. In addition, it has been shown that PBM improve axonal restoration, increase neurogenesis, stimulate angiogenesis and the production of anti-inflammatory factors, and cause mitochondrial respiration enhancement and neural cell survival.[21-23,44,45] Studies have shown that low-level laser radiation (red or near-infrared light) can be absorbed by cytochrome c oxidase (mitochondrial chromophore structures), ultimately leading to increased ATP production and cellular respiration, and it can also modulate the production of free radicals and NO.[46] In this regard, some researcher examined the effect of PBM (AlGaInP, 660 nm, and GaAs, 904 nm) in an animal model of MS (experimental autoimmune encephalomyelitis). The results of their study revealed that laser therapy was able to significantly reduce NO expression. Also, they observed a significant reduction in the level of inflammatory markers such as IL-17, IFN-γ, and IL-1β. In addition, histological data showed that this treatment reduced neuroinflammation by acting on lymphocytes and ultimately reduced demyelination.[47] Recent clinical studies in MS patients have reported promising therapeutic effects of PBM. The data from these studies

Table 1. Some Studies About the Effect of PBM on MS

Author	Year	Title	Length of Radiation
Muili et al[49]	2012	Amelioration of experimental autoimmune encephalomyelitis in C57BL/6 mice by photobiomodulation induced by 670 nm light	(GaAlA) LED arrays (75 cm^2) of 670 nm
Goncalves et al[47]	2016	Low-level laser therapy ameliorates disease progression in a mouse model of multiple sclerosis	AlGaInP, 660 nm, GaAs, 904 nm
Kubsik et al[48]	2016	Application of laser radiation and magnetostimulation in the treatment of patients with multiple sclerosis	Wavelengths 650 nm and of power 50 mW
Duarte et al[9]	2018	Low-level laser therapy modulates demyelination in mice	(GaAlA) 36 J/cm^2, 50 mW, 0.028 cm^2
Silva et al[19]	2020	Effects of photobiomodulation on interleukin-10 and nitrites in individuals with relapsing-remitting multiple sclerosis–Randomized clinical trial	wavelength: 808 nm; power output: 100 mW

clearly demonstrated that PBM was able to significantly increase IL-10 levels, improve motor recovery and functional status of patients, enhance the quality of life, and significantly reduce pain in these patients.[19,48] Researchers have determined that the main pathological causes of MS are a combination of inflammatory factors and mitochondrial dysfunction. The results of this studies showed that PBM was able to significantly reduce levels of pro-inflammatory factors (IFN-γ, TNF-α) but increased levels of anti-inflammatory factors (IL-10, IL-4). Researchers suggested that PBM might slow disease progression by regulating inflammatory processes.[49] In another study, researchers used cuprizone (a classic model of demyelination) to induce the animal model of MS. The results of this study indicated that PBM could improve motor performance, decrease demyelination, raise the number of oligodendrocyte precursor cells, and regulate astrocyte and microglia activation[9] (Table 1).

Discussion

Various studies have proved the positive therapeutic effect of PBM therapy on different diseases. Since laser treatment is a non-invasive procedure, researchers suggest it is a promising treatment for neurological disorders such as SCI, AD, HD, and MS.[50-52] Hence, extensive research has been conducted in this field. However, the exact mechanism of PBM is still poorly understood and needs further investigation. The results of the studies suggest that PBM can affect various cellular functions such as cell survival, apoptosis, ATP production, autophagy, production of growth factors, and inflammatory processes.[21,41,52,53] Previous studies have widely demonstrated the neuroprotective potential of laser radiations. Based on the results of these studies, researchers have suggested the use of PBM in neurodegenerative diseases can reduce symptoms and neurological defects through the inhibition of cell programming death, suppression of autophagy, improvement of mitochondrial function, increase of ATP production, regulation of inflammatory cell activity, and control of the inflammatory process.[21,38,51] In addition, it has been found that the use of PBM along with other common treatments has increased the effectiveness of these treatments.[29,54] Some recent studies showed that PBM causes an increase in neuronal growth factors as well as an improvement in remyelination in some animal models of neurodegenerative diseases.[10,55]

Conclusion

According to the results of previous studies, since many of them show positive effects of PBM on neurodegenerative diseases, particularly MS, nowadays the bulk of studies suggest that PBM can be a novel and promising treatment, in a safe and non-invasive manner, for MS patients.

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Conflict of Interests

The authors declare that they have no conflict of interest

Ethical Considerations

All protocols were confirmed by the Ethics Committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.RETECH.REC.1400.009).

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