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The Role of Low-Level Laser Therapy in the Treatment of Multiple Sclerosis: A Review Study

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Abstract

Introduction: Multiple sclerosis (MS) is an autoimmune disease. Inflammatory cells, cytokines and chemokines play a major role in the pathogenesis of the disease. Low-level laser therapy (LLLT) as a photobiostimulation approach could affect a wide range of cellular responses. LLLT inhibits the inflammatory signaling pathway, improves cell viability, inhibits apoptosis, modulates immune responses and induces the production of growth factors.

Methods: In this review, we discuss the effect of LLLT on cellular responses and its application in the treatment of MS. Such keywords as "low-level laser therapy", "photobiomodulation" and "multiple sclerosis" were used to find studies related to laser therapy in MS in Google scholar, PubMed and Medline databases.

Results: LLLT reduced the inflammatory immune cells and mediators. It also enhanced the regeneration of neurons.

Conclusion: Investigations showed that besides current treatment strategies, LLLT could be a promising therapeutic approach for the treatment of MS.

Keywords: Low-level laser therapy (LLLT), Multiple sclerosis (MS), Photobiomodulation, Laser therapy, Autoimmune disease

Introduction

Multiple sclerosis (MS) is a central nervous system (CNS) autoimmune disease, characterized by chronic inflammation, demyelination of the white matter and finally axon loss. Although the exact etiology of the MS disease is not fully understood, genetic predisposition and environmental conditions are some of the contributed etiological factors. Dysregulation of the immune system plays a major role in the pathology of the MS disease.[1,2] Chronic inflammation which occurs in MS disease activates innate and adaptive immune responses.[2] The prolonged production of the inflammatory cytokines and chemokines could activate autoreactive immune responses against CNS antigens and cause the loss of self-tolerance. Immune cells such as macrophages, dendritic cells (DCs) and T helper (TH) cell subsets (TH1, TH17, TH22) cause excessive inflammation and CNS tissue injury.[3-5] Current treatment strategies, including anti-inflammatory and immunosuppressive treatments, have limited benefits, especially in the progressive stage of the disease.[1] It seems that new treatment options are needed in order to control the inflammation and prevent the demyelination of the CNS.[6,7] Laser immunotherapy as a photo-thermal approach is focused on the photo-immunomodulation properties of the lasers which could regulate the immune responses in various autoimmune disorders and cancers.[8] In this review, we focused on the effects of low-level laser therapy (LLLT) on the cellular responses and also immunomodulatory effects of LLLT on immune responses in the MS disease as a binary treatment approach.

Inflammatory Responses in the Pathogenesis of MS

Inflammatory responses play a crucial role in the pathogenesis of MS. Autoreactive $CD4^+$ T cell subsets, including TH1, TH17, and TH22, against myelin antigens, have a pivotal role in autoimmune responses.[9] These cells produce a large number of inflammatory cytokines such as interleukin 1 beta (IL-1β), interferon gamma (IFN-γ), interleukin-17 (IL-17A), IL-17F, interleukin 23 (IL-23) and interleukin 22 (IL-22).[10-12] Recently, it has been shown that besides T CD4 cells, T CD8 cells and B cells

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and macrophages play a major role in the pathogenesis of MS.[13] Moreover, the function of the regulatory T cell subsets (CD4+CD25+ Treg) which produce anti-inflammatory cytokines like interleukin 10 (IL-10) and transforming growth factor beta (TGF-β) is impaired. It has also been indicated that T reg cells migration, survival and cytokine production decreased during the MS inflammatory responses.[14,15]

Low-Level Laser Effects on Cell Biology

LLLT consists of non-thermal red or near infrared light (600–1000 nm) which might affect many cellular processes, including mitochondrial activity, cell proliferation, differentiation, cell death, production of adenosine triphosphate (ATP), synthesis of DNA, and so on.[16,17] Due to the beneficial effects of LLLT, it is widely used as a treatment approach in a variety of diseases.[18-21] One of the important effects of laser radiation is the inhibition of apoptosis and regulating cell viability.[22] It was shown that low-power laser radiation caused the sharp expression of the B-cell lymphoma 2 (Bcl-2) anti-apoptotic gene.[23] Moreover, it could markedly inhibit the BCL2-Associated X Protein (BAX) proapoptotic gene. Laser radiation also induced cell cycle progression and proliferation.[24,25]

Low-power laser radiation suppressed the inflammatory responses and at the same time stimulated anti-oxidant activity.[26,27] It was revealed that laser radiation inhibited nuclear factor kappa B (NF-κB), the key inflammatory transcription factor, and the related signaling pathways like inflammatory cytokines.[28,29] LLLT also reduced oxidative stress by inhibiting the production of reactive oxygen species (ROS) and inducible form of nitric oxide synthase (iNOS) expression in oxidatively-stressed cells.[24,29-31]

Moreover, low-level laser radiation enhanced the production and release of various small molecules and growth factors, including TGF-β, brain-derived neurotrophic factor (BDNF), platelet-derived growth factor, and glial-derived neurotrophic factor.[32-34]

In regenerative medicine, besides the secretion of the growth factors, inhibiting the inflammatory microenvironment is crucial. As mentioned above, LLLT could attenuate the inflammatory conditions and has the ability to increase the production of various growth factors. Such properties make this physical, non-invasive strategy a promising tool in regenerative medicine.[16]

Effect of the Laser on the Central Nervous System

LLLT is widely used in neurological conditions, including degenerative brain disease, stroke, traumatic brain injury, and spinal cord injury.[35-38] LLLT could stimulate neuron regeneration and induce the proliferation of Schwann cells.[39] LLLT also increased the BDNF which is a crucial growth factor for neuronal survival and growth. It was shown that LLL had beneficial effects on Alzheimer's disease through the inhibition of Aβ-induced neurotoxicity and neurons loss.[40,41] Moreover, it was reported that laser therapy boosted nerve conduction.

Investigations indicated that the post-stroke LLLT approach improved brain injury and neurons function.[42,43] LLLT significantly influenced brain lesions and induced the generation of new neurons in stroke-induced rats. LLLT inhibited neuron apoptosis and enhanced neurons viability. LLLT also increased BDNF in brain injuries.[43-45] This treatment approach was also approved in the rabbit embolic stroke model.[42] It seems that LLLT has beneficial effects on ischemic tissues.

Low-power laser irradiation induced peripheral nerve injuries.[46] It was also reported that laser irradiation augmented sciatic nerve injury and inhibited spinal cord neurons degeneration.[47,48] Moreover, it was shown that combination therapy using LLLT (660 nm) and chondroitinase ABC enzyme had more beneficial effects on the functional recovery of the spinal cord injury than each treatment alone.[49] A recent in vitro study also indicated a novel mechanism by which LLLT could decrease excitotoxicity which contributed to neurodegenerative disorders and brain trauma.[50-52] It was revealed that LLLT photons were absorbed into the cytochrome c, increased ATP production, and decreased NO and oxidative stress in the lesions.[30] Thus, LLLT preserved and altered excitotoxicity in cultured cortical neurons.[53]

Low-Level Laser Therapy in the Treatment of MS

It was indicated that laser therapy is a promising approach for numerous diseases.[54,55] Previous studies indicated that LLLT had beneficial effects in controlling inflammation and induced tissue repair. It was indicated that LLLT possessed modulating properties and could reduce brain inflammation.[56] Laser photobiomodulation protected the cells and tissues from inflammatory mediators.[57] Elaine et al indicated that the LLLT strategy (AlGaInP LLLT (660 nm) and GaAs LLLT (904 nm)) could reduce the severity of the disease in the C57BL/6 experimental autoimmune encephalomyelitis (EAE) model. LLLT could significantly ($P<0.001$) postpone the onset of the disease manifestations. LLLT caused the inhibition of the weight loss and mortality of the animals and reversed the weight loss process.[58] NO contributed to most of the neurodegenerative disorders like MS.[59] NO is highly expressed in MS lesions and is an indicator of macrophages and microglia activation and disease progression.[60] Elaine et al showed that LLLT reduced the amount of NO in the brain, spinal cord and spleen compared to the EAE control group. Another aspect of the LLLT strategy is the inhibition of immune cell trafficking. LLLT could markedly slow down the infiltration of the lymphocytes into the CNS and also limit the injured

demyelinated parts. Using LLLT also had a great impact on inflammatory cytokines including IL-17, IL-1β and IFN-γ. In this manner, LLLT reduced the expression of mentioned cytokines [58] (Figure 1).

Recently, due to the promising results of laser therapy in various diseases, the application of laser biostimulation has been investigated in 120 MS patients. The study showed that laser therapy could significantly improve the Expanded Disability Status Scale (EDSS) index of the patients and highly refine the patients' physical condition. In addition, laser radiation improved MS patients' quality of life. It was also reported that the combination of laser therapy and low-frequency magnetic stimulation could augment the beneficial effects.[61]

Interestingly, another randomized clinical trial on 14 MS patients showed that photobiomodulation (wavelength: 808 nm; power output: 100 mW) successfully induced the expression of the serum IL-10 anti-inflammatory cytokine in the MS patient with no statistical difference in nitrites levels.[62] It was also reported that LLLT had a great impact on optic nerve improvement in MS individuals.[63]

Mesenchymal stem cells (MSCs) are multipotent stem cells and have great immunomodulatory properties and differentiation abilities.[4,64-66] These cells have been used as a therapeutic modality in a wide range of diseases, including MS.[67] MSCs therapy reduced the inflammation and stimulated re-myelination of the neurons.[68,69] A recent study indicated that pre-treated cells with LLLT before injection had better viability and proliferation rate. Treated cells also induced myelin formation.[70] Combination therapy using human adipose-derived stem cells and laser irradiation on spinal cord injury showed that such a treatment approach enhanced the improvement of motor function.[44] It was also shown that LLLT induced epidermal growth factor (EGF) secretion from MSCs, which leads to better *in vitro* maintenance of MSCs[71] (Table 1)

Altogether, it seems that laser therapy could add to the rehabilitation and physiotherapy regime of MS patients.

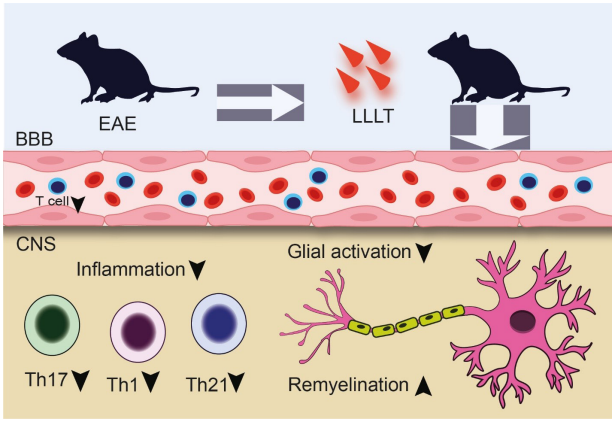

Figure 1. LLLT anti-inflammatory effects on the EAE animal model. LLLT reduced the inflammatory cells and mediators and inhibited inflammation and neuronal loss. Moreover, LLLT caused remyelination in neurons. Low-level laser therapy (LLLT), blood brain barrier (BBB), experimental autoimmune encephalomyelitis (EAE), T helper (TH).

Discussion

Developments in LLLT devices make them a promising therapeutic approach for the treatment of various diseases. Several studies have indicated that LLLT had immunomodulatory effects on biological processes. LLLT reduced inflammation, decreased immune cell trafficking and downregulated inflammatory cytokine secretion. *In vitro* and *in vivo* studies also showed that the LLLT could modulate the regeneration of neurons and had beneficial effects on the improvement of MS manifestations. It also delayed the onset of the disease in animal models. Clinical studies revealed that LLLT inhibited inflammatory responses in MS patients and improved patients' physical conditions. It seems that LLLT through these mechanisms could be an additional treatment option for the treatment of MS and other neurodegenerative disorders.

Conclusion

LLLT leads to a reduction in inflammatory immune cells, including TH1 and TH17, inhibits inflammation, and augments brain tissue regeneration. Although studies indicated that LLLT modulated the inflammatory cascades and immune cells, the mechanisms of action of such a treatment strategy are unclear. Future investigations need to clarify the exact mechanism of LLLT on immunomodulation.

Table 1. Animal model and clinical trial studies of LLLT on MS

Year	Study	Intervention	Result
2016	Experimental autoimmune encephalomyelitis (EAE),	LLLT (AlGaInP, 660 nm and GaAs, 904 nm)	Reduced the clinical score, delayed disease onset, down-regulated NO
2016	120 MS patients	Wavelengths 650 nm and of power 50 mW generated by the device TERAPUS	Improved the functional status of patients
2019	Canine model of MS	MSC treated with LLLT	Increased remyelination, prevented the scar formation
2018	C57BL/6 mice	LLLT (36 J/cm^2, 50 mW, 0.028 cm^2 spot area)	Improved motor performance, attenuated demyelination
2019	19 MS patients	LLLT	Induced pain relief
2020	14 MS patients	Wavelength of 808nm, output power of 100 mW	Increased the level of IL-10, unchanged nitrite levels

Conflict of Interests

The authors declare no conflict of interest.

Ethical Considerations

Not applicable.

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