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A Review of Low-Level Laser Therapy for Spinal Cord Injury: Challenges And Safety

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Abstract

Introduction: Damage to the spinal cord is a central nervous system disorder that results in direct damage to neural cells (axons, cell bodies) and glia, followed by autonomic, motor and sensory impairments. Inflammatory response after this injury can contribute to secondary tissue damage that leads to further behavioral and functional disorders. Inflammation is a complex process, which occurs after an injury. If this progressive process is not well controlled can lead to additional damage to the spinal cord which is preventing neural improvement and regeneration and, which ultimately will not provide good clinical consequences. Inflammation in the injured spinal cord is a physiological response that causes the death of glial and neuronal cells. The reduction of the initial inflammatory process after damage to the spinal cord is one of the important therapeutic strategies. It has been proposed that low-level laser (LLL) therapy, as a noninvasive manner, can modulate inflammatory processes, which leads to a significant improvement in neurological symptoms after spinal cord injury (SCI).

Methods: A comprehensive review was performed on SCI, the etiologies, and treatment methods using the keywords spinal cord injury, low-level laser, and inflammation in valid medical databases such as Google Scholar, PubMed, and Elsevier (76 articles). Among the collected papers, articles that were most relevant to the purposes of the study were selected and studied.

Results: LLL therapy was able to reduce inflammation and also attenuate neuronal damage after spinal cord damage.

Conclusion: The present study illustrates that LLL therapy has positive effects on improving functional recovery and regulating the inflammatory function in the SCI.

Keywords: Spinal cord injury (SCI); Inflammation; Low-level laser therapy.

Introduction

Spinal cord injury (SCI) is the main disorder in the central nervous system that specified by sensory, motor, and autonomic function impairments. SCI is followed by interruption of neuronal signaling along the spinal pathways. Restrictions on SCI have negative economic, social, and individual effects on patients with SCI.[1-5] The incidence of SCI which is more common in men than in women has approximate ranges from 3.6 to 195 cases per million each year.[6,7]

In previous studies, according to the mechanism of injury, spinal cord injuries have been classified into two traumatic and non-traumatic types.[8,9] The traumatic type of SCI is caused by such events as falling, vehicle accidents, sport, and violence. These events may cause a fracture in the spinal column, which is an important factor in exerting physical pressure on the spinal cord tissue, leading to loss of neurological function below the level of injury.[8,10] In the non-traumatic type of SCI, factors like the infection, degenerative disk disease, and the tumor can cause SCI. As a result, SCI can cause extensive cellular damage, necrosis, and apoptosis, in neuronal and glial cells.[11,12] In addition to the division mentioned above, according to the pathophysiology of injury, researchers have divided the spinal cord injuries into primary and secondary injuries.[13-16] Primary injury begins immediately after injury which often results from mechanical impactions on the spinal cord, such as contusion, compression, stretching, penetration, and laceration.[1,16] This phase is well characterized by acute

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hemorrhage and ischemia in the spinal cord tissue. The secondary injury which is characterized by neuronal and glial cell death starts after primary injury and can last up to weeks.[17-19] In addition, the injury site can be extended to non-injured tissue. In the center of the injury site, fluid-filled cysts and glial scars are often formed. However, the precise mechanism of secondary injury is incompletely understood.[20] Previous studies suggested that secondary damage can be divided into three phases: the acute phase, the subacute phase, and the chronic phase, each with different various pathophysiological processes.[16,21,22] Secondary injury is a complex and progressive process that includes inflammation, the death of neurons and glial cells, ischemia, excitotoxicity and electrolyte imbalances, free radical's production, lipid peroxidation, and demyelination of surrounding neurons.[11,20,23-26] The secondary phase makes the principal cause for the morbidity occurring in patients with damage to the spinal cord.[19]

Inflammation in Spinal Cord Injury

Stress and inflammation are major causes of damage to the central nervous system.[27] The results of earlier studies have shown that the damage does not affect the whole structure of the spinal cord. In the animal model, Contusion and compression types of SCI are common in research.[3,15] The primary injury in contusion and compression models can cause tension and rupture in the spinal cord vessels.[1] Traumatic SCI initiates an inflammatory response that is one of the main causes of symptoms of SCI.[19] Immediately after an injury to the blood-brain barrier, the inflammatory response is initiated by resident immune cells (astrocytes and microglia), peripheral immune cells (neutrophils, macrophages, and monocytes) and also the release of their chemical mediators.[3,27,28] 8–24 hours after the lesion, peripheral immune cells can be observed inside the spinal cord tissue. Activated microglia can be observed on the first day after the injury, reaching their highest levels from day 3 to day 7. Neutrophils are the first leukocytes present in the lesion site from the first 3 to 12 hours after the lesion.[29,30] Subsequently, 3-4 days after SCI, monocytes and macrophages infiltrate into the lesion site.[3] It is well documented that, in an inflammatory response, the immune cells are one of the most important causes of neural cell degeneration.[15,19] This reaction starts within hours after damage to spinal cord tissue and achieves peak values within a few days and it may continue for several years.[15]

The expression of TNF-α and IL-1β was observed by astrocytes and microglia 5–15 min. after injury.[12,27] The peak of TNF-α and IL-1β expression are at 1 hour and 12 hours after injury, respectively.[12] An in vitro study has shown that TNF-α and IL-1β can cause oligodendrocyte death and also inhibit glutamate transporters in astrocytes.[31] In the secondary phase, TNF-α release from astrocytes can stimulate the additional release of this cytokine. It can also cause the accumulation of calcium in the neuronal cells.[12,32] The principal effects of TNF-α on the SCI have not been clearly established. However, the researchers have suggested that in the primary phase of CNS damage, it can cause edema and immune cell migration, neuronal cell death, and also some neuroprotective effects.[20]

The inflammatory reactions expand within hours after damage to the spinal cord, achieving peak values within a few days. Likewise, the infiltration of peripheral immune cells is followed by macrophages and monocytes.[8,15,33] TNF-α levels in the spinal cord elevate one hour after trauma. However, it is thought that it may lead to edema and immune cell migration, cell death, and some neuroprotective effects in the primary phase of SCI.[20]

Different approaches have been proposed to treat SCI in animal studies, such as the reduction of inflammation, the infusion of neurotrophic factors, the reduction of endogenous growth suppressors, and the transplantation of growth-promoting cells.[34,35] In both developed and developing countries, the reduction of neurological impairments after SCI is the main problem facing the healthcare sector.[6] Nowadays despite the use of various therapies such as drug therapy, gene therapy, hypothermia, tissue engineering, and transplantation of stem cells in patients with damage to the spinal cord, none of the above methods has completely eliminated the complications of this injury.[11,36-41] It is well documented that reducing and controlling inflammation in SCI can reduce the complications in SCI models.[33, 42]

Low-Level Laser in SCI

The results of some preliminary studies have clearly shown that the application of low-level laser (LLL) may have useful effects on central nervous system damage.[43,44] Recently, the use of laser therapy, as a noninvasive procedure, has been considered one of the new therapeutic strategies for the treatment of wounds and burns, pain, osteoporosis, and periodontal diseases.[36,43,45-50] Previous studies have suggested that lasers can affect the level of inflammatory factors such as TNF-α and IL-1β.[51,52] They are also useful for neurological and neurodegenerative disorders such as traumatic brain injury, stroke, and damage to the spinal cord.[44,53-56] In previous studies, lasers were divided into high and low power. High-power lasers have immediate effects and are most commonly used in surgical operations. Unlike high-power lasers, low-power lasers had no rapid tissue effects.[57] Moreover, the results from animal CNS injury studies have indicated that LLL may have helpful effects on the treatment of inflammatory conditions after CNS injury.[58-60] Experimental investigations in animals indicate that the use of LLL can decrease the post-traumatic inflammatory reactions and prevent the effects of reactive oxygen species (ROS) release and NF-κB activation.[42,61,62] It is well documented that LLL can attenuate inflammation response and TNF-α

level in Broncho alveolar lavage fluid animal models.[51]

The use of LLL can have an effect on cell performance by affecting the enzymes, organelles, and cell membranes. It is well documented that LLL can change physiological reactions by activating transcription factors, enhancing mitochondrial respiration, decreasing main inflammatory factors, increasing angiogenesis and neurogenesis to increase wound healing, repairing tissues, and decreasing inflammation.[63,64] Evidence has also suggested that photobiomodulation is useful in reducing neuropathic pain and programmed cell death.[65] Furthermore, some investigations have demonstrated that transcranial infrared laser therapy used in 6 and 24 hours after an ischemic stroke in animal models leads to significant recovery of neurological defects.[56,66,67] Animal studies have shown that laser therapy prevents the aggregation of macrophages at the site of neuronal tissue injury and modulates the inflammation process, which promotes improvement in neuronal tissue repair and decreases injury complications by reducing the secretion of PEG2 and LTB4.[68,69]

A study by Gonçalves et al demonstrates that LLL therapy after SCI can decrease the inflammation reactions in the spinal cord by regulating the migration of immune cells in the spinal cord and it can prevent the destruction of axonal myelin. Also, it can cause a decrease in the size of the central cavity and enhance motor function.[70] Oron et al proposed the transcranial application of LLL after traumatic brain injury could provide a striking functional neurological benefit and reduces brain tissue damage.[71] It is well documented that LLL can promote axonal regeneration and functional recovery in rat SCI.[72,73] Previous studies[36,42,43,63-69] (Table 1) have clearly documented that the application of photobiomodulation can have beneficial effects on the treatment of ischemic-reperfusion model through decreasing inflammatory factors, inhibiting programmed cell death, stimulating angiogenesis, and enhancing neurogenesis.[74] In addition, it has been shown that laser therapy can significantly decrease CD68 positive cells in the site of neuronal injury, and the beneficial results of this therapeutic manner in the regulation of immune cell proliferation have been demonstrated, which may have impressed the reduction in neural cell death, having significant effects on the recovery of function behavior.[75]

The results of Rochkind and colleagues' study have shown that the treatment of a transected SCI animal model by a composite implant and laser irradiation (780 nm) can improve axonal re-growth and spinal cord healing.[76] On the other hand, experimental studies by Wu et al determined that photobiomodulation (810 nm) had striking effects on improving axonal restoration and functional recovery in both dorsal hemisection and contusion models of SCI.[73]

It is also proposed that LLL can regulate the inflammatory reactions, modulate the secondary damage, and reduce programmed cell death and edema in the primary phase of recovery.

Conclusion

According to the results of previous studies, LLL can promote functional recovery in a contusion model of the SCI, which can emphasize LLL application in CNS injury as a favorable non-invasive therapy for clinical usage.

Table 1. Some Studies About the Effect of LLL in SCI

Author	Year	Title	SCI Model	Length of Radiation
Svobodova et al[63]	2019	The effect of 808 nm and 905 nm wavelength light on recovery after SCI	Compression	808 and 905 nm
Kim et al[64]	2017	Low-level laser irradiation improves motor recovery after contusive SCI in rats	Contusion	850 nm
Janzadeh et al[36]	2017	Combine effect of Chondroitinase ABC and low level laser (660 nm) on SCI model in adult male rats	Compression	660 nm
Veronez et al[65]	2017	Effects of different fluences of low-level laser therapy in an experimental model of SCI in rats	Contusion	808 nm
Song et al[42]	2017	Low-level laser facilitates alternatively activated macrophage/microglia polarization and promotes functional recovery after crush SCI in rats	Compression	810 nm
Hu et al[66]	2016	Red LED photobiomodulation reduces pain hypersensitivity and improves sensorimotor function following mild T10 hemicontusion SCI	Hemicontusion	670 nm
Paula et al[67]	2014	Low-intensity laser therapy effect on the recovery of traumatic SCI	Contusion	780 nm
Ando et al[43]	2013	Low-level laser therapy for SCI in rats: effects of polarization	Contusion	808 nm
Wu et al[68]	2009	810 nm Wavelength light: An effective therapy for transected or contused rat spinal cord	Contusion and Hemisection	810 nm
Byrnes et al[69]	2005	Light promotes regeneration and functional recovery and alters the immune response after SCI	Hemisection	810 nm

Ethical Considerations

Not applicable.

Conflict of Interests

The authors declare no conflict of interest.

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