Effectiveness of Low Level Laser Therapy and Low Intensity Pulsed Ultrasound on Neurotrophic Factors in Experimentally Induced Peripheral Nerve Injury Wistar Rat: A Systematic Review

SathyaSiva¹, Ramana. K², Prathap Suganthirababu³, Lavanya Prathap⁴, Mydhili Govindarasu⁵, Kumaresan. A⁶, Vignesh Srinivasan⁷

¹Post Graduate, ²Assistent Professor, ³Professor, Saveetha College of Physiotherapy, SIMATS, Chennai, Tamil Nadu, India, ⁴Saveetha Medical College and Hopsital, Chennai, Tamil Nadu, ⁵Assistant Professor, Saveetha Dental College and Hospital, Chennai, Tamil Nadu, India.

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Abstract

Background: Peripheral nerve injury is developed from the various etiological factors such as crushing, traction, long bone fracture, cutting injury, entrapment neuropathies, infection, inflammation and various degree of tumours. LIPUS and LLLT has a variety of biological impacts on tissues, including increasing bone fracture repair, accelerating soft-tissue regeneration, and suppressing inflammatory reactions.

Purpose: The main purpose of this research is to determine the efficacy of LLLT and LIPUS in relation to neurotrophic factors in experimentally induced peripheral nerve damage.

Materials and Methods: A systematic review was done to investigate the effectiveness of LLLT and LIPUS in experimental induced rat model. Articles are systematically searched in search engines PubMed, MEDLINE and Google Scholar database according to inclusion and exclusion criteria.

Results: Out of the four review articles that are eligible, three support low intensity pulse ultrasound therapy’s potential to promote nerve regeneration, while one article supports low level laser therapy’s enhance nerve regeneration.

Conclusion: The study conclude that LIPU has huge supporting evidence on nerve regeneration influencing the neurotrophic factors and LLLT has least supporting evidence on influencing the neurotropic factors on experimental induced rat model. Advance research need to carried out in vivo animal model to evaluate the effectiveness of both the LLLT and LIPU in experimentally induced rat model at proven dosages.

Key Word: Neurotrophic factors, laser therapy, ultrasound, sciatic nerve, regeneration

Introduction

Peripheral nerve damage results from a variety of etiological reasons, including crushing, traction, long bone fracture, cutting injury, entrapment neuropathies, infection, inflammation and various degree of tumours¹. In accordance with the severity...
of the nerve injuries. Seddon divided Peripheral nerve damage into three categories: Neurapraxia, Axonotmesis, and Neurotmesis. The mildest form of traumatic peripheral nerve injury is neuropraxia. It is distinguished by focal segmental demyelination at the damage site with no loss of axon continuity or surrounding connective tissues. Either neurotmesis, in which the entire nerve fibre is ruptured, or axonotmesis, in which the axons and myelin sheaths are damaged, but the connective tissue is maintained. When a peripheral nerve is injured, it causes various levels of impairment as well as secondary muscle atrophy. peripheral nerve system axons can regenerate and remyelinate following traumatic damage, after a process known as Wallerian degeneration. The sciatic nerve, the body’s largest nerve, is made up of two parts: tibial and common peroneal components, both originated from the lumbar sacral plexus.

Endogenous chemicals that regulate cell proliferation and differentiation, migration, survival in the nervous system are known as neurotrophic factors. The neurotrophins NGF, BDNF and NT-3 have a beneficial effect on the survival and phenotypic expression of primary sensory neurons in the dorsal root ganglia and motoneurons in the spinal cord during peripheral nerve regeneration. Other neurotrophic factors, including as CNTF, GDNF, and LIF, act on neuronal cells in a variety of ways that appear to overlap and enhance the effects of neurotrophins. GGF also has a role in nerve regeneration in an indirect manner. The close interaction between neuronal and glial cells during peripheral nerve regeneration is highlighted by the creation of GGF by neurons, which promotes Schwann cell proliferation. BDNFs have been shown to regulate myelogenesis, while GDNF influences sensory nerve regeneration. NGF has demonstrated the effectiveness of neuroprotection and axon development. Motor neuroprotection has been found to be effective by the CNTF. Schwann cell proliferation and myelogenesis are influenced by bFGF. IGF-2 protects motor neurons. NF3 has a negative influence on myelogenesis and NF4 has a sensory neuroprotective effect.

In LLLT, a biological reaction is induced by low-power laser light with a wavelength range of 632 to 1064 nm and a power range of 1-1000 mW. Biostimulation or photobiomodulation is the term used to describe the process by which LLLT causes a photochemical reaction in the cell. Gallium arsenide is used as a semiconductor or diode to create an invisible infrared laser with a wavelength of 904 nm. The ability to provide either a continuous or pulsed output is a benefit of a semiconductor laser diode. Rochkind et al. conducted an double-blind randomized study. According to morphological data, the laser-treated group had more myelinated axons overall after the reconnection of the nerve deficit with a PGA neurotube during postoperative 780 nm laser phototherapy.

LLLT was found to be an effective treatment for radial nerve palsy in a research. Rats with crush injuries to the sciatic nerve were treated with low-power pulsed lasers (wavelength of 904 nm, dose of 4 J/cm2, Gallium Arsenide) and the results showed that the lasers successfully facilitated nerve regeneration.

LIPUS (low-intensity pulsed ultrasound) is a type of ultrasound that uses substantially less energy (<3 W/cm2) than standard ultrasound. LIPUS has a variety of biological impacts on tissues, including increasing bone fracture repair, accelerating soft-tissue regeneration, and suppressing inflammatory reactions. LIPUS of 250 mW/cm2 greatly accelerated axonal regeneration, according to functional and pathological data. This indicated that nerve regeneration in autografts had improved.

**Methods**

**Search Strategy**

The effectiveness of LLLT and LIPUS in peripheral nerve injury induced rat model was investigated by the researcher’s independent search of the published studies from 1995 to 2022 in December 2022. Screening for articles are conducted systematically in the MEDLINE, Google Scholar, and PubMed databases. Open access articles are screened in the database. “Neurotrophic factor, Nerve regeneration, Rat model, Low level laser therapy, Low intensity pulsed ultrasound” represent a number of related search terms. Language limitations are observed. Only English-language articles are chosen.
Inclusion Criteria:

- Open access and full text articles
- Neurotrophic Factors outcome includes “brain-derived neurotrophic factor, NT-3, NT-4, vascular endothelial growth factor, wet weight ratio of the gastrocnemius muscles”
- Sciatic Nerve Crush injury.
- The article published in the year between 1995-2022

Exclusion Criteria:

- Systematic reviews and meta-analysis articles are excluded.
- Articles which were not published in English language are excluded.

Data Extraction:

The species and strain, sample size, nerve injury, crush injury procedure, intervention, intervention parameters, and outcome measurements are among the data that are separately extracted by researchers from each publication (Table 1).

Table 1: DATA EXTRACTION

<table>
<thead>
<tr>
<th>Author</th>
<th>species and strain</th>
<th>sample size (n)</th>
<th>nerve injury procedure</th>
<th>interventions</th>
<th>interventions parameters</th>
<th>outcome measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wenli Jiang et al.</td>
<td>Sprague-Dawley rat</td>
<td>n = 80</td>
<td>Sciatic nerve</td>
<td>low intensity</td>
<td>ultrasound</td>
<td>Catwalk automated gait analysis system, a function analysis of the sciatic nerve is performed.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CG = 20</td>
<td>The reverse autograft was 10 millimetres long.</td>
<td>pulsed ultrasound</td>
<td></td>
<td>CMAP electrophysiological assessment measurement of axon development using the nfn200 protein and toluidine blue staining</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LIPUS-LOW DOSE</td>
<td>20</td>
<td></td>
<td></td>
<td>gastrocnemius wet weight muscles</td>
</tr>
<tr>
<td></td>
<td></td>
<td>=20</td>
<td></td>
<td></td>
<td></td>
<td>gastrocnemius muscles blood perfusion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LIPUS-MID DOSE</td>
<td>20</td>
<td></td>
<td></td>
<td>Western blotting for identifying the NF-kB p65 protein expression.</td>
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<td></td>
<td></td>
<td>=20</td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td>LIPUS-HIGH DOSE</td>
<td>20</td>
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<td>=20</td>
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<tr>
<td>Lessandra Espé et al.</td>
<td>Wistar rat</td>
<td>n = 36</td>
<td>Sciatic nerve</td>
<td>low level</td>
<td>Laser therapy</td>
<td>mRNA expression of:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>group 1 (n=12)</td>
<td>The right hind paw’s thigh level was cut, and an incision was made 5 mm before the sciatic nerve bifurcation over the course of 30 seconds using the highest pressure setting (three clicks) of a hemostatic forceps.</td>
<td>632.8 nm, the wavelength size of spot: 0.10 cm2.</td>
<td>5.0 mw</td>
<td>BDNF</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IG = 6</td>
<td>anesthetic agent: intraperitoneal injection, with a xylazine (10 mg/kg) and ketamine hydrochloride (100 mg/kg).</td>
<td>beam shape: collimated mode: continuous power:</td>
<td>power density: 0.5 mw/cm²</td>
<td>NGF</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CG = 6</td>
<td></td>
<td></td>
<td>irradiation time 20 sec</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>group 2 (N=12)</td>
<td></td>
<td></td>
<td>number of points irradiated 10</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>IG = 6</td>
<td></td>
<td></td>
<td>energy density: 10 j/cm²</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>CG = 6</td>
<td></td>
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<td>GROUP 3 (N=12)</td>
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<td></td>
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<td>IG = 6</td>
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<td></td>
<td></td>
<td>CG = 6</td>
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</table>
Results

Peripheral Nerve Induced Rat Model With Low Level Laser Therapy:

Only one of the four eligible articles support to claim that low level laser treatment is effective in treating peripheral nerve damage and accelerating nerve regeneration. The article has demonstrated the significant impact on four major neurotrophic factors.

Peripheral Nerve Induced Rat Model Using Low Intensity Pulsed Ultrasound:

Three of the four eligible articles support the evidence that low intensity pulsed ultrasound can heal damaged peripheral nerves and promote nerve regeneration. According to this study’s outcome measure, these articles have a considerable impact on a variety of different outcomes. They demonstrate a favorable effect on neurotrophic factors and the wet weight ratio of the gastrocnemius muscles.

Discussion

The review’s studies, which were conducted in
three different species of Sprague Dawley rats, Wistar rats, and Lewis rats and focused on the sciatic nerve crush because it can be quickly and easily exposed, found that LIPUS AND LLLT had positive effects on axonal growth, wet weight ratio of gastrocnemius muscle, Sciatic functional index, and neurotrophic factors. Wenli Jiang et al. performed sciatic nerve reversed autologous nerve transplantation on the right side of Sprague-Dawley rats, and then randomly administered 250mW/cm², 500mW/cm², or 750mW/cm² LIPUS for 2-12 weeks following surgery. Axonal regeneration was greatly accelerated by LIPUS of 250mW/cm², according to functional and pathological outcomes. FABRCIO et al. came to the conclusion that therapeutic ultrasound and low-level laser therapy are effective for nerve regeneration. In comparison to the use of ultrasound in the neuromotor recovery following sciatic nerve compression damage, it also shown better recovery after laser therapy intervention. To support the findings of this experimental demarcation, it is recommended that additional research be done with the aim of analyzing the morphological changes in this tissue.

Tianshu Wang et al. conducted research on the modulation of neurotrophic factors and functional recovery of LIPUS in a rat model. The results show that both of these outcomes are positively regulated by brain-derived neurotropic factors. IHSAN F.R. et al. arrived to the conclusion that LLLT speeds up healing, aids in nerve regeneration, and appears to cause a significant amount of structural and cellular change in 2007. Additional clinical trials may produce therapeutic relevance in planned surgery or microsurgery and plausible clinical advancements. Juanita J. et al. came to the conclusion that infrared light with optimized parameters promotes quicker nerve regeneration and increased functional recovery in a surgically repaired peripheral nerve.

HUA ZHANG, M.D. et.al states that LIPUS administration to Schwann cells is effective in promoting cell division and neurotrophin gene expression. The in vitro results presented in our study already indicate that this approach should prove useful for research on peripheral nerve regeneration, even though additional studies are undoubtedly needed to further optimize the delivery of LIPUS and identify the signal-regulated mechanisms accountable for the molecular responses. TIANSHU WANG et al. came to the conclusion that LIPUS upregulates the expression of BDNF’s gene and proteins. How rapidly functional and histologic changes take place in rats after sciatic nerve compression injury may be affected more by the higher expression of BDNF at the region farthest from the lesion. In a study to determine the impact of low intensity pulsed ultrasound on neurotrophic factors, XUE-JUN NI. et al. found that there were significant mRNA expression alterations of brain-derived neurotropic factors. The recovery of Vibrissa movement in the laser + crush group was noticeably higher than that of the crush group, and similar to sham group values, according to a study on the effects of LLLT on facial nerve regeneration following crush damage in rats by Bohan Li. et al. Additionally, when compared to the crush group, laser + crush treated mice had larger regenerated axons and thicker myelin sheaths. The damaged facial nerve caused by crushing was effectively restored by LLLT.

Limitation

This systematic review made no note of the animal’s gender or age. The location of the study’s execution is also unknown.

Conclusion

According to the results of this systematic review, LLLT and LIPU have a substantial impact on accelerating nerve regeneration by enhancing neurotrophic factors and shortening the recovery time. To assess the efficacy of both LLLT and LIPU, advanced research must be conducted in an in vivo animal model.

References


