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REVIEW ON EFFECTS OF LOW LEVEL LASER THERAPY ON NERVE REGENERATION IN DIABETIC PERIPHERAL NEUROPATHY SUBJECTS.

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ABSTRACT:

One of the most major complications of diabetes mellitus is Diabetic peripheral neuropathy where it is related to micro and macro-vascular structures. The estimation of DPN prevalence in India was varied widely from 9.6% to 78% in different populations. Low-level laser therapy (LLLT) has a great contribution of nerve regeneration in diabetic neuropathy. The study is to review the literature regarding LLLT in treating neuropathic pain. The objective of the study was to review literature to find the effect of laser therapy in nerve regeneration and also to investigate the intimate relationship with tissue recovery in peripheral neuropathy. The main aim of this article to review the influence of low level laser therapy on nerve regeneration in diabetic neuropathy. Materials and Methods: The search was done in PubMed/Medline, Google scholar and list of bibliographic references of article from 2004 to 2021 with keywords: low level laser therapy, nerve regeneration, diabetic neuropathy. In database up to 10 article were selected in search engine with the use of keywords which is relevant to the study. As per literature review it states that the laser therapy accelerates nerve regeneration, release of neural factors, release of growth factor, reduce inflammation, pain, increases vascular permeability. But there are controversy in parameter like wavelength, type, energy density, power and frequency of treatment. Conclusion of the literature review there is improvement in nerve regeneration and function with laser therapy in diabetic neuropathy.

KEYWORDS:

LOW LEVEL LASER THERAPY, NERVE REGENERATION, DIABETIC PERIPHERAL NEUROPATHY.

INTRODUCTION

Diabetic peripheral neuropathy (DPN) is frequently the most common microvascular and macrovascular complication of both type I and II diabetes; it is thought to be progressive and irreversible[1]. The peripheral nerve injuiry occurs due lack blood flow through vasa nervorum, leads to loss of axon, axonal atrophy[2]. All nerve fibres may be injured but small myelinated an unmyelinated fibres that conduct pain an temperature are most affected[4]. Not only the nerve die but also it has defect in repairing mechanism of nerve regeneration[1]. In neuropathy The disturbed microcirculation leads to diabetic infections, ulcers, gangrene and also involves bones in long standing[4]. Only 30 % of diabetic population get the pain symptoms with diabetic neuropathy, symptoms are localized to the lower extremities, primarily involves the soles and toes[5].

Recent treatments are symptomatic which aims to reduce the pain through administration of various pharmacological analgesic drugs. These analgesic drugs are effective only upto 40-60% but it doesn't slow the progression of the disease and also it has side effects on central nervous system[6]. Some symptomatic non pharmacological treatment have also proposed, like acupuncture[7], near infrared radiation therapy [8], low-intensity laser therapy [9,10], static and pulsed electromagnetic magnetic field therapies [11,12], and various electrotherapies, including transcutaneous electrical nerve stimulation (TENS) [13], percutaneous electrical nerve stimulation [14] and spinal cord electro-stimulation [15]. There is still doubt in most of the conservative treatment for painful diabetic neuropathy and nerve regeneration.

In physiotherapy among all the electrotherapy modalities the Low Level Laser therapy (LLLT) has biostimulation effect on nervous system[16-17]. In clinical and experimental research studies LLLT is used to improve microcirculation in the irradiated area increases nerve functional activity, the rate of axon growth, myelination and promotes nerve regeneration in peripheral nerve injuries[18–21]. Some other symptoms like pain, inflammation, edema are relieved by release of endorphin, altered interleukin, TNF, fibrinogen and ATP synthesis.

When peripheral nerve is injured, the nerve can lose its function and causing sensitive or motor deficits. There is retrograde axonal degeneration occurs in the area of the lesion, so the nerve regeneration occurs gradually and sometimes incompletely[22–23]. Still present days also LLLT has difficulties in setting the dosage parameter in the recovery of injured peripheral nerves [23–24]. The depth and penetration of the laser irradiance in the tissue depends on the wavelength, where the absorption and dispersion coefficients are greater at the lower wavelengths.

There are still divergence regarding wavelength, whether

continuous or pulsed, when is the best to chose pulse parameters [25]. PBMT presents difficulties due to the lack of standardization in selecting the most suitable parameters for its application, because it has repercussions on the biological effects[26].

MATERIALS & METHODS:

The search was done in Pubmed/Medline, Google scholar and list of bibliographic references of article from 2004 to 2023 with keywords: low level laser therapy, nerve regeneration, diabetic neuropathy. In database up to 10 article were selected in search engine with the use of keywords which is relevant to the study.

LITERATURE REVIEW

Zinman L. H., et.al (2004) conducted randomized, double masked, sham-controlled, parallel-group, single-center study on 50 patients (25 per group) with painful Distal Symmetrical Polyneuropathy. The LILT (Theralase Model TLC 5000; Theralase, Toronto, Canada) device with wavelength of 905 nm and an average power of 0–60 mW. All LILT treatments were 5 minutes per site. Baseline assessment were done like medical history, demographics, physical and neurologic examination were initially performed on all the eligible patients. Pretest measurement were done with Quantitative sensory testing (QST) include a 10-g Semmes- Weinstein monofilament examination, vibration perception thresholds, cooling detection thresholds, and heat-pain threshold, bilateral peroneal motor nerves, sural sensory nerves, and sympathetic skin response (SSR) in the lower limb and nerve conduction studies (NCSs), and HbA1c. All the subjects received sham laser therapy for first 2 weeks and then randomized to receive either active laser or sham laser therapy over the next 4-week period. Treatment was withdrawn over the final 2 weeks. Treatments were administered 2 sessions/ week and were applied to on site of pain area along the sole or dorsum of the foot. The instrument has five prongs covering a 6-cm-diameter area of skin. The laser was applied on 2 painful sites on each foot duration of 5 minutes. Both groups noted a decrease in weekly mean pain scores after 2 weeks of sham laser therapy. After the 4-week intervention (after week 6 of study), pain scores in the sham group remained unchanged, but there was a further reduction in pain scores in the laser-treated group.

Prathap, S. et.al (2011) conducted study on 42 Healthy adult male albino wistar rats. The animals were induced with Alloxan intraperitonealy and blood glucose status was examined with Glucometer. Diabetic neuropathy status was measured with EMG-NCV for MNCV. The rats were than divided into 7 groups and irradiated with laser dosages ranging from 3j/cm2 to 8j/cm2 and one group was kept as control. On analyzing pre and post MNCV values, dosages of 3-4j/ cm2 showed extremely significant p values 5-6j/cm2 showed satisfactorily significant results and 7-8j/cm2 and control groups did not show any significant effect. This MNCV results are important finding of the study that the calculation of correct dosage of laser is very important, like higher dosage can have photo -bioinhibitory effect.

Khamseh M.E., et.al (2011) conducted study on 107 subjects with type 2 diabetes using Michigan Neuropathy Screening Instrument (MNSI). After screening 17 subjects were eligible to included in the study based on inclusion and exclusion criteria. Then pre test measurement is done using the Nerve conduction studies (NCS) to all eligible subjects to confirm the neuropathy. Then subjects were treated with Ga(Al)As laser with the following parameters: a wavelength of 808 nm, maximum power of 1,000 mW, wavelength of 905 nm, maximum power of 25 W, pulsation of 100 ns, energy per pulse of 2.5 μJ, frequency of 1,100 Hz. There were ten consecutive sessions with an energy dose of 10 J/cm2. Then the laser was applied with multidiode applicator with diameter of 1cm2 on 6 paravertebral points(L4-S1) to irradiate bilateral nerve roots and 4 points along the sciatic nerve course in each lower extremity. LLLT given 3 session/week upto 10 session. After completion of treatment post test measure was taken using nerve conduction study. There were significant mean differences showed that an increase in neural amplitudes of NCV parameters on comparison of pre and post measurement values. At the end of the study, the subjects showed a significant increase in neural potential amplitudes ($p< 0.05$). This study clearly demonstrated a significant positive effect of LLLT on improvement of nerve conduction velocity on diabetic distal symmetric polyneuropathy (DSP). So these findings helps to know that LLLT has therapeutic potential in treating in treating diabetic distal symmetrical polyneuropathy.

Bashiri, H., et.al (2013) conducted study on the 60 patients with diabetic peripheral neuropathy and base line assessment were on their sex, age, BMI, type of diabetes, duration of diabetes, and duration of pain was done and randomized to case and control groups based on their established scores on the visual analog scale (VAS) and the Toronto clinical scoring system (TCSS). Case group received laser therapy with wavelength of 780 nm and 2.5 j/cm2 two sessions per week, each session for 5 min, upto one month. At the same time, controls group received sham laser therapy. compared differences between groups VAS and TCSS mean scores before treatment of the 2nd weeks and 4th weeks after the intervention there was statistically significant difference between the two groups ($P<0.05$). On the other hand, when we compared their VAS and TCSS mean scores 4 weeks and 2 weeks after the intervention we did not find any statistically significant difference between the two groups. We achieved the same results when we examined cases' and controls' pre and post VAS and TCSS scores independent from each other; no improvement in the assessment based on their 2 and 4 weeks comparisons tests. Laser therapy resulted in improved neuropathy outcomes in diabetic patients who received it relative to the group that received sham therapy, evaluating before and after LLLT assessments. Further studies are needed to test types of lasers, as well as different dosage and exposure levels required in

different phase of neuropathic care, so as to obtain reproducible results.

Wang C. Z, et.al (2014) conducted a study on 36 male sprague dawley rats were divided into 6 experimental groups were divided into normal group without or with 808-nm LLLT at 8 J/cm2 and a sciatic nerve crushed injury group without or with 808-nm LLLT at 3J, 8J or 15 J/cm2. Rats were given consecutive transcutaneous LLLT at the crush site and then sacrificed 20 days after the crush injury. Functional assessments of the nerve regeneration was analyzed with sciatic functional index (SFI), hind limb range of motion (ROM). Nerve regeneration was analyzed by measuring the myelin sheath thickness of the sciatic nerve with transmission electron microscopy (TEM) and analyzed the expression of growth-associated protein 43 (GAP43) in sciatic nerve by using western blot and immune-fluorescence staining. Author found that sciatic nerve injured rats that were irradiated with LLLT at both 3 and 8 J/cm^2 had significant improvement in SFI but significant improvement of ROM was found in rats with LLLT only at 8 J/cm^2. There is significant enhancement in the myelin sheath thickness and GAP43 expression levels in sciatic nerve-crushed rats receiving 808-nm LLLT at 3 and 8 J/cm^2. Finally the study has concluded these results suggested 808-nm LLLT at a low energy density 3 J/cm^2 and 8 J/cm^2 is capable of enhancing sciatic nerve regeneration following a crush injury.

Akgul T, et. al (2014) conducted study on 30 male wistar rats were divided into three groups after the sciatic nerve was crushed: control group without laser treatment, in early group laser treatment started immediately after surgery and lasted up to 14 days, and in delayed group laser treatment starting on the postoperative day 7 and lasted until day 21. The material used is 650- nm diode laser (model: DH650-24-3(5), Huanic, China) with an output power of 25 mW and irradiated transcutaneously at 3 equidistant points on the site of surgical mark corresponding to the crushed nerve. The duration of the laser application was calculated as 57 s to satisfy approximately 10 J/cm2. A Sciatic Functional Index (SFI) was used to evaluate functional improvement in groups at pre- and post-surgery on the days 7, 14, and 21. After the sacrifice of the wister rats the Compound action potential (CAP) and histological examination was performed for all the groups. Finally the SFI results shown that there was no significant difference between groups at different days ($p>0.05$). but in the delayed group shown significant difference in the latency of CAP decreased. In histological examination confirmed that the number of mononuclear cells was lower ($p<0.05$) in both early and delayed groups. In conclusion, results supported the hypothesis that LLLT could accelerate the rate of recovery of injured peripheral nerves in this animal model. Though both laser groups had positive outcomes, delayed group showed better recovery.

Cg, S. K.,et. al (2015) conduct study on 19 subjects with type2 diabetis mellitus. This study design is pre-post observational design. All the 19 subjects were underwent screening test to confirm diabetic neuropathy biochemical parameter, pain scale and Michigan Neuropathy Screening Instrument (MNSI). Low Level Laser therapy was given through scanning mode with dosage of 3.1J/cm^2 on the plantar and dorsum of the foot and 3.4j/cm^2 with contact method for upto 10days. After completion of LLLT all the subjects were reassessed with the measure showed significant reduction in Pain using VAS scale, MNSI. In addition there is significant reduction in Vibration perception threshold and significant increase in the temperature from baseline to post intervention. Finally this study showed that low level laser therapy was found effective in type 2 DM with peripheral neuropathy.

Yamany A. A., et.al (2016) conducted study on 30 diabetic neuropathy patients with pain and reduced nerve conduction velocity were randomly divided into two groups; an experimental group or active laser group, n=15 and a control group or placebo laser group, n=15. Pre and post test assessment was measured with Peak static and dynamic planter pressure under the heel, big toe and little toe, sural nerve, peroneal nerves conduction velocity, amplitude and pain levels in both groups. The active laser group had received laser therapy through scanning mode with 850 nm He–Ne infrared laser on foot planter surface and lumbosacral area with 5.7 J/cm2 for 15 min/site/session, 3 session /week for four weeks. Finally the author concluded that 850 nm He–Ne therapy with this applied parameter and technique was effective in improving nerve conduction, redistributing foot plantar pressures and relief on pain in painful diabetic polyneuropathy patients.

Suganthirababu, P., et al (2018) did randomized controlled trial was conducted on 40 subjects. The materials required for conducting the study are Tuning Fork, Reflex Hammer, 10gm Semmes Weinstein monofilaments, Goggles and a Ga As LASER unit. The study was conducted in the age group of 40-60 years and were randomly assigned in to control(Group-A) and experimental group(Group-B). Pretest analysis were assessed for degree of neuropathy and pain using Toronto clinical neuropathy score and Numerical Pain Rating Scale (NPRS) respectively. Participants in the respective groups are treated for five weeks with energy intensity of 4 joules for 4 days in a week. This study shows that Low-Level Laser Therapy is more effective in patients with Diabetic sensorimotor Polyneuropathy in reducing Pain and relieving symptoms.

Anju M et. al (2019) conducted a study on 40 patients. Then the Pre-post test analysis was done on 40 patients with Numerical pain rating scale (NPRS), serum samples were collected to estimate Vitamin D and Magnesium levels, Vibration pressure threshold, Michigan neuropathy screening instrument . All patients were given LLLT with 3.1 J/cm2 on the plantar and dorsal surface of the foot for 10 days. After completion of intervention post test analysis were done using NPRS and serum samples to estimate Vitamin D and Magnesium levels. In analysis data the final result has shows that there was a significant increase in Vitamin D and Magnesium levels after LLLT. They

considered that there were improvement in the quality of life after LLLT demonstrated by a decrease in Vibration pressure threshold, Michigan neuropathy screening instrument and reduction in NPRS in DPN patients.

Author/ Year	Type of Laser	Wave length	Energy density (J/cm)	Radiation amount	Frequency of treatment	Main Result
Zinman L. H., et.al (2004)		905 nm		5 minutes / site	2 session/ week	Reduction in VAS score
Prathap, S., et.al (2011)	Unilaser type B	632.8 nm	4 J/cm^2		4 session /week for 4 weeks.	improvement MNCV, nerve regeneration
Khamseh M.E., et.al (2011)	Ga(Al)As laser	905 nm	10 J/cm^2		10 session for 10 days	Reduction in VAS score
Bashiri, H., et.al (2013)	He-Ne laser	850 nm	2.5 J/cm^2	15 min/site	2 session /week for 1 month	Improvement in pain and TCSS
Wang C. Z, et.al (2014)	Ga As Laser	808-nm	3J/cm^2 8J/cm^2 15J/cm^2	30 seconds/ site	20 session/ for 20 days	morphological changes and the increased neuronal growth marker GAP43.
Akgul T, et. al (2014)	Diode Laser	650-nm	10J/ cm^2	57 seconds	10 session consecutive daily	red'n mononuclear cells in damaged nerve, lead dec in edema & regeneration.
Cg, S. K.,et. al (2015)	EC laser Thor laser	632.8 nm 660nm & 850 nm	3.1 J/cm^2 3.4J/cm^2	9 minutes	10 session/ week for 10 weeks.	reducing Pain and regeneration nerve in DPN.
Yamany A. A., et.al (2016)	He–Ne infrared laser	850 nm	5.7 J/cm^2	15 min/site	3 session /week for 4 weeks.	improving NCV relieving pain and redistributing foot plantar pressures.

CONCLUSION

Based on this literature review using low level laser therapy has immense effect in treating diabetic peripheral neuropathy. According to the literature review low level laser therapy has some photobiomodulation effects like change in interleukin level, Tumor Necrotic Factor, endorphin, mRNA, release of neural growth factor, which helps in nerve regeneration in diabetic peripheral neuropathy. But there is contraversies in dosage parameter in treating diabetic neuropathy with various wavelength, type of laser, energy density, power output, frequency, and duration of treatment.

Most of the studies has limitation in particular dosage parameter, quantitative assessment, type of laser, small sample size. Further recommendation is to select particular type of laser, wavelength, parameter of dosage,

duration of treatment and frequency of treatment is decided based on weekly evaluation can be done to find the exact dosage of nerve regeneration in diabetic neuropathy.

Declaration by Authors

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