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Review

Low level laser therapy for the patients with painful diabetic peripheral neuropathy - A systematic review

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ABSTRACT

Background: Low Level Laser Therapy (LLLT) is an emerging treatment modality for management of neuropathic pain. It works by triggering biochemical changes with in cells.**Objective:** This systematic review focused on finding evidence on the effectiveness of LLLT on treatment of painful diabetic neuropathy.**Methods:** We conducted a systematic review (PubMed, Web of Science, CINAHL and Cochrane) to find the evidence on effectiveness of LLLT on treatment of painful diabetic neuropathy. Randomized and non-randomized studies were included in the review.**Results:** A total of 627 studies were screened. After the exclusion criteria (duplicate, animal studies, LLLT for treating other neuralgias) 6 studies were included in the study. The outcome measure that were considered were the difference in pain score and nerve conduction velocity test and quality of life questionnaire.**Conclusion:** The evidence obtained shows LLLT has a positive effect in controlling diabetic neuropathic pain.

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1. Introduction

Diabetic peripheral neuropathy (DPN) is one among the common complication accompanying long term Diabetes Mellitus. It arise due damage of small blood vessels that supply to the nerve (vas nervorum). DPN is the 3rd commonest neurological disorder with a life time prevalence of approximately 50% [1,2]. It primarily affects the hands and feet due to injury to the smaller unmyelinated C fibers that regulate light touch, pain and temperature sensation. Damage progress affecting myelinated A delta fibers responsible for vibratory sensation, proprioception and joint position. Further it leads to Charcot foot and Diabetic foot ulcer [3]. 20–30% of people with DPN suffers from severe neuropathic pain [4,5]. Painful diabetic peripheral neuropathy can be presented with mild pins and needle sensation to stabbing, burning, continuous, or even unpleasant electric shock sensation. It is a leading cause for foot

ulceration and amputation and fall related injury. Symptoms gets worsen during night causing disturbed sleep and tiredness further preventing them from doing routine work. This may result in withdrawal from social events there by affecting the quality of life and considerably increasing the financial burden of treatment [6–8].

Primary step in treatment of DPN includes glycemic control, patient education and life style changes. Small changes in diet and exercise could slow down the progression [9]. Existing therapy for PDPN is aiming for symptomatic relief by administering drugs like antidepressants and anticonvulsants [10]. Most of these drugs are regularly related with systemic aftereffect and do not retard advancement of the neuropathy [11]. Non pharmacological method of treatment includes Acupuncture, Transcutaneous electrical nerve stimulation (TENS) infrared [12,13] and low level laser therapy.

Low Level Laser Therapy (LLLT) also known as soft laser was introduced by Mester and colleagues. It consumes low powered laser of 1–1000 mW, to promote a biological reaction at wavelengths from 632 to 1064 nm [14–16]. Low level laser can be a) Helium–Neon laser (He–Ne) which functions at 632.8 nm (red

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light), b) Aluminium Gallium Arsenide (Al Ga As) or laser diode which function at 780–830 nm (infrared rays), or could be a combined laser of Helium–Neon diode [17]. It is a noninvasive procedure which do not generate heat, sound, or vibration [14–16,18]. The tissue or skin is exposed to low levels of red and near infrared light. As it uses very low light densities than other forms of laser therapy it is called as Low level laser. Various parameters that express LLLT are the power density (mW/cm²), wavelength (nm), pulse rate (Hz), Irradiation time (seconds), dose (J/cm²), treatment protocol (duration/interval) [18,19].

LLLT functions by bringing about a photochemical reaction in the cell, known as biostimulation or photobiomodulation [14,20]. The biological response achieved is because of photonic radiation and of thermal process. This may be achieved by absorption of red light by the mitochondrial chromophore specifically cytochrome oxidase which results in a series of reaction in mitochondria resulting in biostimulatory effect [21]. There are several other mechanisms that are assumed to account for the effect of laser therapy such as increasing collagen synthesis and reducing oxidative stress, increased oxygen consumption by quickening the rate of redox reaction, increased ATP (adenosine triphosphate) synthesis, increased production of anti-inflammatory cytokines [22–26].

The aim of this review is to examine whether the clinical use of LLLT is effective in treating patients with diabetic neuropathic pain when compared with standard of care treatment.

2. Materials and methods

2.1. Search strategy

The research resources available in Manipal academy of Higher education was used extensively. A systematic review of the literature was carried out after a bibliographical search on the database Pub Med, Science Direct and CINAHL, Cochrane, Scopus and active search lists of bibliographical references of articles selected up to May 2019. The literature search was carried out using key words including “Painful Diabetic Neuropathy” “Diabetic peripheral Neuropathy” “diabetic neuralgia” “diabetic neuropathy” AND “Low Level Laser Therapy” “Low intensity laser therapy” “photobiomodulation” “Phototherapy”. This review was carried out in accordance with PRISMA guidelines by including the clinical trials that compared the effectiveness of Low level Laser therapy on DPN over control group who was not treated with laser.

2.2. Study selection

The original research articles that met the following criteria were included in this review.

Randomized controlled trials and experimental studies that analyzed the efficacy of LLLT for the management of Painful Diabetic Neuropathy in participants with 18 years or above.

Studies on Neuropathies of other etiologies, Animal studies, case reports, and LLLT for treatment of other clinical conditions were excluded. Studies used intervention other than LLLT also were excluded. We also did not include those studies that didn't report the details of laser such as wavelength, duration and site. Non English articles and articles whose full text were not available were also excluded from the study.

3. Results

A total of 627 articles were retrieved from various databases. When the titles and abstracts were reviewed for relevance to the topic 524 articles were excluded. Out of 103 articles selected, 43 articles were included after final analysis of abstracts for very

similar studies, quality of the data analysis and availability of the full texts. Further analysis of the whole content of each article could finally select only 6 articles which are eligible for the analysis. The articles were excluded due to improper study design, language other than English, different population, and no control group (Fig. 1)..

3.1. Effect of LLLT on painful diabetic neuropathy

The evidence obtained shows a moderate efficacy of LLLT on controlling the diabetic peripheral neuropathy. The wavelength used in most studies range in between 800 and 900 nm for a duration of ranging from 10 days to 4 week. All Studies used Visual analogue Scale (VAS), Toronto clinical scoring system (TCSS), Nerve conduction Studies to measure the outcome.

4. Discussion

In a case control study conducted by Yamany.A.A et al. on patients with painful diabetic neuropathy demonstrated a significant reduction in neuropathic pain after treating with scanning helium neon (He–Ne) infrared laser 4 weeks. Here the treatment group was given Scanning helium neon (He- Ne) infrared laser. The wavelength used was 850 nm. LLLT was given at lumbosacral area and the plantar surface of the foot with a power density of 5.7J/cm² for a duration of 15 min each site/session three times per week for four weeks (i.e. 12 sessions). 30 cm was fixed as the distance between the treated area and laser head (height). Control group received a placebo laser. At the end of four weeks there was a substantial decrease in the pain [5.33 ± 0.97] along with an improved foot microcirculation was observed in study group when compared with control group [6.93 ± 0.7] ($p \leq 0.005$) [27].

A double blinded Randomized Controlled Trial with sham therapy by Zinman et al. on 50 patients with painful diabetic sensorimotor polyneuropathy, received biweekly session of LLLT for a period of four weeks and control received sham laser for the same period. After four weeks of intervention pain score remained same in control group and a decrease was observed in test group treated with laser, though it was not statistically significant. No effect was noticed by after LLLT on the Toronto Clinical Neuropathy Score, nerve conduction studies, sympathetic skin response, or quantitative sensory testing [28].

Another prospective study by Bashiri et al., investigated the efficacy of LLLT on 60 patients with DPN. Here the Study group

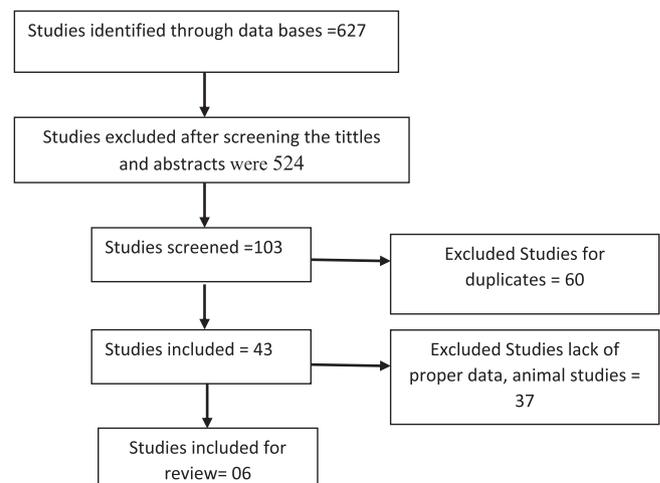


Fig. 1. Flow chart for selection process of studies for the Systematic review.

received LLLT of power 2.5 J/cm^2 with a wave length of 78 nm two times weekly for 5 min for a period of one month. They observed a statistically significant difference in VAS and Toronto clinical scoring system (TCSS) scores after 2 weeks and 4 weeks of intervention. The outcome was improvement of neuropathy in diabetic patients treated with LLLT compared to controls treated with sham therapy [29].

Khamseh M E et al. conducted a study on 17 diabetic patients with distal symmetric polyneuropathy (DSP). A multi wave locked system therapy by MIX 5 that produced a combination of two lasers, InGa (Al) As and InGaAs laser, was used to treat patients. InGa (Al) As produced Continuous emission at 808 nm and 1000 Mw whereas InGaAs laser produced Pulse emission at 905 nm, and 25 W. The subjects were given 10 sessions of laser therapy as three times a week with an energy dose of 10 J/cm^2 . The significant increase in nerve conduction velocity and right and left peroneal, right and left sural, and left tibial neural potential amplitude, demonstrated a positive effect of LLLT on diabetic DSP [30].

CG SK et al. did a pre - post observational study on 19 patients with painful diabetic neuropathy treated with both EC laser and Thor laser given for 9 min for ten days. EC laser was given at scanning mode on the plantar and dorsum of foot at 632.8 nm of 3.1 J/cm^2 . Thor laser was used over popliteal fossa and neck of fibula by contact method at 660 and 850 nm of 3.4 J/cm^2 with a power density of $50\text{--}150 \text{ Mw/cm}^2$. There was a significant decrease in the pain as well as vibration perception threshold with an increase in the temperature after 10 days [31].

A randomized placebo controlled trial conducted by Swislocki A et al. on 63 patients with PDPN received four photon stimulations and 58 received placebo therapy. They used self-assessed

questionnaires to measure pain qualities, severity and relief and protective sensation was measured by monofilament testing. For Quality Of Life they used Medical Outcomes Study Short Form-36 (SF-36). LED treatment module for 350 mW of optical energy at 870 nm used for the treatment. At activation, Control Unit delivered 1,800 J. The duration of the treatment was for 7-min to each lower extremity. A significant decrease in pain quality scores was noticed in Patients who received photon stimulation over time and an improvement in sensation was observed when compared with placebo [32]. (Table 1).

DPN is a distressing complication of diabetes mellitus resulting in significant morbidity and mortality. Lack of an effective treatment modality has greatly impacted the quality of life of these patients. Now LLLT has been emerging as a better treatment option for DPN. In this systematic review we analyzed the available research reports on the efficacy of LLLT in treating DPN patients to confirm the effectiveness of treatment as well as the various factors that can influence the efficacy.

We could see that LLLT is an effective, noninvasive, safe and cost-efficient means to treat DPN. The main effects of LLLT were a reduction in the pain. The effect was dependent on irradiation and treatment parameters. Further studies on effect of LLLT on the modulation of neuron specific proteins, growth factors and angiogenesis is needed to ensure its systemic effect.

5. Conclusion

The studies evaluated in this review showed that LLLT has the potential to become a new treatment modality in the supportive care of patients with diabetic neuropathy. These results further

Table 1
Low level laser therapy in the treatment of Diabetic neuropathy.

Study	Study Design	Neuropathy type	Energy settings [laser power(nm) radiation power (mW) Energy density (J/cm^2)]	Total sessions	Follow up month/days	Neuronal function evaluation	Result
Sashi kumar et al., 2015	pre- post observational design 19 patients (7 female and 12 male)	Diabetic peripheral neuropathy	The EC laser wave length of 632.8 nm with a dosage of 3.1 J/cm^2 . Thor Laser wave length of 660 nm & 850 nm with a dosage of 3.4 J/cm^2 and power density of $50\text{--}150 \text{ mW/cm}^2$	9 min/10 days (10)	10th day	Visual Analogue Scale, MNSI, Vibration Perception Threshold and temperature by infrared thermal imaging	Effective
Yamany et al., 2012	Case control study 30 patients (20 females and 10males)	Diabetic peripheral neuropathy	850 nm and density of 5.7 J/cm^2	15 min each site/ session three times per week for four weeks(12)		Visual Analogue Scale, bilateral peroneal motor nerves, sural sensory nerves conduction velocity, and amplitude and foot skin microcirculation	Effective
Zinman et al., 2004	RCT, Double masked. 50 patients 16 females and 34 males	Diabetic sensorimotor polyneuropathy	905 nm with an average power of 0 –60 mW	5 min each site/two sessions/week for four weeks (8)	Six weeks after treatment	Visual Analogue Scale, Toronto Clinical Neuropathy Score, Quantitative sensory testing (QST), nerve conduction studies (NCSs) sympathetic skin response (SSR)	Ineffective
Bashiri, H et al., 2013	Randomized prospective study 60 patients 46 females and 24 males	Diabetic peripheral neuropathy	wavelength of 78 nm and 2.5 J/cm^2	two times a week, each time for 5 min, for one month	After two weeks and four weeks of intervention	visual analog scale (VAS) and the Toronto clinical scoring system (TCSS).	Effective
Khamseh M E et al., 2011	17 patients 12 females and five males	distal symmetric polyneuropathy	wavelength of 808 nm, maximum power of 1,000 mW	three times a week for ten sessions		Nerve conduction studies (NCS)	Effective
Swislocki A et al., 2010	randomized, placebo-controlled trial, 121 patients	Diabetic peripheral neuropathy	Wavelength of 870 nm, power of 350 mW	Four times within five days for 7 min	Before and after each session	Numeric pain rating scale, Pain Qualities Assessment Scale and Medical Outcomes Study Short Form-36 (SF-36)	Effective

needs to be confirmed by further research on modulation of neuron specific proteins, growth factors and angiogenesis is needed to ensure its systemic effect of LLLT by randomized double-blinded controlled trials in a larger group of patients. It may give new insight into the mechanism of nerve regeneration and may be useful to know the prognosis.

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