

## **CHAPTER 7**

### **DISCUSSION**

Diabetic peripheral neuropathy is a common complication of long-standing Diabetes mellitus and its most serious complication is the diabetic foot, which is responsible for diabetes-related hospitalizations. During its natural course it progresses from initial functional to late structural changes. Neuropathy frequently results in clinically significant morbidities, such as pain, loss of sensation, foot ulcers, gangrene and amputations.

Optimal metabolic control is the only available measure with proven efficacy in preventing or at least halting the progression of diabetic neuropathy .However, to be effective it should be instituted at an early stage since, as is the case with other late complications of diabetes, the late phases of diabetic neuropathy are poorly reversible or even irreversible. Moreover, ample evidence of the defective nerve regeneration in DM is available.

In the present study comparison was done on various dosage of low level laser therapy to find out its neuroregenerative effect in experimentally induced diabetic neuropathy in wistar rats. The diabetes status was confirmed by repeated measures of blood glucose analysis from day 0, day1, day15, day30 and day60. The dosage to induce diabetes was selected as 150mg/ kg b.w of Alloxan intraperitonealy based on Szkudelski in 2001.

The MNCV result analysis within the groups showed that laser dosage of 3, 4, 5 and 6 j/cm<sup>2</sup> are having more motor regenerative effect as compared with the higher dosage and control group did not show any significant effect, and on analyzing experimental group

MNCV values between groups with dosages of 3-6j/cm<sup>2</sup> showed a significant p values and 7,8j/cm<sup>2</sup> and control group did not show any significant effect.

The SNCV result analysis within the groups showed that laser dosage of 3,4j/cm<sup>2</sup> are having more sensory regenerative effect as compared with 5-8j/cm<sup>2</sup> dose and control group also did not show significant effect. This MNCV and SNCV results are important finding of the study that the calculation of correct dosage of laser is very important. This proves that if dosage is not selected properly it can inhibit the nerve regeneration process like higher dosage can have photo inhibitory effect.

As laser light penetrates the skin, its photons are absorbed by cellular chromophores (light-absorbing molecules) that undergo photobiomodulation via influence over respiratory chain enzymes in the form of photobiostimulation or photobioinhibition according to the Arndt-Schultz law of photobiologic activation. This asserts a dose-response interaction effect whereby low dosages trigger a photobiostimulation response and higher dosages trigger a photobioinhibition Response.

Special properties of laser light allow the potential for direct delivery of electromagnetic light energy to tissue depths slightly below the dermis and possible indirect physiologic effects at deeper levels. The ability of laser light to penetrate is a function of tissue type and the laser's wavelength and resistance to scatter, allowing a direct tissue penetration depth due to 1cm.

Possibly these lower dosages of 3-4j/cm<sup>2</sup> produced significant results in our study due to photobiostimulatory effects and higher dosages did not show regeneration due to photobioinhibitory effects.

Eliasson (1964) & Dharmesh kumar (2008) in their study considered 200mg/dl as base line value for their study and Butler (1995) stated that around 90 mg/dl of blood is normal blood glucose levels for 15-24 hrs fasted rats and they also stated that in diabetic induced rats it may go up to 200-400mg/dl in 3-4 weeks after diabetic induction. In this study also the same parameters were followed, which might be an reason for the accuracy in outcome of diabetic induction.

As per the earlier studies by Coste (2003) and Dharmeshkumar (2008) confirmed that diabetic neuropathy will start by 15 days of uncontrolled diabetes and PK Thomas 1981 recorded neuropathic changes after 8 weeks and Biessels (1999) also confirmed this by proving that impairments of sciatic nerve conduction velocities developed fully during the first 2-3 months of diabetes. J. G. R. Jefferys 1978 proved in his experiment that normal nerve conduction velocity of wistar rats was around 52m/sec ranged from 46 m/sec to 57m/sec.

Eliasson(1964) found that the induction of experimental diabetes in rats by pancreatectomy or alloxan administration resulted in impaired sciatic motor and sensory nerve conduction velocities within 2 wk. However, Eliasson was unable to prevent the development of impaired nerve conduction velocities by insulin treatment.

Eliasson' (1964) first reported that reduced nerve conduction velocity in the sciatic nerves of rats made diabetic with Alloxan. In a later study on isolated nerve fibers, he attributed this to a diminution in the electrical resistance of the myelin. Reduced nerve conduction velocity was found by numerous other authors in Alloxan-diabetic rats. Eliasson' was unable to show any improvement in conduction velocity with insulin treatment but this was later claimed by Preston- and others. It was therefore suggested by Jakobsen and Lundbaek(1976) that the reduction might be equivalent to the changes found in newly

diagnosed diabetes in man that are rapidly corrected by the institution of treatment. Mayher et al(1967) reported that the reduced conduction velocity in Alloxan-diabetic rats could be improved by hypophysectomy and Greene et al( claimed that a small dietary myoinositol supplement prevents the reduction in diabetic rats. The explanation for the reduced nerve conduction velocity has been a matter of dispute. Preston(1967) and Hildebrand(1968) et al reported paranodal and segmental demyelination, but this was not con-firmed by Jakobsen(1976) or Thomas(1981). Eliasson(1964) Thomas(1981) found that no alteration in fibre diameter but Jakobsen and Lundbaek (1976) later showed that nerve fibre diameter was less in the diabetic animals than in age-matched controls, this affecting axon diameter to a greater extent than myelin thickness. Sharma et al could not demonstrate any absolute reduction in the external diameter of myelinated nerve fibres that is with measurement taken to the outer aspects of the myelin sheaths, in serial observations on diabetic rats before and after the induction of diabetes. Rats are known to continue growing until approximately 9 months of age, this affecting both nerve fibre diameter and conduction velocity. Insulin administration is effective to some extent but there is limitations as well as draw backs for this therapy. Some oral hypoglycemic agents are also employed in this regard, but they are also not without adverse effects

Anders et al in 2004 underwent study on Neuro regenerative and Neuro protective effects of low level laser and concluded that there is massive axonal sprouting and increase in various molecules such as growth associated protein – 43 (GAP- 43), calcitonin gene related (CGRP) and transforming growth factors betal. They concluded that laser irradiation stimulates the proliferation of the Schwann cells which are key factors for successful nerve recovery.

Lorne H. Zinman(2003) conducted a randomized, double-masked, sham therapy-controlled clinical trial in 50 patients with painful Diabetic Sensory motor Polyneuropathy(DSP) diagnosed with the Toronto Clinical Neuropathy Score. After the 4-week intervention, the LILT group had an additional reduction in weekly mean pain scores of  $-1.0 \pm 0.4$  compared with  $-0.0 \pm 0.4$  for the sham group ( $P = 0.07$ ). LILT had no effect on the Toronto Clinical Neuropathy Score, nerve conduction studies, sympathetic skin response, or quantitative sensory testing. Although an encouraging trend was observed with LILT, the study results do not provide sufficient evidence to recommend this treatment for painful symptoms of Diabetic neuropathy. the possible causes for the poor results may be due to very low level of energy parameter which was less than  $2\text{j/cm}^2$  selected for irradiation.

Based on the study done by Anders et al on Neuroregenerative effects of laser, this study was aimed to analyze the significance of laser therapy in stimulating nerve conduction velocity in diabetic neuropathy and an objective was set to find out the appropriate dosage and our study result showed significant levels with low dosage of laser.

Although this study demonstrated a significant improvement in motor and sensory nerve conduction velocity in diabetic neuropathy with low level laser therapy (LLLT), the observed trend warrants further investigation. The study results showed significant improvement with LLLT with 3-4 joules of irradiation, no significant adverse effects were reported in any of the groups. Therefore, LLLT could be offered safely to patients with diabetic neuropathy. Further studies would be worthwhile because diabetic neuropathy is a disorder with multiple symptoms which affects function, produces pain, autonomic involvement and since no significant adverse effects were observed with

LLLT treatment future studies can consider functional improvements, pain threshold, axonal morphometrical analysis, assessing sensory and motor impairment etc.,.