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Effect of Low Level Laser Irradiation on Motor Nerve Conduction Velocity of Experimentally Induced Diabetic Neuropathy in Wistar rat

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Abstract: Peripheral neuropathies have been described in patients with primary and secondary diabetes of diverse causes suggesting a common etiologic mechanism based on chronic hyperglycemia. The extensive review of literature reveals that there is paucity of studies on scope of management for this particular complication, this urges to do a study on this problem with low level laser irradiation which is recognized worldwide for its tissue healing properties. The Effect of various dosages of low level Laser Therapy in Experimental Diabetic Neuropathy was evaluated with 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/cm^2 and one group was kept as control. On analyzing pre and post MNCV values, dosages of 3-4j/ cm^2 showed extremely significant p values 5-6j/cm^2 showed satisfactorily significant results and 7-8j/cm^2 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 bio-inhibitory effect.

Key Words: Low Level Laser Irradiation, Diabetic Neuropathy, Motor Nerve Conduction Velocity

Introduction:

Diabetes mellitus is a metabolic disorder and is characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both.[2] Indians are genetically more susceptible to diabetes and the World Health Organization predicts the number of diabetic persons in India would go up to 40 million by 2010 and to 74 million by 2025.It is also estimated that there are about 30 to 33 million diabetic patients in India and every fourth diabetes patient in the world today is an Indian[19].

Diabetes is one among the major healthcare problem in India. According to Diabetes Atlas published by the International Diabetes Federation (IDF) in 2005, the countries with the largest number of diabetic people will be India, China and USA by 2030. Due to these increasing numbers, the economic burden caused by diabetes in India is amongst the highest in the world. The real burden of the disease is however due to its associated complications which lead to increased morbidity and mortality. [20]

WHO estimated that mortality from diabetes, heart disease and stroke costs about $210 billion in India, much of the heart disease and stroke in these estimates was associated with diabetes. WHO estimates that over the next 10 years in India about $ 333.6 billion will be spent for treating diabetes, heart disease and stroke.

Increased economic and urbanized life style have produced advancement in developing countries such as India which have resulted in dramatic lifestyle changes leading to lifestyle related diseases like diabetes. The transition from a traditional to modern lifestyle, consumption of fast food diets rich in fat and calories combined with a high level of mental stress has compounded the problem further. There are several studies from various parts of India which reveal a rising trend in the prevalence of type II diabetes in the urban areas. A National Urban Survey in 2000 observed that the prevalence of diabetes in urban India in adults was 12.1 per cent. Recent data has illustrated the impact of socio-economic transition occurring in rural India. The transition has occurred in the last 15 years and the prevalence has risen from 2.4 per cent to 6.4 per cent. [21]
Diabetes affects all the systems of the body among which its impact over peripheral nerve is severe leading to diabetic neuropathy which produces neuropathy pain, sensory loss, weakness etc. Peripheral nerve dysfunction is a common complication of human diabetes mellitus[5]. Clinical symptoms of peripheral neuropathy are present in approximately 25% of diabetic individuals, while nearly all diabetics have a reduction of nerve conduction velocity[3]

The development of the most common form of diabetic neuropathy the distal symmetrical Polyneuropathy, is thought to be caused by some chronic metabolic disturbance and recent pathological studies seem to exclude occlusive vascular disease as a primary causative factor. However, the importance of insulin deficiency in the pathogenesis of diabetic neuropathy is still disputed because of positive and negative data concerning the

relationship between the degree of antecedent 'diabetic control" and the development of this syndrome, and the response to insulin treatment in patients with diabetic neuropathy [10].

Patients with diabetic polyneuropathy exhibit decreased peripheral motor and sensory nerve conduction velocities, and similar alterations have been found in long-standing diabetics who have no evidence of polyneuropathy, in both of these instances the decreased nerve conduction velocities are associated with lesions in peripheral nerve biopsies, which are more marked in the patients with polyneuropathy. These lesions include loss of myelinated axons, evidence of segmental demyelination and remyelination, and in some instances Schwann cell proliferation [4].

Peripheral neuropathies have been described in patients with primary and secondary diabetes of diverse causes, suggesting a common etiologic mechanism based on chronic hyperglycemia [7]. Pathologically, numerous changes have been demonstrated in both myelinated and unmyelinated fibers. Diabetic peripheral neuropathy is a common complication of diabetes that can cause significant morbidity and mortality. Some 30% of hospitalized and 20% of community-dwelling diabetes patients has peripheral neuropathy; the annual incidence rate is approximately 2% [13].The pathology of diabetic neuropathy involves oxidative stress, advanced glycation end products, polyol pathway flux, and protein kinase C activation all contribute to micro vascular disease and nerve dysfunction.

Lasers have proved their significance in physiotherapy interventions on various studies conducted on it for the past 3 decades, Nowadays laser plays a major role in physiotherapy departments for treating various ailments like non healing wounds, inflammatory tissue responses, neuropathic pain , scar tissue management, arthritis, sprains, strains etc,. Low level laser have gained popularity because it appear to have only positive effects ,Currently lasers are recognized as non significant risk devices. Although many empirical and clinical findings show promising results, more controlled studies are essential to determine the types of lasers and dosages that are required to attain reproducible results. From the extensive research conducted by various researchers with low level laser irradiation on its physiological and therapeutic effects on biological tissues and nerve regenerating effects.

This study aims to analyze the effect of various dosages of low level laser irradiation on motor nerve conduction velocity (MNCV) in regenerating peripheral neuropathy induced due to experimental diabetes. The extensive review of literature reveals that there is paucity of studies on role of neuro regenerative effect of low level laser therapy in experimentally induced diabetic neuropathy The scope of management in physiotherapy is also very less for this particular complication, this urges to do a study on this problem with laser which is recognized worldwide for its tissue healing properties.

Methodology:

Materials Used

1. Laser Unit – Physitalia (Unilaser Scan – 2000), Class-1, Type-B, 230V-50Hz
2. Nerve Conduction Velocity Unit – BIOTECK-NEUROCARE
3. Glucometer: one touch ultra (Johnson & Johnson, USA)

Study Design: Randomized trial
Sampling: Simple Random Sampling

Study Centre:

Biomedical Research Unit & Laboratory Animal Centre (BRULAC) - CPCSEA Approved, Saveetha University, Chennai.
RESEARCH LAB - College of Physiotherapy, Saveetha University

Inclusion:

Species:	Rattus norvegicus
Age :	2-3months
Weight:	180-200gms
Sex :	Male
Study Duration:	3 months

Procedure:

Phase I:

The experimental rats were selected based on the inclusion criteria and were kept on fasting for 12 hours prior to experimentation and were rendered diabetic by a single dose of intra- peritoneal injection of Alloxan 150 mg/kg body weight by dissolving in normal saline[26].

Blood glucose level of the rats were measured prior to Alloxan induction and after 24hrs post induction and all the rats were screened for blood glucose levels and rats with blood glucose levels of more than 200 mg/dl were selected for further intervention. Diabetes was confirmed with help of Glucometer readings by obtaining blood samples from tail vein of the rat .Diabetic levels of the rats were monitored prior to Alloxan induction and on day 1, 15, 30 and 60 after Alloxan induction. Booster dose of 50 mg/kg body weight of Alloxan was administered on the 30th day to maintain diabetic status.

Nerve Conduction Study:

Nerve conduction velocities were recorded initially pre Alloxan administration and 30 days and 60 days post induction. Experimental animals were anesthetized with Ether solution and electrode placement areas were shaved and cleaned with alcohol, MNCV recordings were done by fixing stimulating electrode at sciatic notch and the tibial nerve posterior to the medial malleolus. Recording electrode was fixed in the dorsal interosseous space of foot. Supra maximal stimulation (6mA) was given and conduction velocity was calculated by measuring distance between two electrodes. The frequency band was 10 Hz muscle potential recordings (orthodromic, motor).After analyzing motor nerve conduction velocity tests values, the neuropathic status deficits was confirmed and the rats were grouped into study and control group for next phase of experimentation.

Phase II:

The experimental animals with motor degeneration which confirmed neuropathic status were divided into seven groups (six rats in each group) and irradiated with low level laser with various dosages.

Groups:

I Group- 3 j/cm^2 of He-Ne laser irradiation
II Group- 4 j/cm^2 of He-Ne laser irradiation
III Group- 5 j/cm^2 of He-Ne laser irradiation
IV Group- 6 j/cm^2 of He-Ne laser irradiation
V Group- 7 j/cm^2 of He-Ne laser irradiation
VI Group- 8 j/ cm^2 of He-Ne laser irradiation.
VII Group is kept as control

Laser Therapy:

Low level He-Ne laser therapy of 632.8nm was irradiated at the site of sciatic notch of the rat where the nerve is superficial and the irradiation was given for 4 days in a week for 4 weeks with various dosage of laser ranging from 3 to 8j/cm^2. The effect of laser induced nerve regeneration was again measured with motor nerve conduction velocity to find regeneration status of the nerve.

In each Laser group the dosage was calculated using following formula:

$$D = P \times T/A$$

D = Dose measured in joules per square centimeters
P= Laser output in milli-watt and it needs to be converted into Watts. In our equipment it has 10 mw output (divided by 1000 to convert to Watts) = 0.01W
T= Time in seconds
A= Area of the irradiation site measured in centimeters square

Outcome Measures

Blood glucose values measured from one touch ultra Glucometer.

MNCV values measured from EMG-NCV from Bioteck-Neurocare

Data Analysis:

Data analysis done by SPSS version 17 with paired t-test, one way ANOVA and post hoc analysis.

Blood glucose: ***Table 1*** Blood glucose levels were initially noted on the day 0 with M= 82.42 , on day1 after alloxan induction as M=261.71,on day 15 as M=342.07, on day 30 as M=389.14 and on day 60 as M=401.42 as shown in fig1.

MNCV recording for confirming motor degeneration*:* ***Table 2*** MNCV results of tibial branch of sciatic nerve in all the animals were recorded on day 0 prior alloxan induction with M=51.71 and on day 30 after alloxan induction which showed M=46.9 and on 60th day which confirmed M=33.19 and statistical analysis were made with values of day 0 with day30 & day 60 which showed significant changes in MNCV with p value <0.0001 of t values10.637 &12.195 as shown in ***Table 3.***

MNCV recording for confirming Neuro regeneration: Results shown in ***Table 4*** were statistically analyzed with comparing the pre and post laser irradiation among all the 7 groups and the results showed that Group I with 3j/cm^2 showed extremely significant changes with p value <0.0001 of t value=14.08 and Group II with 4j/cm^2 also showed extremely significant changes with p value <0.0001 of t value=60.9 and Group III with 5j/cm2 showed very significant changes with p value=0.0022 of t value=5.787 and Group IV with 6j/cm^2 also showed very significant changes with p value =0.0068 of t value=4.435 and Group V with 7j/cm^2 showed no significant changes with p value =0.4421 of t value=0.834 and Group VI with 8j/cm^2 showed non significant changes with p value =0.768 of t value=0.3109 and Group VII which were kept as control without laser irradiation also showed statistically non significant effect with pvalue 0.6563 of t value=0.4728 as shown in ***Table 5.***

Comparison of MNCV values between the groups after laser irradiation using one way ANOVA & Post Hoc test: Analysis of variance of MNCV values Post laser irradiation revealed significant p value <0.0001 with F value 92.084 ***(Table 6)*** and post hoc analysis revealed that groups 1,2,3,4 showed significant improvement and groups 5,6,7 did not show statistical significance for 95% confidence interval as shown in ***Table 7 and 8.***

Table 1: **Mean and SD of Blood glucose levels at pre Alloxan (Day 0) administration and various days post Alloxan Administration.**

N	Day 0 (mg/dl)		Day 1 (mg/dl)		Day 15 (mg/dl)		Day 30 (mg/dl)		Day 60 (mg/dl)	
42	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
	82.42	3.46	261.71	3.49	342 .07	3.74	389.14	3.87	401.42	14

Table 2: **MNCV Values in m/sec of Experimentally Diabetes Induced Wistar Rats**

N	Pre test (Day 0) (m/sec)		Post test (Day 30) (m/sec)		Post test (Day 60) (m/sec)	
42	Mean	SD	Mean	SD	Mean	SD
	51.71	2.56	46.9	1.220	33.19	2.682

Table 3: **Comparison of MNCV values (m/sec) between day 0 (PreAlloxan) to Day 30 & Day 60 (Post Alloxan) by Paired't' test**

S. No	N	Comparison	Pre Alloxan (m/sec)		Post Alloxan (m/sec)		T value	P value
			Mean	SD	Mean	SD		
1	42	Day 0 vs Day 30	51.7	2.56	46.90	1.220	10.637	<0.0001
2	42	Day 0 vs Day 60	51.7	2.56	33.19	2.682	12.195	<0.0001

Table 4: **MNCV values Pre & Post Laser irradiation**

Groups (N=6)	Pre test		Post test	
	Mean	SD	Mean	SD
Group I-3j/cm²	32.3	2.034	44.3	1.264
Group II-4j/cm²	29.8	0.914	49.1	0.794
Group III-5j/cm²	32.8	2.190	41	2.097
Group IV-6j/cm²	33.1	2.192	39.7	1.544
Group V -7j/cm²	34.8	0.802	35.3	1.38
Group VI-8j/cm²	34.6	2.699	34.2	1.277
Group VII-control	34.3	2.679	34.9	1.195

Table 5: **Comparison of MNCV values (m/sec) prior and 30 days after laser irradiation by paired t test**

Groups (n=6)	Pre laser irradiation (m/sec)		Post laser irradiation (m/sec)		t value	P value
	Mean	SD	Mean	SD		
Group I-3j/cm²	32.3	2.034	44.3	1.264	14.08	<0.0001
Group II-4j/cm²	29.8	0.914	49.1	0.794	60.9	<0.0001
Group III-5j/cm²	32.8	2.190	41	2.097	5.7877	0.0022
Group IV-6j/cm²	33.1	2.192	39.7	1.544	4.4355	0.0068
Group V -7j/cm²	34.8	0.802	35.3	1.38	0.8344	0.4421
Group VI-8j/cm²	34.6	2.699	34.2	1.277	0.3109	0.7684
Group VII-control	34.3	2.679	34.9	1.195	0.4728	0.6563

Table 6: **MNCV values Post laser irradiation Results analysis with one way ANOVA.**

Comparison	Sum of squares	df	Mean square	F-value	P value
Between Groups	1,102.851	6	183.89	92.04	0.000
Within groups	69.863	35	1.99	-	-

Table 7: **Post hoc Analysis for MNCV values between Confidence intervals of the groups.**

S.No	Comparison	Mean 1	Mean 2	Mean1 - Mean2	95% CI of difference
1	Group I-3j/cm²	32.3	44.5	12.2	9.9 to 14.5
2	Group II-4j/cm²	29.8	49.1	19.3	17 to 21.6
3	Group III-5j/cm²	32.8	41.0	8.2	5.9 to 10.5
4	Group IV-6j/cm²	33.1	39.7	6.6	4.3 to 8.9
5	Group V -7j/cm²	34.8	35.3	0.5	1.8 to 2.8
6	Group VI-8j/cm²	34.6	34.2	0.4	1.9 to 2.7
7	Group VII-control	34.3	34.9	0.6	1.7 to 2.9

Mean Square= 1.996 DF= 35

Table 8: **Significance level of groups with MNCV values Post Laser Irradiation**

S.No	Comparison	Significance (P <0.05?)	t
1	Group I-3j/cm²	<0.0001-Yes	14.957
2	Group II-4j/cm²	<0.0001-Yes	23.661
3	Group III-5j/cm²	0.0002-Yes	10.053
4	Group IV-6j/cm²	0.0005-Yes	8.091
5	Group V -7j/cm²	0.5667-No	0.613
6	Group VI-8j/cm²	0.6449-No	0.490
7	Group VII-control	0.4948-No	0.736

Post hoc comparisons of the groups MNCV values showed significant p values in Group I (3j/cm2), Group II (4j/cm2) & Group IV (5j/cm2) rest of the groups from 6-8j/cm2 and control Group did not show significant p value with 95% confidence interval.

Discussion:

Diabetic peripheral neuropathy is a common complication of long-standing diabetes mellitus and its most serious complication, the diabetic foot, 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 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, day 1, day 15, day 30 and day 60. The dosage to induce diabetes was selected as 150mg/ kg b.w of Alloxan intraperitonealy[23].

The MNCV result analysis within the groups showed that laser dosage of 3, 4, 5 and 6 j/cm^2 is having more motor regenerative effect as compared with higher dosage and control group did not show significant effect, and on analyzing experimental group MNCV values between groups with dosages of 3-6j/cm^2 showed significant p values and 7,8j/cm^2 and control group did not show any significant effect.

The MNCV results obtained is a important finding of the study which proves that the calculation of correct dosage of laser is very important. This proves that if dosage not selected properly it can inhibit the nerve regeneration process like higher dosage can have photo bio-inhibitory effect. In the present study nerve regeneration is confirmed through nerve conduction velocity studies.

Eliasson & Dharmesh kumar [6,8] in their study considered 200mg/dl as base line value for their study and Linda.K.Butler [15] 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. As per the earlier studies by Thierry C. Coste [24] and Dharmeshkumar [6], confirmed that diabetic neuropathy will start by 15 days of uncontrolled diabetes and PK Thomas[25] recorded neuropathic changes after 8 weeks and Greet Jan Biessels [9] 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 [12] proved in his experiment that normal nerve conduction velocity of wistar rats was around 52m/sec ranged from 46 m/sec to 57m/sec.

In 1964 Eliasson[8] 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, or to affect it by the addition of insulin to the isolated nerve *in vitro* Although there have been two reports that impaired nerve conduction velocity in rats with experimental diabetes can be improved by insulin treatment it has not been possible to prevent its development, and Sharma and Thomas[25] concluded that "the influence of insulin on conduction velocity in diabetic animals is so far uncertain".

Eliasson[8] first reported 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 [18] and others. It was therefore suggested by Jakobsen and Lundbaek [11] 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[17] reported that the reduced conduction velocity in Alloxan-diabetic rats could be improved by hypophysectomy and Greene et al.[10] claimed that a small dietary myoinositol supplement prevents the reduction in streptozotocin-diabetic rats.

The explanation for the reduced nerve conduction velocity has been a matter of dispute. Preston[18] and Hildebrand[14] et al reported paranodal and segmental demyelination, but this was not con-firmed by Jakobsen[11] and Thomas[25] Eliasson [8] and Thomas[25] found no alteration in fibre diameter but Jakobsen and Lundbaek [11] 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. [22] 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 streptozotocin-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.[1] 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 [16] 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. All patients received sham therapy over a 2-week baseline period and were then randomized to receive biweekly sessions of either sham or low intensity laser therapy (LILT) for 4 weeks. The primary efficacy parameter was the difference in the weekly mean pain scores on a visual analog scale (VAS). The patients had similar baseline characteristics for pain intensity, HbA_{1c}, and duration of DSP. Both groups noted a decrease in weekly mean pain scores during sham treatment. After the 4-week intervention, the LILT group had an additional reduction in weekly mean pain scores of −1.0 ± 0.4 compared with −0.0 ± 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.

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, Assesing sensory and motor impairment etc,.

Conclusion:

In the present study it is proved that motor nerve conduction velocity in diabetic neuropathy can be improved with low level laser irradiation. The main morphological features of established neuropathy include a combination of demyelinization and axonal degeneration of myelinated fibers, degeneration with regeneration of unmyelinated fibers and endoneurial microangiopathy, with nerve fiber loss in its final stage. Increased nerve conduction velocity with selective dosages of laser proves that laser has neuroregenerative effects and by analyzing the results it can be concluded that low level laser of 3&4j/cm2 is found to be effective in regenerating MNCV of experimentally induced diabetic neuropathy as compared with control group and with dosage of higher energy with 5-8j/cm2. The present investigation highlights the possible utility of Helium-Neon laser with appropriate energy density as an adjunctive modality for diabetic neuropathy in clinical practice.

Ethical Clearance:

Ethical Clearance was obtained from Institutional Ethical Committee of Saveetha University vide Number: IAEC. NO. BPT/001/2008

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