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Original Article

SUPPLEMENTATION OF A-LIPOIC ACID IN DIABETIC PERIPHERAL NEUROPATHY: A PROSPECTIVE OPEN LABEL RANDOMIZED CONTROLLED TRIAL

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ABSTRACT

Objective: Diabetic peripheral neuropathy is the most common long term complications associated with reduced nerve conduction and blood flow. The present study was designed to investigate the effect of oral supplementation of α-lipoic acid (600 mg/day) on peripheral, sensory and motor nerve conduction and glycaemic control in type 2 diabetes mellitus with peripheral neuropathy.

Methods: A total of 20 patients were enrolled in this study, then randomly allocated to two groups control (n=10) and intervention group (n=10). Patients in control group received only oral hypoglycaemic treatment and in intervention group received α-lipoic acid (600 mg/day) oral supplementation along with their oral hypoglycaemic treatment for a period of 3 months. Nerve conduction and glycaemic control were measured at the base line and at the end of 3 months by using specific methods.

Results: In intervention group α-lipoic acid supplementation significantly improves 6 of 15 electrophysiological parameters of nerve conduction. Distal latency of peroneal (mean ± SD 5.13 ± 0.52 *vs* 4.92±0.55; $p<0.02$), median (mean ± SD 3.66 ± 0.76 *vs* 3.53±0.63; $p<0.03$) & ulnar motor nerves (mean ± SD 2.91 ± 0.32 *vs* 2.82±0.36; $p<0.01$), and Nerve Conduction Velocity of peroneal (mean ± SD 42.0 ± 3.07 *vs* 43.4±2.13; $p<0.03$), median (mean ± SD 51.4 ± 3.31 *vs* 52.2±3.59; $p<0.01$) & ulnar motor nerves (mean ± SD 51.0 ± 5.84 *vs* 52.1±5.46; $p<0.03$) shows significant improvement.

Conclusion: Oral supplementation of α-lipoic acid was found to be effective in improving motor nerve conduction of upper and lower extremities in patients with diabetic peripheral neuropathy.

Keywords: α-lipoic acid, Diabetic peripheral neuropathy, Nerve conduction, Glycaemic control.

INTRODUCTION

About half of the type 2 diabetes mellitus patient population is suffering from peripheral neuropathy and it is one of the long term complications in these patients [1]. It is associated with reduced nerve conduction and blood flow [2]. Diabetic neuropathy is defined as a condition of peripheral nerve dysfunction in people with diabetes after exclusion of other causes, which lead to both somatic and autonomic nerve dysfunction [3, 4]. The peripheral neuropathy detected by electrophysiological testing or by quantitative assessment of vibratory and thermal sensitivity [5, 6, 7]. Evidence suggests that oxidative stress resulting from enhanced free radical formation and/or defects in antioxidant defence is implicated in the development of various disorders, including neurodegenerative diseases [8] and diabetic complications [9.10]. Oxidative stress is linked with development of apoptosis in neurons and supporting glial cells. So it could be unifying mechanism that leads to nerve dysfunction in diabetes [11, 12]. Treatment with a-lipoic acid, a potent lipophilic free radical scavenger [13], results in prevention of neurovascular abnormalities associated with experimental diabetic neuropathy [14].

Though numerous animal studies have been reported on its beneficial effects on diabetes neuropathy, only limited clinical data are available concerning its potential effects, especially on Indian population. The present study was, therefore, aimed to investigate the effect of α-lipoic acid on nerve conduction and glycaemic control in diabetic peripheral neuropathy.

MATERIALS AND METHODS

Study design and patients

A randomized open label controlled trial include 20 patients divided into two groups, control (n=10) and intervention group (n=10). The study was conducted at S. P. Institute of Neurosciences, Solapur, Maharashtra, India from June 2007 to January 2008. All subjects gave written, informed consent, which was approved by the Institutional Review Board, JSS College of Pharmacy, Ootacamund, Tamil Nadu, India. Type 2 diabetes mellitus patients with stage 2 peripheral nephropathy of either sex, aged between 40 to 65 years, receiving oral hypoglycaemic agents, with duration of diabetes≥ 10 years and HbA1C≤ 10% were enrolled in the study. None of the patients were on antioxidant supplementation. Patients with type 1 diabetes, juvenile diabetes, pregnant women and lactating mothers, voluntary withdrawals and patients with any significant hepatic and renal dysfunction were excluded. The assessment of peripheral neuropathy consisted first in evaluating the clinical stage: stage 0, no functional signs or clinical abnormalities; stage 1, presence of mild neuropathy, revealed by sensory signs and/or symptoms, and/or absence of at least one tendon reflex; stage 2, severe neuropathy with motor deficit or trophic disorders unrelated to arterial disease, infection, or traumatic processes.

Patients were randomized by using computer assisted randomization procedure and assigned to control (n=10) and intervention group (n=10). Control group received only oral hypoglycaemic agent, whereas, intervention group received α-lipoic acid oral supplementation (600 mg/day) along with oral hypoglycaemic agent for a period of 3 months. The demographic characteristics were collected on standard data collection form by face to face interview. Primary outcome of the study was assessment of distal latency (DL), amplitude & nerve conduction velocity (NCV) for electrophysiological evaluation of the upper and lower extremities and secondary outcome was fasting plasma glucose (FPG), 2 hours post-load of oral glucose tolerance test (OGTT) & HbA1c level and were determined for glycaemic control. All the parameters were measured at the baseline and at the end of 3 months study.

Glycaemic control

Blood samples were obtained after at least 10 hours overnight fast. Plasma glucose concentrations & 2 hours post-load of oral glucose tolerance test (OGTT) were determined by using an enzymatic kit (glucose oxidase). HbAlc values were determined using Nycocard kit and Nycocard Reader II (Axis-Shield PoC AS).

Electrophysiological evaluation

Electrophysiological evaluation were performed by measuring the median, ulnar & peroneal motor nerve and median, ulnar & sural sensory nerve conduction by using RMS EMG EP Mark II, version 1.1, (Recorder and Medicare System, India). Stimulating electrode (10 mm), recording electrode (surface electrode, 20 mm), and ground electrode (round ground electrode, 20 mm) were used for all the stimulation and recordings. Lower and upper filter frequencies were 2 Hz to 10 kHz for the motor nerve studies and 2 Hz to 3 kHz for the sensory nerve studies. Negative peak amplitude and peak-to-peak amplitude measurements were done for the motor and sensory response respectively. *Peroneal nerve s*urface stimulation was performed at ankle (distal site) and near the knee (proximal site). Surface recording electrodes were used with active electrode over the belly of the extensor digitorum brevis muscle and the reference electrode was distal to active electrode over the muscle tendon. Ground electrode was placed between distal site and recording electrodes. *Median nerve s*urface stimulation was performed at wrist (distal site) and elbow (proximal site). Surface recording electrodes were used with active electrode over the belly of Abductor Pollicis Brevis and the reference electrode was over the tendon of this muscle. Ground electrode was placed over the dorsum of the hand. *Ulnar nerve s*urface stimulation was placed at the wrist (distal site) and above the ulnar groove at the elbow (proximal site). Surface recording electrodes were used with active electrode over the belly of Abductor digiti V muscle with a reference electrode distal to active electrode. Ground electrode was placed over the dorsum of the hand.

*Median nerve s*urface stimulation was performed at wrist. Surface recording electrodes were used with active electrode over the proximal interphalangeal joint of second digit and the reference electrode was over the distal Phalanx of the same digit. Ground electrode was placed over the dorsum of the hand. *Ulnar nerve s*urface stimulation was performed at wrist. Surface recording electrodes were used with active electrode over the proximal interphalangeal joint of fifth digit and the reference electrode was over the distal Phalanx of the same digit. Ground electrode was placed over the dorsum of the hand. *Sural nerve s*urface stimulation was performed distal to lower border of bellies of the gastrocnemius. Surface recording electrodes were used with active electrode placed between the lateral malleolus and the Achilles tendon at the malleolar level with the reference electrode distal to active electrode. Ground electrode was placed between stimulating and recording electrodes.

Statistical Analysis

Statistical analysis was performed by using GNU PSPP version 0.7.5-g70514b software. Data are presented as mean± SD or geometric mean (95% CI). Differences between baseline and 3 months values within the groups were checked by paired Student's *t* test, p value less than 0.05 was considered significant.

Table 1: Demographic, anthropometric and life style characteristic of study population

Variables	Control group	Intervention group
Age (years)	55.7±8.1	54.7 ±8.0 NS
Sex (Male/Female)	8/2	7/3
Duration of disease (years)	11.5±3.5	13.5±8.7 NS
Body Mass Index (kg/m2)	24.75 ±3.09	24.52±2.89 NS
Family history	6	5
Alcoholic	4	3
Smoker	2	2
Vegetarian/Non vegetarian	4/6	2/8

Values are given as mean ± S.D (*p≤0.05, NS-Not Significant)

Table 2: Effect of α-lipoic acid on electrophysiological parameters of nerve conduction

Parameters	Control group (n=10)			Intervention group (n=10)		
	Baseline	**3 months**	**p value**	**Baseline**	**3 months**	**p value**
Electrophysiological parameters						
Peroneal Motor Nerve						
DL	3.55±0.75	3.77±0.69	0.11	5.13±0.52	4.92±0.55	0.02*
Amplitude	3.55±1.94	3.61±2.11	0.87	3.84±2.11	4.38±2.44	0.15
NCV	42.4±6.75	43.1±7.25	0.48	42.0±3.07	43.4±2.13	0.03*
Median Motor Nerve						
DL	3.41±0.68	3.33±0.64	0.17	3.66±0.76	3.53±0.63	0.03*
Amplitude	9.19±2.70	8.67±2.61	0.17	7.83±3.23	8.45±3.52	0.07
NCV	52.2±3.90	51.9±2.94	0.90	51.4±3.31	52.2±3.59	0.01*
Ulnar Motor Nerve						
DL	2.78±0.64	2.67±0.72	0.18	2.91±0.32	2.82±0.36	0.01*
Amplitude	8.98±3.87	8.56±3.23	0.37	9.83±2.55	9.20±1.83	0.22
NCV	53.2±4.05	53.1±4.05	0.91	51.0±5.84	52.1±5.46	0.03*
Median Sensory Nerve						
DL	2.58±0.74	2.74±0.44	0.39	3.00±0.32	2.90±0.30	0.09
Amplitude	14.6±10.0	15.7±0.77	0.64	17.5±3.32	18.2±3.48	0.39
Ulnar Sensory Nerve						
DL	2.03±0.26	2.21±0.37	0.13	2.88±0.18	2.27±0.19	0.18
Amplitude	11.6±3.10	13.5±6.02	0.30	10.7±3.02	10.8±2.58	0.95
Sural Sensory Nerve						
DL	3.01±0.94	2.88±0.81	0.63	2.94±0.51	2.97±0.72	0.83
Amplitude	18.3±7.95	16.6±6.66	0.64	15.8±9.22	16.4±9.24	0.22

Values are given as mean ± S.D (*p≤0.05, NS-Not Significant)

DL, distal latency; NCV, nerve conduction velocity

RESULTS

Demographic characteristics

Demographic characteristics of the patients enrolled in this study are summarised in Table 1. Out of 14 patients in the control group, 2 relocate to other place for job and 2 discontinued for personal reasons. Of the 13 intervention patients, 2 were lost during follow up and 1 discontinued for personal reasons. In total, data for 10 patients on control group and 10 patients for intervention group were used for the analysis at the end of three months. Control group patients had mean age of 55.7±8.1 years and mean duration of diabetes 11.5±3.5 years. Whereas intervention group patients had a mean age of 54.7±8.0 years and duration of diabetes 13.5±8.7 years. Body mass index was higher in both the groups.

Electrophysiological evaluation

Table 2 shows effect of α-lipoic acid on electrophysiological parameters of nerve conduction in both the groups. In intervention group α-lipoic acid supplementation significantly improves 6 of 15 electrophysiological parameters of nerve conduction. Distal latency of peroneal (mean ± SD 5.13 ± 0.52 vs 4.92±0.55; p<0.02), median (mean ± SD 3.66 ± 0.76 vs 3.53±0.63; p<0.03) & ulnar motor nerves (mean ± SD 2.91 ± 0.32 vs 2.82±0.36; p<0.01), and Nerve Conduction Velocity of peroneal (mean ± SD 42.0 ± 3.07 vs 43.4±2.13; p<0.03), median (mean ± SD 51.4 ± 3.31 vs 52.2±3.59; p<0.01) & ulnar motor nerves (mean ± SD 51.0 ± 5.84 vs 52.1±5.46; p<0.03) shows significant improvement.

Glycaemic control

Table 3 shows the effect of FPG, OGTT, and HbA1c at baseline and after three month supplementation with alpha lipoic acid in both control and intervention groups. The fasting plasma glucose (FPG) level in control and intervention group at base line and after three months supplementation showed no significant change (p ≥ 0.05). The oral glucose tolerance test (OGTT) in control and intervention groups at base line and after three months supplementation was 143±15 & 170±50 mg/dl and 174± 24 & 169±24 mg/dl respectively. The Glycosylated haemoglobin (HbA1c) percentage in control and intervention at base line and after three months supplementation was 8.0±0.8 & 8.1±0.7 and 7.9±0.6 & 7.6±0.4 respectively. None of these values showed significant change between the groups.

Table 3: Effect of α-lipoic acid on glycaemic index in both control and intervention group

Parameters	Control group (n=10)		Intervention group (n=10)	
	Baseline	3 months	Baseline	3 months
Glycaemic Index				
FPG (mg/dl)	108±17	114±21^{NS}	122±27	120±28^{NS}
OGTT (mg/dl)	143±15	170±50^{NS}	174±24	169±24^{NS}
HbA1c (%)	8.0±0.8	8.1±0.7^{NS}	7.9±0.6	7.6±0.4^{NS}

Values are given as mean ± S.D (NS-Not Significant), **FPG**- fasting plasma glucose, **OGTT**-Oral Glucose Tolerance Test, **HbA1c**- Glycosylated haemoglobin, mg/dl- milligram/decilitre, %- percentage

DISCUSSION

In this present study electrophysiological parameters revealed more pronounced abnormalities in lower-extremity, particularly in the sural nerves compared to upper extremity at the baseline and there were no significant differences in electrophysiological parameters among both the groups with respect to age, gender and duration of disease. Since it is a prospective randomised control study, the baseline variation in covariate distribution was minimized which is the major strength in this study. The placebo effect attributed to open label design and relatively small sample size were the limitations of this study.

Sensory fibre defects were observed in the upper (median and ulnar) and lower (sural) extremity distal nerves, in particular the peroneal and the sural nerves, which were found to be the most significant abnormalities among the patients. These findings are similar to previous reported study [15]. Nerve conduction velocity was found to be significantly increased in the intervention group, which was similar to the previous findings, suggesting that the improvement in neurovascular changes were induced by improving oxygen free radical scavenging activity of α-lipoic acid[14,16,17,18,19] and also helps in inhibiting the free radical induced endothelial damage and decrease oxidative stress in the diabetic individual in whom the antioxidant capacity is defective because of active polyol pathway [20]. Distal latency is the most frequent measure of F- wave activity. The patients suffering from axonal polyneuropathy can be assessed by F-wave procedure that is reported as more sensitive and reliable tool [21], but the F-wave changes in distal segment of the axon poorly represents the therapeutic effect in this method. However, present study demonstrates that distal latency was significantly decreased in peroneal motor nerve, median motor nerve and ulnar motor nerve. In the present study no change was observed in glycaemic control with α-lipoic acid supplementation in comparison with control group. The present findings are similar to earlier report [22].

CONCLUSIONS

Oral supplementation of α-lipoic acid may be effective in the management of diabetic peripheral neuropathy along with oral hypoglycaemic agents to improve the motor nerve conduction of upper and lower extremity. Alpha-lipoic acid also slows the progression of nerve degeneration and improves patient compliance. This short period study provide the data about the possible clinical effects of α-lipoic acid supplementation on the electrophysiological parameters of nerve conduction in type 2 diabetic peripheral neuropathy patients and provide the base for future studies with larger number of patients with at least than one year follow up.

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CONFLICT OF INTERESTS

Declared None

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