Effect of Vitamin E Supplementation on Electrophysiological Parameters of Median Nerve in Polyneuropathic Type 2 Diabetes Mellitus Patients

Pravin Dhepe[1], Aruna Vinchurkar[2]

[1]Department of Physiology, S.N. Medical College, Bagalkot, Karnataka, India,

[2]Department of Biophysics, Government Institute of Science, Aurangabad, Maharashtra, India.

Abstract

Background: Nerve conduction study is widely used for the assessment of diabetic polyneuropathy. Vitamin E is a group of compounds that are potent lipophilic antioxidants.

Aim: To assess the efficacy of antioxidant vitamin E on motor nerve conduction analysis in polyneuropathic type 2 diabetes mellitus (PND) patients.

Materials and Methods: Sixty PND patients were divided into two groups. Group I consisted of 30 PND patients supplemented with vitamin E (200mg/day) and Group II consists 30 patients supplemented with placebo for the duration of six months. After treatment routine clinical investigations were done. Vitamin E, fasting and post prandial plasma glucose levels were estimated. Electrophysiological parameters like motor distal latency, amplitude and conduction velocity were recorded.

Results: Vitamin E supplemented and placebo supplemented PND patients showed no statistical significant difference in mean age, height, weight, body mass index, waist and duration of disease. Vitamin E supplementation showed statistically significant increase in serum vitamin E and decrease in fasting and 2-h plasma glucose levels as compared to placebo group. Analysis of electrophysiological parameters of right and left motor nerve depicts statistically significant decrease in mean motor distal latency and increase in amplitude and conduction velocity after vitamin E supplementation when compared with placebo group. All the analyzed electrophysiological parameters were correlated with 2-h plasma glucose and vitamin E levels in both the study groups.

Conclusion: Present study revealed that PND patients were ameliorated following supplementation of vitamin E. This study may help in prevention of further complications of diabetic polyneuropathy.

Keywords: Type 2 diabetes mellitus; polyneuropathy; electrophysiology; vitamin E

Introduction

Diabetes mellitus is a global problem. It is estimated to increase from 4% in 1995 to 5.4% by the year 2025. The International Diabetes Federation (IDF) estimated the total number of diabetic subjects to be around 40.9 million in India and this is further set to rise to 69.9 million by the year 2025. The prevalence of diabetes is rising more rapidly in middle and low-income nations.[1] Despite increasing knowledge regarding risk factors for type 2 diabetes and evidence for successful prevention programmes, the incidence and prevalence of the disease continues to rise globally. Diabetes mellitus a metabolic disorder is one among the diseases that affects peripheral nervous system and symptomatic neuropathy in uncontrolled diabetes is one of the commonest long term incapacitating complications.[2] A widely accepted definition of diabetic peripheral neuropathy is the presence of symptoms and/or signs of peripheral nerve dysfunction after exclusion of other causes. It is estimated that 35% to 45% of type 2 diabetic patients have diabetic polyneuropathy.[1] The pathogenesis of diabetic polyneuropathy is multifactorial, including increased mitochondrial production of free radicals

Corresponding author

Mr. Pravin Dhepe

Lecturer, Department of Physiology, S.N. Medical College, Bagalkot, Karnataka, India.

Email: dhepe_pravin@yahoo.com

due to hyperglycemia induced oxidative stress.[3-5] It has been established that electro diagnostic assessments are sensitive, specific and reproducible measures of the presence and severity of polyneuropathy. Nerve conduction study is widely used for the assessment of diabetic polyneuropathy not only to evaluate the degree of abnormality but also to document serial changes in the clinical course of the disease.[2] Multiple consensus panels recommend the inclusion of electrophysiological testing (Nerve conduction studies and electromyography) in the evaluation of diabetic neuropathy. In many instances if the diabetic peripheral neuropathy is diagnosed earlier, it can be treated, at least in the initial stages. The early and precise detection can help in better understanding the pattern of patho-physiological changes as well as in controlling crippling illness like peripheral neuropathy.[6] Vitamin E plays a central role in the health and maintenance of central nervous system. Treatment with Vitamin E may alter the development or progression of neuropathy or other micro vascular complications of diabetes.[7] Researchers concluded that vitamin E is important in the re-growth of damaged nerve tissue following nerve damage. Vitamin E has the ability to protect neuronal tissue in several neurodegenerative disorders including Alzheimer's disease.[8] The studies of Jargar et al revealed that supplementation of α-tocopherol improve glucose transport and insulin sensitivity in diabetic rats.[9] The study of Paolisso also showed a relationship between vitamin E (α-tocopherol) and glucose metabolism.[10] Hence, the present study was designed to evaluate the effect of vitamin E in the alteration of electrophysiological parameters (latency, amplitude and conduction velocity) of motor nerve in polyneuropathic type 2 diabetes mellitus.

Materials and Methods

Source of data: The present study was carried out in the Department of Physiology, SN Medical College and HSK Hospital and Research Centre, Bagalkot, Karnataka in collaboration with Tulsigirish Diabetes Hospital and Diabetes Research Foundation Bagalkot, Karnataka and Department of Biophysics, Government Institute of Science, Aurangabad, Maharashtra. The Study duration was for a year from October 2015 to October 2016. A total of 60 male polyneuropathy type 2 diabetes mellitus patients (n=60) in the age range of 35-65 years were selected for the study. The details of study were explained and informed consent was taken from each of the subjects. The study protocol was approved by Institutional Ethical Committee of SN Medical College, Bagalkot before the study being started.

Study groups: Present study is a prospective randomized controlled trial. Out of 60 polyneuropathic type 2 diabetes mellitus patients, 30 patients were treated with vitamin E tablet supplement (Tocopheryl Acetate IP, 200mg, manufactured by Merck Limited, Goa, India) and served as Group I; whereas, 30 patients were treated with placebo tablet (which do not contain vitamin E) supplement served as Group II. The study subjects of both the groups were given a daily dose with their respective tablet. Study parameters were evaluated after six months of treatment.

Inclusion criteria: Male individuals suffering from type 2 diabetic polyneuropathy and age above 30 years were included in this study.

Exclusion criteria: Patients who had physical deformities, individual suffering from any chronic illnesses other than diabetes, individual with history of chronic exposure to substances which result in altered neuronal functions and individuals suffering from any neurological disease other than diabetic polyneuropathy were excluded from this study.

Demographic and clinical data: All study subjects were examined and physical examination included determination of anthropometric indices (age, height, weight, body mass index and waist circumference), duration of disease and blood pressure measurements. Anthropometric measurements (height and weight) were taken by using scales on bare foot. Waist circumference was measured such as midway between lateral lower ribs and iliac crest after gentle expiration while patient was standing (in centimeters). Body mass index (BMI) was calculated by using Quetelet's Index.[11] Blood pressure was recorded using a mercury sphygmomanometer with consideration of 120 / 80 mmHg as cut off normal value with standard protocol of measurement.

Biochemical parameters: Both fasting and post prandial blood glucose (2h-plasma glucose) levels were estimated by glucose oxidase (GOD/POD) method.[12] Serum vitamin E was estimated by the plain non-antibody coated plate ELISA method of Jargar et al.[13]

Electrophysiological parameters of median nerve: Motor nerve conduction study of median nerve was performed on both arms and exact location of median nerve in an environment with room temperature ranging from 23°C to 25°C using computerized RMS EMG EP MK II machine and surface electrodes. With

the help of stimulating electrodes supramaximal stimulation was given first at the wrist then at elbow to obtain compound muscle action potential (CMAP). The Distance between wrist and elbow was measured. The recording (active) electrode was placed close to the motor point of Abductor Pollicis Brevis muscle and reference electrode 3cm distal to the active electrode at first metacarpophalageal joint. Ground electrode was placed between stimulating and recording electrodes.[14] Motor Distal latency (MDL), Amplitude (Amp) and Conduction Velocity (CV) were measured.

Statistical Analysis: Analysis of data was done using Microsoft Excel and EPI INFO 2002. Standard statistical methods were used to determine the mean and standard deviation (SD). Paired t-test was used to compare the results of various study parameters in the two groups. All the values were quoted as the mean ± SD. The *p* value of <0.05 was considered statistically significant difference and represented y asterisk'*' between two groups. Correlation between the variables was examined using the Pearson's correlation coefficient.

Results

The clinical data of polyneuropathic diabetic patients after six months supplementation in Group I (vitamin E supplemented) and Group II (placebo supplemented) is listed in Table 1. Vitamin E supplemented diabetics patients and placebo supplemented diabetic patients showed no statistical significant difference between mean age in years (55.93 vs 50.64, p=0.1008), height in centimeters (170.21 vs 169.64, p=0.6414), weight in kilograms (60.20 vs 63.50, p=0.3811), waist circumference in centimeters (31.33 vs 32.64, p=0.2156), body mass index in kg/m^2 (21.37 vs 22.06, p=0.3273), and duration of disease in years (8.93 vs 7.46, p=0.0825). But there was statistically significant difference in systolic blood pressure (130.27 vs 138.14 mmHg, p=0.0084) and diastolic blood pressure (83.20 vs 89.00 mmHg, p=0.0005) between Group I and Group II.

In Table 2, Group I (vitamin E supplemented) showed statistical significant increase and percent change in mean serum vitamin E level (6.39±0.23mg/dL) which is 52.58% elevation, fasting blood glucose level (131.67±4.84mg/dL) which is -7.95% reduction, post prandial blood glucose level (208.40±5.77mg/dL) which is -11.28% reduction as compared to Group II (placebo supplemented) (3.03±0.72mg/dL, 142.14±3.80mg/dL and 231.86±7.86mg/dL respectively) after six months of treatment in polyneuropathic diabetic patients.

Group I (vitamin E supplemented) patients showed statistically significant difference in all the electrophysiological parameters of median nerve after six months treatment when compared with Group II (placebo supplemented) (Table 3). Right median nerve showed mean motor distal latency (3.20 vs 3.50 mSec, p = 0.0002, -9.38% reduction), amplitude (8.10 vs 4.80 mV, p = 0.0001, 40.741% elevation) and conduction velocity (50.95 vs 44.25 m/s, p = 0.0001, 13.15% elevation). Left median nerve showed mean motor distal latency (3.16 vs 3.52 mSec, p = 0.0001, -11.39% reduction), amplitude (8.24 vs 5.16 mV, p = 0.0001, 37.38% elevation) and conduction velocity (52.21 vs 43.03 m/s, p = 0.0001, 17.58% elevation).

As regards correlation matrix (Table 4), there was a significant positive correlation detected between 2-h plasma glucose and motor distal latency, serum vitamin E and amplitude; whereas conduction velocity showed negative correlation with 2-h plasma glucose in median nerve (right and left) of both the groups. There was a significant positive correlation detected between serum vitamin E and motor distal latency, serum vitamin E and amplitude; whereas conduction velocity showed negative correlation with serum vitamin E in right median nerve of both the groups. In left median nerve, motor distal latency showed negative correlation in Group I and positive in Group II, amplitude showed positive correlation in Group I and negative in Group II; whereas conduction velocity was negative correlated in both the groups with respect to serum vitamin E.

Table 1: Demographic and Clinical data in both the study groups (n=60)

Data	Group I (Vitamin E Supplement)	Group II (Placebo Supplement)	p-value
Age (years)	55.93±7.39	50.64±9.33	0.1008 [NS]
Height (cm)	170.20±3.26	169.64±3.10	0.6414 [NS]
Weight (kg)	60.20±10.26	63.50±9.66	0.3811 [NS]
Waist circumference (cm)	31.33±2.82	32.64±2.73	0.2156 [NS]
BMI (Kg/m^2)	21.37±3.85	22.06±3.31	0.3273 [NS]
Systolic BP (mmHg)	130.27±7.05	138.14±7.86*	0.0084
Diastolic BP (mmHg)	83.20±2.52	89.00±4.56*	0.0005
Duration of disease (years)	8.93±2.29	7.46±2.11	0.0825 [NS]

BMI: Body mass index; BP: Blood pressure. All the values quoted as the Mean ±Standard deviation. Paired t-test was used to compare the results between two groups. The p value of <0.05 was considered statistically significant difference and represented by asterisk '*'. NS: statistically not significant.

Table 2: Biochemical parameters after treatment in both the study groups (n=60)

Biochemical Parameters	**Group I** (Vitamin E Supplement)	**Group II** (Placebo Supplement)	p-value	**Percent change** (Group I vs Group II)
Serum Vitamin E (mg/dL) Fasting	6.39±0.23	3.03±0.72*	0.0001	52.58% (elevation)
Plasma Glucose (mg/dL)	131.67±4.84	142.14±3.80*	0.0001	-7.95% (reduction)
2-h Plasma Glucose (mg/dL)	208.40±5.77	231.86±7.86*	0.0001	-11.28% (reduction)

All the values quoted as the Mean ±Standard deviation. Paired t-test was used to compare the results between two groups. The *p* value of <0.05 was considered statistically significant difference and represented by asterisk'*'.

Table 3: Electrophysiological parameters of median nerve after treatment in both the study groups(n=60)

Nerve	Electro-physiological Parameters	**Group I** (Vitamin E Supplement)	**Group II** (Placebo Supplement)	p-value	**Percent change** (Group I vs Group II)
Right Median	Motor Distal Latency (mSec)	3.20±0.68	3.50±0.42*	0.0002	-9.38% (reduction)
	Amplitude (mV)	8.10±3.44	4.80±2.16*	0.0001	40.74% (elevation)
	Conduction Velocity (m/s)	50.95±3.37	44.25±5.73*	0.0001	13.15% (elevation)
Left Median	Motor Distal Latency (mSec)	3.16±0.66	3.52±0.44*	0.0001	-11.39% (reduction)
	Amplitude (mV)	8.24±2.12	5.16±2.29*	0.0001	37.38% (elevation)
	Conduction Velocity (m/s)	52.21±3.18	43.03±3.35*	0.0001	17.58% (elevation)

mSec: Milli second; mV: Milli volt; m/s: Meter/second. All the values quoted as the Mean±Standard deviation. Paired t-test was used to compare the results between two groups. The p value of <0.05 was considered statistically significant difference and represented by asterisk '*'.

Table 4: Correlation of electrophysiological parameters with 2-h plasma glucose and serum vitamin E

Nerve	Electro-physiological Parameters	Correlation with 2-h plasma glucose		Correlation with serum vitamin E	
		Group I (Vitamin E Supplement)	**Group II** (Placebo Supplement)	**Group I** (Vitamin E Supplement)	**Group II** (Placebo Supplement)
Right Median	Motor Distal Latency (mSec)	r = 0.1670	r = 0.0772	r = 0.0972	r = 0.0401
	Amplitude (mV)	r = 0.3833	r = 0.0623	r = 0.0497	r = 0.0592
	Conduction Velocity (m/s)	r = -0.3312	r = -0.1899	r = -0.1367	r = -0.2468
	Motor Distal Latency (mSec)	r = 0.0217	r = 0.0719	r = -0.4438	r = 0.0209
Left Median	Amplitude (mV)	r = 0.0975	r = 0.0121	r = 0.1963	r = -0.2938
	Conduction Velocity (m/s)	r = -0.2910	r = -0.2925	r = -0.0789	r = -0.3224

mSec: Milli second; mV: Milli volt; m/s: Meter/second. Correlation between the variables was examined using the Pearson's correlation coefficient (r value).

Discussion

Polyneuropathy is a common complication in diabetic patients. The physiological properties of nerve and muscle were modified due to pathophysiological changes resulting from diabetes.[15] The present study revealed that polyneuropathic type 2 diabetic patients were ameliorated following treatment with the vitamin E supplement (200mg/day). The possible role of vitamin E in the management of diabetic neuropathy may be attributed to the concept of oxidative stress

and antioxidant treatment, which has been shown to play a role in experimental diabetic neuropathy.16 Some researchers have shown that defective nerve conduction in diabetic subjects with peripheral neuropathy may be improved by pharmacological doses of vitamin E supplementation.17 In a randomized, double blind, placebo controlled trial, which evaluated the effect of vitamin E on nerve function in type 2 diabetic patients diagnosed with neuropathy, the results showed a reduction of symptoms.18 Vitamin E is relatively nontoxic and most long term trials had found no negative side effects with its supplementation.19-21 It is observed that the clinical examinations in our study were comparable between Group I and Group II. Only blood glucose values in Group I were reduced significantly as compared to Group II. From these findings, it may be inferred that age, duration of disease and anthropometric indices do not influence in treatment of polyneuropathic type 2 diabetic patients with vitamin E.

The systemic effect of polyneuropathy type 2 diabetes mellitus disease is shown by marked increase in fasting blood glucose and post priandal glucose levels in present study. Our results also showed statistically significant improved fasting glucose and post prandial glucose levels in vitamin E supplemented polyneuropathic type 2 diabetics as compared to placebo supplemented patients. These results elucidate the α-tocopherol attenuated adverse effects from hyperglycemia mediated oxidative damage. Further it revealed that α-tocopherol supplementation improved the free radical defense system potentially and has a protective influence on blood glucose regulation in diabetes.9 In accordance to our study, previous studies[22,23] showed link between hyperglycemia and neuropathy and suggested that the aggressive management of hyperglycemia represent an important strategy to prevent the occurrence of neuropathy in patients with type 2 diabetes. Decreased vitamin E levels in patients with polyneuropathy type 2 diabetes mellitus probably suggests that, it is being consumed for scavenging of free radicals and elucidating the mechanism of disease pathogenesis.9 Our findings confirm an association between oxidative stress and polyneuropathy type 2 diabetes mellitus.

The present study revealed alteration in electrophysiological parameters of median nerves in polyneuropathic type 2 diabetic patients after vitamin E supplementation. Oxidative stress may play an important role in cellular injury from hyperglycaemia. High glucose levels can stimulate free radical production and reactive oxygen species formation. There are many mechanisms by which hyperglycemia causes nerve damage. Hyperglycemia leads to elevated intracellular glucose and cellular toxicity in the endothelial cells of the capillaries associated with peripheral nerves.[24] Another proposal is that the hyperglycemia induces decreased formation of neurotropin like nerve growth factor (NGF) and contributes to neuropathy by preventing normal axonal repair and regeneration.[24] In addition, intracellular glucose can be converted to so called Amadori product, and these in turn can form advanced glycosylated end products (AGEs), which cross-link matrix proteins. This damages the blood vessels.[25] This results in ischemia to the nerves of the patient which may be responsible for neuropathy. Many previous studies[25-27] also found electrophysiological parameters alteration of median nerve suggestive of neuropathy in diabetics. This study also revealed positive association of post prandial blood glucose (2-h plasma glucose) with electrophysiological parameters except nerve conduction velocity. Further there was positive correlation found between serum vitamin E and electrophysiological parameters in right median nerve, whereas in left median nerve showed significant association in both the groups with respect to serum vitamin E. These findings supports positive role of vitamin E supplementation in polyneuropathic type 2 diabetic patients.

Conclusion:

Our findings suggest that the vitamin E is an effective in the management of type 2 diabetes mellitus individuals who have polyneuropathy. Treatment with Vitamin E may alter the development or progression of neuropathy complications of diabetes. This preliminary study has been conducted on a relatively small population and provides evidence of a link between hyperglycemia and polyneuropathy.

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