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Original research article

Assessment of antioxidant supplementation on the neuropathic pain score and quality of life in diabetic neuropathy patients – A randomized controlled study

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ABSTRACT

Background: Diabetes is a chronic disease characterized by elevated blood glucose levels. The appropriate goals in the management of diabetes include maintaining blood glucose levels as close to the normal range as possible, minimizing the adverse effects of free radicals by enhancing antioxidant defenses. Supplementation with appropriate vitamins may therefore be of value in the prevention and treatment of diabetes.

Methods: A total of 92 patients with diabetic neuropathy were enrolled in this randomized controlled study from the general medicine department of a tertiary care hospital. Patients were randomized into two groups viz., usual care ($n = 46$) and intervention group ($n = 46$). Usual care group patients received pregabalin with oral hypoglycemic agents. Patients in the intervention group received vitamin-E along with their regular medicines. Pain intensity and quality of life (QoL) of patients were assessed using Neuropathy Pain Score and RAND 36 questionnaire. Blood samples were analyzed for the levels of random blood sugar level and HbA_{1c} at the baseline and on the 12th week.

Results: Significant ($p < 0.05$) decrease in the random blood sugar level was observed in intervention group when compared with the usual care group and a significant ($p < 0.01$) reduction in total pain score, and a significant ($p < 0.05$) improvement in physical health after 12 week treatment of vitamin-E was observed.

Conclusion: The study concluded that vitamin-E is a natural antioxidant and it is found to be effective in reducing pain score in diabetic neuropathy patients. The future studies may be directed towards extended duration of action.

Introduction

Diabetic neuropathy is a chief health problem since it is responsible for generous morbidity, augmented mortality and diminished quality of life [12]. Peripheral neuropathy starts from the toes and may spread to the feet and lower legs. Decrease in sensation is not only a risk factor for the progress of neuropathic foot ulcers but also for neuropathic pain. It can also be a sign of polyneuropathy [2,7,27]. Neuropathic pain can extend as pain, tingling, burning and cramps [30].

Diabetic neuropathy is diagnosed on the basis of clinical presentation, clinical assessment, quantitative sensory testing (QST), electrophysiological study (latency, amplitudes and NCV of sensory and/or motor nerve) and other methods of assessment [17]. Diabetic peripheral neuropathies are managed either by pathogenetic treatments or symptomatic treatment. Pathogenetic treatments do not treat symptoms, but are targeted known pathogenetic mechanisms [21].

Treating this neuropathic pain is difficult and usually does not respond to standard analgesics.

Though there are medications like opioid analgesic, antiepileptics and antidepressants for the treatment of neuropathic pain, they are limited in their efficacy since they have considerable side effects [6,14,23,29]. Furthermore, these medications are only designed to modulate symptoms without influencing the underlying neuropathy. Potential forms of treatment that have emerged from the current concepts on the pathogenesis of diabetic neuropathy include the reduction of increased flux through the polyol pathway using aldose reductase inhibitors such as alrestatin [14,23], substitution of myo-inositol [10,25], inhibition of the formation of advanced glycation end products by aminoguanidine [2], correction of depleted neurotrophic factors by nerve growth factor substitution [14], elimination by vasodilators of endoneurial hypoperfusion resulting in hypoxia [24], correction of alterations

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in essential fatty acid metabolism by γ-linolenic acid [14,29], and substitution of acetyl-L-carnitine [22] and they have no action on the progressions by which hyperglycaemia leads to cell damage.

The state of hyperglycaemia persuades an increased production of oxygen free radicals in the mitochondria i.e. oxidative stress, which leads to the activation of the four known pathways like polyol pathway, hexosamine, protein kinase-C and increased oxidative stress which has been proposed to be one of the major causes of the hyperglycemia-induced trigger of diabetic complications [28]. Therefore, antioxidants may be useful in the treatment of diabetic neuropathy. Moreover, benefits have been observed with antioxidants like α-lipoic acid and vitamin-E [18]. In the light of this, a potential basis is provided for treating diabetic neuropathy using vitamin-E. Only less numbers of studies have been carried out with vitamin-E in diabetic patients with peripheral neuropathy [6,30]. Furthermore, this type of study is not reported in Indian population. With this background, the current study was aimed to explore the role of vitamin-E supplementation on diabetic neuropathy patients.

Materials and methods

Study protocol and recruitment

The study was approved by the Institutional Ethical Committee (196/IEC/2011) and it was undertaken in the general medicine department in SRM Medical College hospital and research centre, Kattankulathur, Chennai, Tamil Nadu, India. This is a randomized open label study. A total of 92 patients with diabetic neuropathy aged between 35 and 65 years, either sex, without co-morbidities, on oral hypoglycemic agents (either metformin or glibenclamide or its combination), having disease ≤10 years with HbA_{1c} level >7% were included in the study. None of the patients were on antioxidant supplement during recruitment. Patient with history of dementia, on treatment with antidepressant therapy, type-1 diabetes, juvenile diabetes, pregnant women and lactating mothers, voluntary withdrawal and significant hepatic and renal dysfunction were excluded from the study. Written consent was obtained from all participants.

Sample size calculation

Considering α error at 0.05% and 80% power ($1 - \beta = 0.8$) of study with an approximate 8.5% difference between two groups for a significant increase in neuropathic pain score with the standard deviation of 0.05 using 1:1 ratio of independent sample *t*-test, 46 patients must complete the study in each group. Considering 20% dropout, 56 patients should be included in each group.

Study design

Patients satisfying above criteria were included in the study and divided into two groups namely usual care group ($n = 46$) and intervention group ($n = 46$). Enrolled patients were randomized by using computer assisted randomization procedure. Usual care group patients received oral hypoglycaemic drugs (either glibenclamide-5 mg or metformin-500 mg), pregabalin tablets (Preganerve, 45 mg, oral, at night time) and intervention group patients received vitamin-E (Evion – 400 capsules, oral) supplementation along with their regular oral hypoglycemic drugs and pregabalin tablets for a period of three months. All the patients' pain intensity and quality of life (QoL) parameters were assessed using NPS questionnaire and RAND 36. Biochemical parameters like random blood sugar level (RBS) and glycated haemoglobin (HbA_{1c}) also were measured at the baseline and at the end of three months. Neuropathic pain scale (NPS) and RAND-36 health survey questionnaire questionnaire were also administered at baseline and at the end of the study. NPS measurement was performed by the physician using 10 g monofilament (vibration perception) testing.

Statistical analysis

Data are expressed as mean ± SD. The probability value less than 0.05 was considered for statistical significance. Demographic characteristics like age and gender, baseline and final visit data were used to assess response rates by comparing usual care and intervention group. Student's *t* test was used for the comparisons within the groups. One-way ANOVA Bonferroni multiple comparison test was used for the comparisons between groups using graph pad prism version 4.03, GraphPad Software, Inc. (USA).

Results

A total of 129 patients attended the screening phase for diabetic neuropathy, out of which 112 patients met the study criteria. The patients who got enrolled after giving informed consent was randomized into 2 groups to receive usual care and intervention care treatment. Flow chart representing patient distribution is illustrated in Fig. 1.

In the usual care group out of 46 patients, 37 patients were male and 9 patients were female and their mean age was 55 ± 8.1 years, mean BMI was 25.3 ± 3.4 and the mean duration of diabetes was 7.5 ± 2.5 years. Out of 46 patients in intervention group 39 patients were male and 7 were female and their mean age was 54 ± 8.0 years, mean BMI was 24.9 ± 2.5 and the mean duration of diabetes was

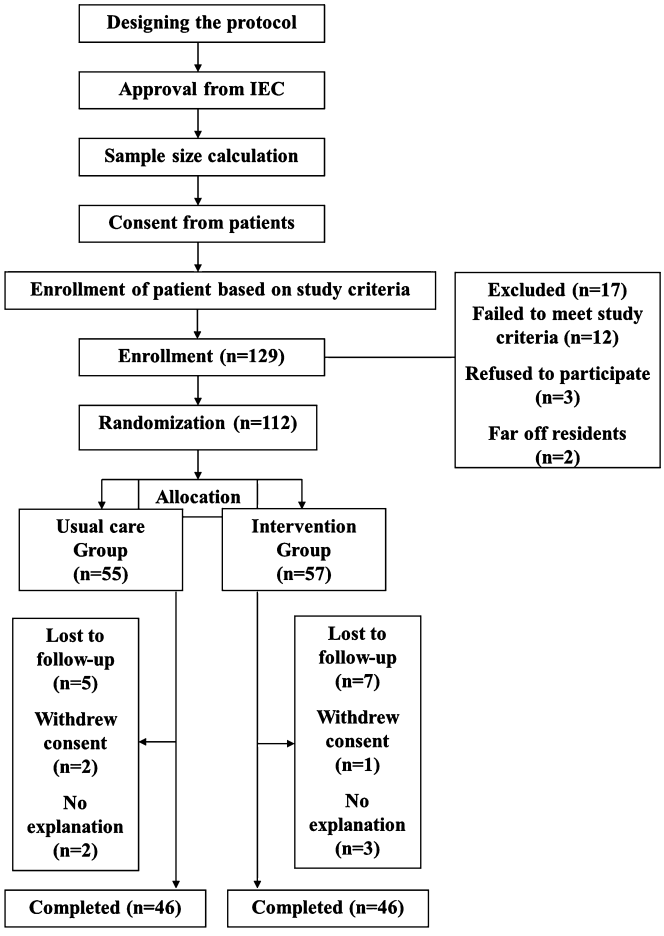

Fig. 1. Study design and CONSORT diagram of flow of participants.