Pharmacological Reports 66 (2014) 44–48

Contents lists available at ScienceDirect

Pharmacological Reports

journal homepage: www.elsevier.com/locate/pharep

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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ARTICLE INFO

Article history:
Received 15 September 2012
Received in revised form 25 June 2013
Accepted 2 August 2013
Available online 30 January 2014

Keywords:
Antioxidant
Vitamin-E
Diabetic neuropathy
Quality of life

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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http://dx.doi.org/10.1016/j.pharep.2013.08.003

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

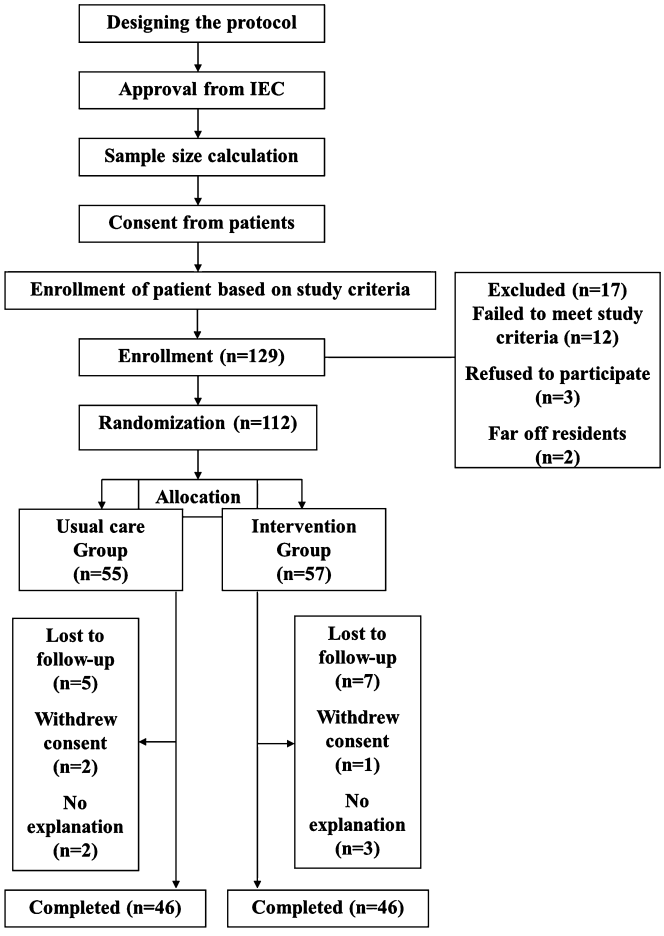

Fig. 1. Study design and CONSORT diagram of flow of participants.

Table 1
Biochemical parameter comparison between usual care and intervention group patients.

Characteristic	Usual care group		Intervention group	
	0 week	12th week	0 week	12th week
RBS	149 ± 32	142 ± 18	161 ± 50	139 ± 13*
HbA_{1C} (%)	8.1 ± 0.1	8.0 ± 0.8	8.2 ± 1.0	8.0 ± 0.9

Data expressed as mean ± SD.
* $p < 0.05$ compared within the group.

7.6 ± 2.4 years. No significant difference was observed in age, BMI and duration of disease between these groups (Table 1).

The glycemic levels like RBS and HbA_{1c} were analyzed in both groups. In usual care and intervention care groups RBS was found to be 149 ± 32 mg/dl, 161 ± 50 mg/dl at the beginning and 142 ± 18 mg/dl, 139 ± 13 mg/dl after 3 months of the therapy respectively. Significant ($p < 0.05$) control in RBS was found in the intervention group (Table 1).

The HbA_{1c} level of usual care and intervention care treated groups were 8.1 ± 0.1% and 8.2 ± 1.0% at the beginning 8.0 ± 0.8% and 8.0 ± 0.9% after 3 months of the therapy respectively. No significant difference was observed in HbA_{1c} within these groups.

Galer and Jenson developed a neuropathic pain scale (NPS). The NPS assesses two global pain domains (pain intensity and unpleasantness), six pain qualities (sharp, hot, dull, cold, sensitive and itchy pain) and two pain locations (deep and surface pain). Scoring the questionnaire was determined by summating the response to all 10 questions. The patients selected a number from 0 to 10 as the response to each question, 0 – indicate that pain had no effect and 10 – indicate a very severe pain. Therefore, a high score indicates a severe pain. The neuropathic pain score was compared between the groups at baseline and on the 12th week. Treatment group baseline (0 week) total pain score was 36.8 ± 12.16 and the final score (12th week) was 30.7 ± 12.16 and usual care group total pain score at baseline was 16.5 ± 7.17 and the final score was 13.7 ± 8.88. The result showed that the patient treated with vitamin-E showed a significant ($p < 0.01$) reduction in pain score. Whereas in the usual care group, no significant change was observed (Table 2).

The RAND-36 item instrument that has been in use since the 1970s and 1980s for various physical and mental functioning measures. The RAND-36 is a multipurpose, short-form health survey with only 36 questions. It is a generalized questionnaire to measure health related quality of life in disease like diabetes, hypertension and asthma and COPD. It contains 36 items and eight scale levels and categorized in 2 domains as physical and mental health summary measures. The total score of all these two domains gives the overall quality of life estimate of each patient. The score ranges from 0–100, where 0 – indicates poorer quality of life. A total score above 50 is considered as clinically significant quality of life. Comparison of RAND 36 score among the groups was shown in Table 3. The results indicated that intervention group showed significant ($p < 0.05$) increase in physical health in comparison to usual care. No significant difference was observed between these groups in mental health RAND 36 scales. Similar results were observed in total RAND 36 score also.

Table 2
Neuropathic pain scores compared between usual care and intervention group patients.

Score	Usual care group		Intervention group	
NPS descriptors	Baseline	Week 12	Baseline	Week 12
Intense	4.0 ± 1.64	3.9 ± 2.14	6.5 ± 2.74	5.4 ± 2.47
Sharp	2.5 ± 1.91	2.6 ± 2.03	4.7 ± 2.86	4.4 ± 2.52
Hot	3.7 ± 2.0	2.9 ± 2.2	5.8 ± 3.40	4.4 ± 2.80
Dull	1.4 ± 1.05	1.4 ± 0.91	3.0 ± 2.62	2.1 ± 2.07
Cold	1.5 ± 1.17	1.0 ± 0.52	2.9 ± 2.56	3.4 ± 2.84
Sensitivity	1.1 ± 0.83	0.00 ± 0.00	2.0 ± 1.64	1.7 ± 1.59
Itchy	1.6 ± 1.45	1.7 ± 1.74	3.7 ± 2.34	3.8 ± 2.66
Unpleasant	3.5 ± 1.55	2.8 ± 1.57	6.4 ± 2.47	5.3 ± 2.21
Deep	2.8 ± 1.72	2.5 ± 1.55	5.8 ± 2.28	5.2 ± 2.03
Surface	2.5 ± 1.46	2.5 ± 1.55	4.1 ± 1.89	3.1 ± 2.30
Total	16.5 ± 7.17	13.7 ± 8.88	36.8 ± 12.16	30.7 ± 12.16**

Data expressed as mean ± SD.
** $p < 0.01$ compared within the group.

Table 3
Quality of life scores compared between usual care and intervention group patients.

Descriptors	Usual care group		Intervention group	
RAND 36	Baseline	Week 12	Baseline	Week 12
Physical health	53.3 ± 17.68	55.8 ± 15.62	59.1 ± 18.41	64.6 ± 14.84*
Mental health	50.0 ± 18.37	53.3 ± 17.68	58.8 ± 15.62	60.6 ± 14.18
Total RAND 36	50.0 ± 21.74	51.0 ± 19.15	59.1 ± 18.41	62.6 ± 14.84

Data expressed as mean ± SD.
* $p < 0.05$ compared with the usual care group.

The effect of age on the neuropathy pain scale RAND 36 descriptors between usual care and intervention group was compared at baseline and at the final visit (week 12). The result showed that in patients with 35–50 years of age did not show any significant changes in pain score, whereas in patients with above 50 years of age, the intervention group showed significant ($p < 0.01$) reduction in pain score after 12 weeks of treatment. Results portrayed that quality of life was improved in both usual care and intervention care group regardless of age but the values are not statistically significant (Table 4).

Discussion

Till date, there is no effective treatment to control the development and progression of diabetic neuropathy. The goals of current therapeutic treatments are to control the glycemic level with supplementation of aldose reductase inhibitors or gamma linoleic acid. ACE inhibition has been shown to be the most effective therapeutic intervention to postpone the progression of microalbuminuria in patients with type 1 and type 2 diabetes mellitus, as well as to delay progression of disease in patients with established nephropathy.

Table 4
Effect of age on NPS and RAND 36 scale in study groups.

Scale	Age group (in years)	Baseline		Final visit (week 12)	
		Usual care group	Intervention group	Usual care group	Intervention group
NPS	35–50	25.75 ± 7.36	22.16 ± 6.88	21.83 ± 8.86	21.0 ± 9.38
	>50	26.54 ± 3.14	24.50 ± 7.42	24.50 ± 2.12	16.0 ± 9.01**
RAND 36	35–50	63.50 ± 18.11	62.50 ± 17.63	65.33 ± 18.19	65.50 ± 10.34
	>50	56.16 ± 19.69	56.50 ± 10.34	58.50 ± 2.12	59.33 ± 18.19

Data expressed as mean ± SD.
** $p < 0.01$ compared with the usual care group.

Antioxidants are also found to have a significant role in controlling diabetic neuropathy. The present study was designed to assess the diabetic neuropathy pain and quality of life of diabetic neuropathy patients with antioxidant supplements. Totally 92 diabetic neuropathy patients were enrolled in the study. They were divided into two groups i.e. usual care and intervention group. Patients in both the groups were more or less of similar age.

Neuropathic pain scale and RAND 36 scale score were compared between baseline and 12th week of both the group. The treatment group showed significant reduction in total pain score in comparison to the usual care group, which is in accordance with previous reports [15,20].

We found that diabetic neuropathy patient above 50 years of age under vitamin-E therapy showed significant decrease in pain score after the 12th week of treatment in comparison to diabetic neuropathy patients under 50 years of age. The exact mechanism could not be found, but it may be due to the antioxidant property of the vitamin-E which is found to be effective in elderly patients [16,33].

The effect of therapy on improving the pain sensation and quality of life is noted only after 12 weeks treatment. It shows that longer duration of therapy is required in diabetic neuropathy condition [1,13,19] on reducing pain sensation and improving quality of life.

Earlier studies reported that when the glucose level is increased, development and progression of diabetic neuropathy is also increased [4,9,21] and glucose derived oxidative stress may play a role in the progression of diabetic neuropathy [3,18,26]. In our study, as sugar level decreases, the total NPS pain score decreases in the intervention group. Thus the result of our present study confirms the earlier reports.

In our study, we found that as sugar level decreased the quality of life increased in diabetic neuropathy patients. It may be due to greater glucose flux and possibly poor diabetes control [5,11].

During oxidative stress the balance between degeneration and regeneration shifts towards more degeneration [31]. During antioxidant therapy this oxidative stress may be reduced and the balance shifts towards regeneration, antioxidant can inhibit the free radical induced endoneural damage [30] and these can also improve the antioxidant tone in the diabetic individual in whom the antioxidant capacity is defective because of the active polyol pathway [8,32]. These can improve nerve conduction. In our study, inclusion of vitamin-E for 3 months improved the neuropathic pain score and it could be due to above mentioned point.

Conclusion

Supplementation of vitamin-E is effective in reducing some of the pains caused in diabetic neuropathy patients. Even though vitamin-E is effective in pain reduction, the Quality of Life does not show significant improvement. Vitamin-E is effective in reducing the pain in diabetic neuropathy patients of above 50 years of age than patients with below 50 years of age. If the dietary intake of vitamins - E fails to meet the recommended daily allowance, health care professionals should encourage the people with the diabetic neuropathy to increase their intake of vitamins, preferably through the consumption of healthy food sources rich in vitamin or otherwise through the use of appropriate vitamin supplements. The future studies may be directed towards extended duration of treatment.

Conflict of interest

None.

Funding

No financial support and no sponsors for the conduct of the research and/or preparation of the article.

Acknowledgments

The authors would like to thank Dr. K.S. Lakshmi, Dean, SRM College of Pharmacy, Dean and MS SRM Medical College Hospital and Research Centre, SRM University for providing enormous support to carry out this project. Rajanandh MG and Sourabh wish to recognize Dr. J.S. Kumar, Diabetologist for his significant contribution towards the methodology design.

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