Role of Antioxidant on Diabetic Retinopathy Patients-A Randomized Controlled Study

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Abstract: Diabetic retinopathy is a chronic progressive sight threatening disease of the retinal microvasculature associated with the prolonged hyperglycemia and other conditions linked to diabetes mellitus. It is usually due to damage to the tiny blood vessels next to the retina and is commonly caused by diabetes. The present study is aimed to assess the effect of antioxidant supplementation on diabetic retinopathy patients. A total of 92 patients with diabetic retinopathy were enrolled in this randomized controlled study from ophthalmology department of tertiary care hospital. Patients were randomized into two groups viz., usual care (n=46) and intervention group (n=46). Patients in intervention group received vitamin-E along with their regular medicines which usual care group patients received. Demographic details and direct fundus ophthalmoscopy were monitored. Blood samples were analyzed for the levels of random blood sugar level, HbA_{1c} and lipid profile for both groups. Quality of life (QoL) of patients were assessed using RAND 36 questionnaire. No significant difference was observed with respect to glycemic levels between usual care and intervention group but there was significant ($P<0.05$) increase in role physical and role emotional after 12 week treatment of vitamin-E. The study concluded that vitamin - E is natural antioxidant and it is found to be effective in improving QoL in diabetic retinopathy patients, suggesting further investigation is warranted.

Key words: Antioxidant · Vitamin-E · Diabetic Retinopathy · Quality Of Life

INTRODUCTION

Diabetic retinopathy is instigated by damage to blood vessels of the retina. The total number of people with diabetes is projected to rise 439 million in 2030. Diabetic retinopathy is responsible for 1.8 million of the 37 million cases of blindness throughout the world [1, 2]. The forecaster of diabetic retinopathy is the duration of diabetes. After 20 years of diabetes, nearly 99% of patients with type 1 diabetes and 60% with type 2 have some degree on diabetic retinopathy. 33% of patients with diabetes have signs of diabetic retinopathy. People with diabetes are 25 times more likely to become blind than the general population [3, 4].

The retina is a thin layer of lightsensitive tissue that lines the back of the eye. Light rays are focused onto the retina, where they are spread to the brain and taken as the images. The macula is a very small area at the center of the retina [5]. It is responsible for pinpoint vision, lettingfor reading, seeing or recognizing a face. The surrounding part of the retina, called the peripheral retina, is accountableforside or peripheral vision [6].

There are two types of diabetic retinopathy namely proliferative and non-proliferative diabetic retinopathy (NPDR). NPDRis the initial stage of diabetic retinopathy. With this condition, damaged blood vessels in the retina begin to leak extra fluid and small amounts of blood into the eye. Sometimes, deposits of cholesterol or other fats from the blood may leak into the retina.NPDR can cause changes in the eye like hard exudates and macular edema [7]. Hard exudates aredeposition of cholesterol or other fats from the blood that have leaked into the retina.Macular edema is swelling or thickening of the macula caused by fluid leaking from the retina's blood vessels. The macula doesn't function properly when it is swollen [8]. Macular edema is the most common cause of

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vision loss in diabetes.Optical coherence tomography (OCT)is currently used for diagnostic hypothesis, qualitative and quantitative monitoring of the pharmacologic treatment of diabetic macular edema [9, 10].

Diabetic retinopathy usually affects both eyes. People who have diabetic retinopathy often don't notice changes in their vision in the disease's early stages. But as it growths, diabetic retinopathy usually causes vision loss that in many cases cannot be reversed. Protracted hyperglycemia is the major etiologic agent in all of the microvascular complications of diabetes, including diabetic retinopathy [11-13]. The cellular mechanisms through which hyperglycemia acts currently remain unclear. Mechanisms that have been proposed are: hyperglycemia may alter the expression of one or more genes, leading to either increasedor decreased amounts of certain gene products that can alter cellular functions.Glycosylated proteins can undergo a series of reactions, leading to considerable alteration of proteins.Chronic hyperglycemia may produce oxidative stress in cells, leading to the formation of an excess of "toxic end products of oxidation" including peroxides, superoxides, nitric oxide and oxygen free radicals [14].

Therefore, antioxidants may be useful in the treatment of diabetic retinopathy. Moreover, benefits have been observed with antioxidants like vitamin-C and E [15, 16]. In the light of this, a potential basis is provided for treating diabetic retinopathy using vitamin - E. Only less number of studies has been carried out with vitamin-E in diabetic patients with retinopathy. 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 supplementationondiabetic retinopathy patients.

MATERIALS AND METHODS

Study Protocol and Recruitment: The study was approved by Institutional Ethical Committee (200/IEC/2011) and it was undertaken at ophthalmology department in SRM Medical College hospital and research center, Kattankulathur, Chennai, Tamil Nadu, India. This is a randomized open label study. A total of 92 patients with diabetic retinopathy aged between 45 to 65 years, either sex, without co-morbidities, on oral hypoglycaemic agents (either Metformin or Glibenclamideor its combination), with HbA_{1c} level >7% were included in the study. None of the patients were on antioxidant supplement during recruitment. Macular diseases other than diabetic maculopathy, patients

previously submitted to macularphotocoagulation or ocular surgery, including cataractextraction, 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 excludedfrom the study. Written consent was obtained from all participants.

Sample Size Calculation: Considering α error at 0.05 and 80% power (1-β =0.8) of study with an approximate 8.5% difference between two groups for a significant increase in retinopathic 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 for the study and divided into two groups namely usual care group (n=46) and intervention group (n=46). The study was carried out at ophthalmology department of tertiary care hospital, Chennai, Tamil Nadu, India. Enrolled patients were randomized by using computer assisted randomization procedure. Usual care group patients received oral hypoglycaemic drugs (Either Glibenclamide-5mg or Metformin-500mg) and intervention group patients received vitamin-E supplementation along with their regular medicines for a period of three months. Biochemical parameters likerandom blood sugar level (RBS), glycatedhaemoglobin (HbA_{1c}), lipid profile and direct fundus ophthalmoscopy were measured at the baseline and at the end of three months. All the patients' pain quality of life (QoL) were assessed using RAND 36 questionnaire.

RAND-36 Health Survey Questionnaire: The RAND-36 items instrument that have 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. Total score above 50 is considered as clinically significant quality of life.

Statistical Analysis: Data are expressed as mean±SD. The probability value less than 0.05 wasconsidered for statistical significance. Demographic characteristics like age and gender, baseline and final visit datawere used to assess response rates by comparing usual care and intervention group. All the tests were performed using graph pad prism version 4.03, GraphPad Software, Inc. (USA).

RESULTS

Demographic Characteristics: A total of 129patientsattendedthe screening phase for diabetic retinopathy, 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 Figure 1. Out of 112patients, 67 were male and 45were female. The mean age of male and female patients was 54±7.3 years.

In usual care group out of 46patients, 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 7.6±2.4 years. No significant difference was observed in age, BMI and duration of disease between these groups (Table 1).

Glycemic Levels: The glycemic levels like RBS and HbA_{1c} were analyzed for both groups. Inusual care and intervention care groups RBS was found to be 139±13 mg/dl and 142±18 mg/dl at the beginning and 161±50 mg/dland149±32 mg/dl after 3 months of the therapy respectively. No significant change in RBS was observed within these groups (Table 2).

The HbA_{1c} level of usual care and intervention care treated groups was 8.0±0.8%and 8.2±1.0% at the beginning and 8.0±0.8% and 8.1±0.7% after 3 months of the therapy respectively. No significant difference was observed in HbA_{1c} within these groups (Table 2).

Fundus Ophthalmoscopy: Total cholesterol, Triglycerides, LDL-Cholesterol,HDL–Cholesterolwas measured between the groups. In intervention group, there was reduction in total and LDL–Cholesterol when compared with usual care group but there was no change in triglycerides and
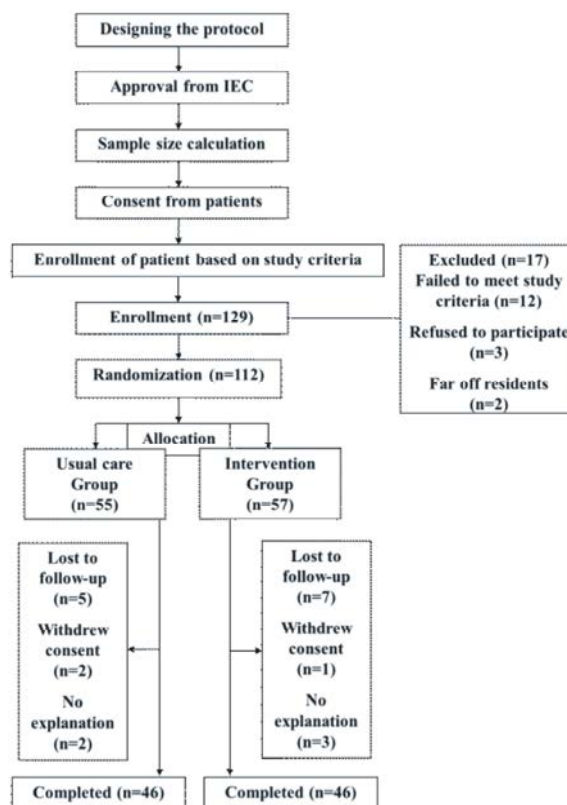

Fig. 1: Study design and CONSORT diagram for flow of participants

HDL-Cholesterol. However, there is no statistically significant changes were observed in any of the cholesterol parameter. The macular thickness in usual care and intervention care was 592±75 and 578±69 respectively. No significant change was observed (Table 2).

Quality of Life (QoL): RAND 36 score was compared between the groups at baseline and on 12th week. The results indicated that treatment group showed significant (P<0.05) increase in role physical and role emotional in comparison to usual care. No significant difference was observed between these groups in other RAND 36 scales. Similar results were observed in total RAND 36 score (Table 3).

Table 1: Demographic detail comparison between usual care and intervention group patients

Characteristic	Usual care Group	Intervention Group
n	46	46
Gender (M/F)	36/10	39/7
Age in years	55±8.1	54±8.0
Duration of disease	7.5±2.5	7.6±2.4
Body mass index (BMI) kg/m^2	25.3±3.4	24.9±2.5

Table 2: Biochemical parameter and fundus ophthalmoscopy comparison between usual care and intervention group patients

Characteristic	Usual care Group	Intervention Group
RBS	161±50	149±32
HbA$_{1C}$(%)	9.6±7.4	8.9±1.0
Total cholesterol	205.7±55.5	197±16.26
Triglycerides	236±102.68	235±34.56
LDL-C	136±42.45	128±18.45
HDL - C	34.46±5.78	34.14±5.16
Macular thickness	592±75	578±69

Data is expressed in mean±SD,[a] p<0.05 compared within groups, [b] p< 0.01 compared within group; HbA$_{1C}$= Glycatedhaemoglobin; LDL-C = Low density lipoprotein cholesterol; HDL-C = High density lipoprotein cholesterol.

Table 3: Quality of life score comparison between usual care and intervention group patients

RAND 36 Descriptors	Usual care Group	Intervention Group
Physical function	56.80±21.10	56.44±25.03
Role physical	40.00±47.01	50.96±47.11[a]
Body pain	44.33±22.26	43.47±20.02
General health	51.56±09.60	50.21±11.53
Vitality	52.01±10.89	53.22±13.21
Social function	57.46±20.51	53.48±20.27
Role emotional	41.20±47.63	48.07±48.45[a]
Mental health	54.16±09.76	53.86±10.97
Physical health	49.00±16.19	50.86±17.07
Mental health	51.28±13.78	51.76±13.54
Total RAND 36	49.72±17.27	51.20±17.35

Data is expressed in mean±SD,[a] p<0.05 compared within groups, [b] p< 0.01 compared within group

DISCUSSION

Totally 92 diabetic retinopathypatients were enrolled in the study. They were divided into two groups i.e. usual care and interventiongroup.Patients in both the groups were more or less of similar age.Diabetic macular edema is a condition characterized byanatomic thickening of the retina, due to the presence of abnormalfluid accumulation within the retina. It is a result ofblood-retinal barrier breakdown [17]. The OCT measures the retinal thickness by consideringthe distance between the anterior surface of the retinal pigmentedepithelium RPE-choriocappillaris region and the vitreoretinalinterface [18]. Even though some improvement was observed in the retinopathy with respect to macular edema and lipid profile in intervention group, it was statistically not significant.

RAND 36 scale score was compared between baseline and 12[th]week of both the group. Treatment group showed significant reduction in total pain score in comparison to usual care group, which is in accordance with previous reports [19-21]. We found that diabetic retinopathy patient above 50 years of age under vitamin-E therapy showed significant decrease in pain score after 12th week of treatment in comparison to diabetic retinopathy patient

below 50 years of age. The exact mechanism could not be found, but it may be due to antioxidant property of the vitamin-E which is found to be effective in elderly patients [22, 23].

The effect of therapy on quality of life is noted only after 12 weeks treatment. It shows that longer duration of therapy is required in diabetic retinopathic condition [24] on reducing pain sensation and improving quality of life.

Earlier studies reported that when glucose level is increased, development and progression of diabetic retinopathyisalsoincreased [25, 26] and also glucose derived oxidative stress may play a role in progression of diabetic retinopathy [27]. In our study also as sugar level increases all the descriptors of NPS pain score also increases. The result of our present study confirms the earlier reports.

In our study, we found that as sugar level increased the quality of life decreases in diabetic retinopathy patients. It may be due to greater glucose flux and possibly poordiabetes control [28]. During oxidative stress the balance between degeneration and regeneration shifts toward more degeneration [29]. 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 [31]. These can improve nerve conduction. In our study, inclusion of vitamin-E for 3 months improved the retinopathic 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 retinopathy 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 retinopathic patients of above 50 years of age than patients with below 50 years of age. If thedietary intake of vitamins-E fails to meet the recommended daily allowance, health care professionals should encourage the people with the diabetic retinopathyto increase their intake of vitamins, preferably through the consumption of healthy food sources rich in vitaminor otherwise through the use of appropriate vitamin supplements. The future studies may be directed towards extended duration of treatment.

ACKNOWLEDGEMENTS

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