Vision Related Quality of Life in patients with Diabetic Macular Edema receiving Intravitreal Ranibizumab

Allen Mathew[a], Simon George[a], S Remadevi[a]

a. Department of Ophthalmology, Regional Institute of Ophthalmology, Thiruvananthapuram, Kerala, India*

Published on 21st October 2024

ABSTRACT

Introduction: Diabetic macular edema is the most common cause of vision impairment in individuals with diabetic retinopathy. Diabetic macular edema develops due to leakage of fluid from diseased microvasculature in the retina. Various treatment modalities exist for diabetic macular edema, the present gold standard being the use of intravitreal anti-VEGF agents.

Aim: To assess the changes in vision-related quality of life among patients with diabetic macular edema receiving intravitreal Ranibizumab.

Materials and Methods: A hospital-based observational longitudinal study was conducted.

Demographic details as well as details about the disease were collected. A validated National Eye Institute Visual Function Questionnaire (using the interviewer-administered format of the questionnaire) was administered by a single interviewer, on the day before the scheduled intravitreal Ranibizumab injection and again repeated over a period of 3 months at 2, 6 and 12 weeks from the date of the first injection.

The overall composite score and the various subscale scores for visual function were computed using a validated scoring method for each patient based on their response to the questionnaire.

Analysis of data was done using Statistical Packages for Social Sciences Version 24 software. Changes in the various parameters contributing to the vision-related quality of life were studied using analysis of variance for repeated measures. The level of significance was determined by the p-value. A p-value less than 0.05 was considered statistically significant.

Results: The baseline composite score was found to be 38.2±9.1, at 2 weeks 41.0±10.3, at 6 weeks 48.2±14 and at 12 weeks 51.1±15.2. Data analysis showed the increase in the mean value of the baseline composite score to be statistically significant with a p value of 0.000.

All subdomains except general health also showed statistically significant improvement.

Conclusion: Patients diagnosed with diabetic macular edema were shown to have an improvement in their vision-related quality of life following a single injection of intravitreal Ranibizumab. Various subdomains of vision which contribute to the vision-related quality of life except general health were also noted to show statistically significant improvement.

Keywords: Diabetic Macular edema, Ranibizumab, Vision-Related Quality of Life, Diabetes Mellitus, Diabetic Retinopathy

*See End Note for complete author details

INTRODUCTION

Diabetes mellitus is a metabolic disease, known to be a major cause of concern for healthcare systems around the globe. According to World Health Organization statistics, more than 422 million adults globally were suffering from diabetes mellitus in 2014 and a continuous rise in diabetes mellitus prevalence is expected.[1] Diabetic retinopathy is one of the microvascular complications of the disease and among individuals suffering from diabetic retinopathy, diabetic maculopathy has been found to be the leading cause of vision loss. Diabetic maculopathy encompasses focal maculopathy, diffuse maculopathy and ischaemic maculopathy. The prevalence of diabetic macular edema in patients with diabetic retinopathy is 2.7% to 11%.[2-6] In diabetic macular edema, the retinal capillaries become hyperpermeable, due to which fluid extravasates out of the capillaries and accumulates within the macula. The pathogenesis behind diabetic macular edema involves

Cite this article as: Mathew A, George S, Remadevi S. Vision Related Quality of Life in patients with Diabetic Macular Edema receiving Intravitreal Ranibizumab. Kerala Medical Journal. 2024 Oct 21;17(3):133–43. | DOI: https://doi.org/10.52314/kmj.2024.v17i3.662

Corresponding Author:
Dr Allen Mathew, Department of Ophthalmology, Regional Institute of Ophthalmology, Thiruvananthapuram, Kerala, India.
E-mail: allenmathew23@gmail.com

a complex interplay of various pathways. The final cause for macular edema could be either a breakdown of the inner blood retinal barrier which occurs due to increased levels of vascular endothelial growth factor (VEGF) or due to vitreomacular traction.

VEGF was first described in 1983 and was initially named vascular permeability factor. It acts as an endothelial-specific mitogen and is able to induce angiogenesis in vivo. VEGF is not a single chemical substance, but rather a group of seven secreted glycoproteins namely VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E and placental growth factors 1 and 2. Among these, VEGF-A, a 45 kilo Dalton homodimer glycoprotein has been known to play a vasoproliferative role in the pathogenesis of proliferative diabetic retinopathy and at the same time it also acts as a potent vasopermeability factor and plays a key role in the pathogenesis of diabetic macular edema. Both the retinal pigment epithelium as well as the neurosensory retina are known to release VEGF.

Clinically significant macular edema (CSME) has been defined in the Early Treatment for Diabetic Retinopathy Study (ETDRS)[7] as either retinal thickening within 500 micrometres of the centre of the macula or when hard exudates are noted within 500 micrometres of the centre of the macula and with an associated retinal thickening or when there is a retinal thickening of one disc area or larger, of which a part needs to lie within one disc diameter of the centre of the macula. Diabetic macular edema (DME), on the other hand, has been defined by the American Academy of Ophthalmology (AAO), as the presence of any retinal thickening or hard exudates within 1 disc diameter of the centre of the macula. Whichever is the definition used to diagnose macular edema in the context of diabetic retinopathy, treatment is imperative to improve the vision of the patient. Various modalities of treatment exist for diabetic macular edema. Laser photocoagulation of the retina served as the mainstay of treatment for diabetic macular edema till recently but has now largely been replaced by the use of intravitreal anti-VEGF agents.

Anti-VEGF agents belong to the group of monoclonal antibodies, which are engineered from mouse antibodies and have the majority of the mouse genetic sequence replaced by human gene sequence to reduce immunogenicity. Ranibizumab, an anti-VEGF agent, is the antigen-binding fragment of a recombinant humanized monoclonal antibody and it specifically binds to VEGF, thereby preventing the interaction between VEGF molecule and its receptor. Ranibizumab has a molecular weight of 48,000 Daltons and has demonstrated good penetration into the retinal pigment epithelium when administered intravitreally.

As per the Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol I, intravitreal Ranibizumab more effectively improves visual acuity than focal or grid laser treatment for centres involving diabetic macular edema.[8] No difference in visual acuity was noted at 5 years irrespective of whether aflibercept, bevacizumab or ranibizumab is used in patients with diabetic maculopathy and a visual acuity of better than 6/15.[8]

METHODOLOGY

Study Design: Hospital-based observational longitudinal study

Study Setting: A tertiary eye care hospital at Trivandrum, Kerala

Study Population: Patients diagnosed with diabetic macular edema and admitted for intravitreal Ranibizumab injection at a tertiary eye care hospital in Trivandrum, Kerala.

Study Subjects: Consecutive patients diagnosed with diabetic macular edema, who fulfil the eligibility criteria were recruited into the study, after receiving their informed consent.

Eligibility Criteria

1) Inclusion Criteria: Patients diagnosed with diabetic macular edema in the outpatient department (OPD) at a tertiary eye care hospital at Trivandrum and admitted by their treating ophthalmologist for intravitreal Ranibizumab injection. Diabetic macular edema is defined as the presence of retinal thickening or hard exudates within 1 disc diameter of the centre of the macula. (Definition by American Academy Of Ophthalmology)

2) Exclusion Criteria: Patients having other ocular pathology which can interfere with their vision related quality of life - viz central corneal ulcer, central corneal opacity, glaucoma and mature cataract.

Patients not willing to give consent for the study.

Patients less than 18 years of age.

Sample Size Calculation

Based on the study conducted by Elif Betel Turkoglu, Erkan Celic,. et al[9] change in the NEI VFQ 25

Table 1. Descriptive statistics showing score and corresponding SD for the overall vision-related quality of life during the period of study

Time of the study at which the scores where calculated	Score for the overall vision related quality of life	Standard Deviation
Baseline	38.2	9.1
At 2 weeks	41.0	10.3
At 6 weeks	48.2	14.0
At 12 weeks	51.1	15.2

Composite score was 12.4 with a standard deviation of the difference between the pairs being 18.2.

Substituting these values in the formula

$$_2N = (Z_\alpha + Z_\beta\left(\frac{\delta}{\sigma}\right)$$

$2 \propto = 1.96$

$Z\beta = 0.84$ σ = Standard deviation of difference between pair δ = Effect size (change in mean)

N = 17

Since the parent study I have analysed[9] is analysing changes in the value of a particular variable, hence the above formula was used for sample size calculation.

As per the sample size calculation, only 17 participants were needed. However analysing the patient load at the study centre, the time period for which my study had gained clearance and to strengthen the output of my study, I enrolled 40 participants for the study.

Table 2. Showing test of within subject effects for the overall vision related quality of life score

Source	Type III Sum of Squares	dF	Mean Square	F	p value
Overall vision related quality of life score	4353.606	3	1451.202	37.110	0.000

Sampling Technique

Consecutive patients satisfying the eligibility criteria were recruited into the study.

Method of Data Collection

Patients diagnosed with diabetic macular edema and admitted for intravitreal Ranibizumab injection, who fulfil the eligibility criteria, were recruited into the study. Demographic details like age and gender, as well as, details about the disease like duration of diabetes mellitus, type of diabetes mellitus, treatment currently taken by the patient for diabetes mellitus was collected. Visual acuity for distance was recorded using the Snellen distance visual acuity chart and expressed as log MAR. Baseline value of the central macular thickness in micrometres from optical coherence tomography report was recorded. Indirect Ophthalmoscopy with a +20 dioptre lens was done to find out the type of diabetic retinopathy in the eye planned for injection prior to the procedure. A validated National Eye Institute Visual Function Questionnaire (using the interviewer administered format of the questionnaire) was administered by a single interviewer, after obtaining

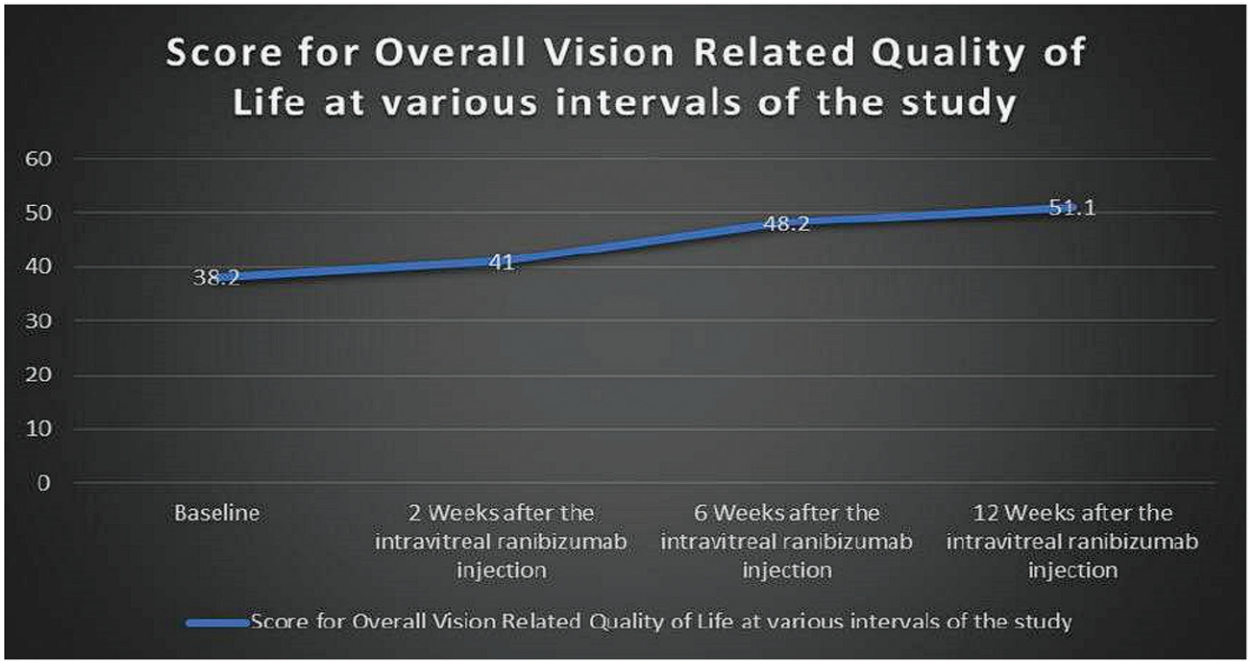

Figure 1. **Changes in the score for the overall vision related quality of life during the period of study**

Table 3. Table showing a test of pairwise comparison for overall vision-related quality of life score

Time interval at which the score for the overall vision related quality of life was measured (A)	Time interval at which the score for the overall vision related quality of life was measured (B)	Mean Difference (A) - (B) Mean Difference (A) - (B)	Standard Error	p Value
Baseline	At 2 weeks	-2.787	0.986	0.044
Baseline	At 6 weeks	-9.979	1.620	0.000
Baseline	At 12 weeks	-12.882	1.943	0.000
At 2 weeks	Baseline	2.787	0.986	0.044
At 2 weeks	At 6 weeks	-7.192	1.212	0.000
At 2 weeks	At 12 weeks	-10.095	1.554	0.000
At 6 weeks	Baseline	9.979	1.620	0.000
At 6 weeks	At 2 weeks	7.192	1.212	0.000
At 6 weeks	At 12 weeks	-2.903	0.690	0.001
At 12 weeks	Baseline	12.882	1.943	0.000
At 12 weeks	At 2 weeks	10.095	1.554	0.000
At 12 weeks	At 6 weeks	2.903	0.690	0.001

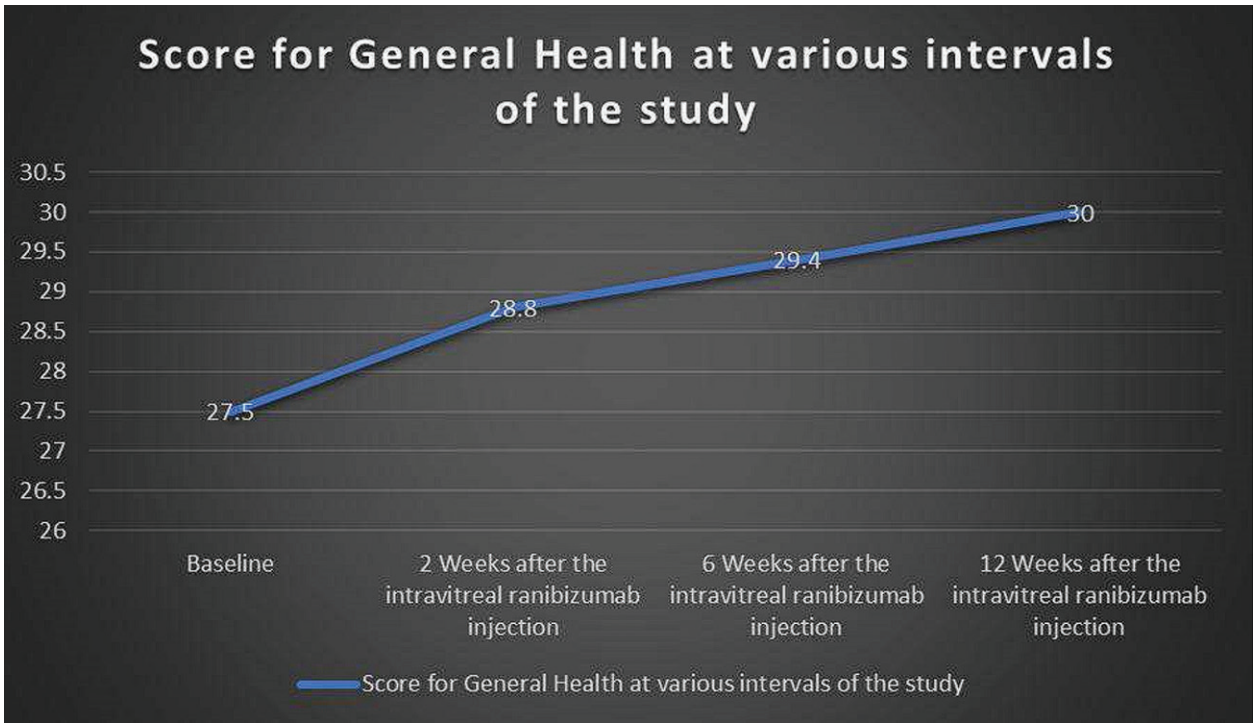

Figure 2. **Changes in the score for general health during the period of study**

informed consent from the patient, on the day prior to the scheduled intravitreal Ranibizumab injection and again repeated over a period of 3 months at 2, 6 and 12 weeks from the date of first injection – either when the patient reported for follow up to the hospital or over the telephone. Out of the 25 questions in the National Eye Institute Visual Function Questionnaire 25, 5 questions were eliminated (2 questions pertaining to driving, 1 question regarding vision specific social functioning, 1 question regarding distance vision activity and 1 question regarding ocular pain) from my study, as these questions are not applicable to my study subjects. Hence, I have administered 20 questions in the questionnaire for my study.

Method of Outcome Measurement

The overall composite score and the various subscale scores for visual function were computed using a validated scoring method for each patient based on their response to the questionnaire.

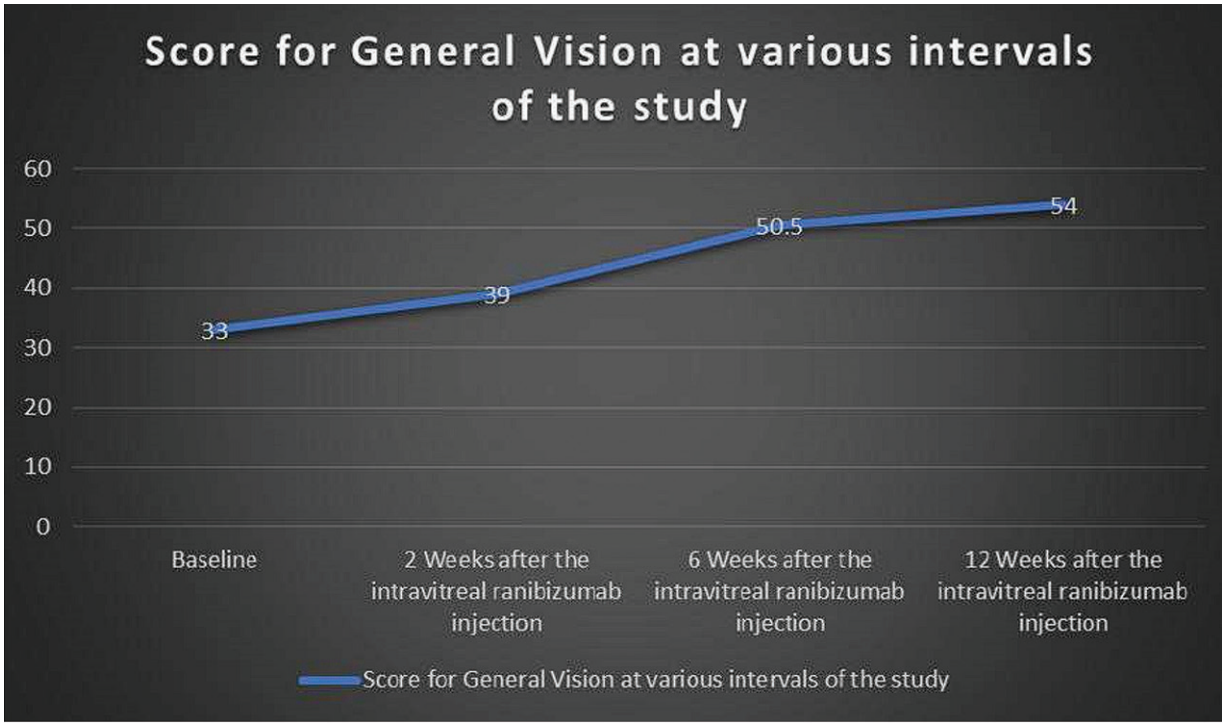

Figure 3. **Changes in the score for general vision during the period of study**

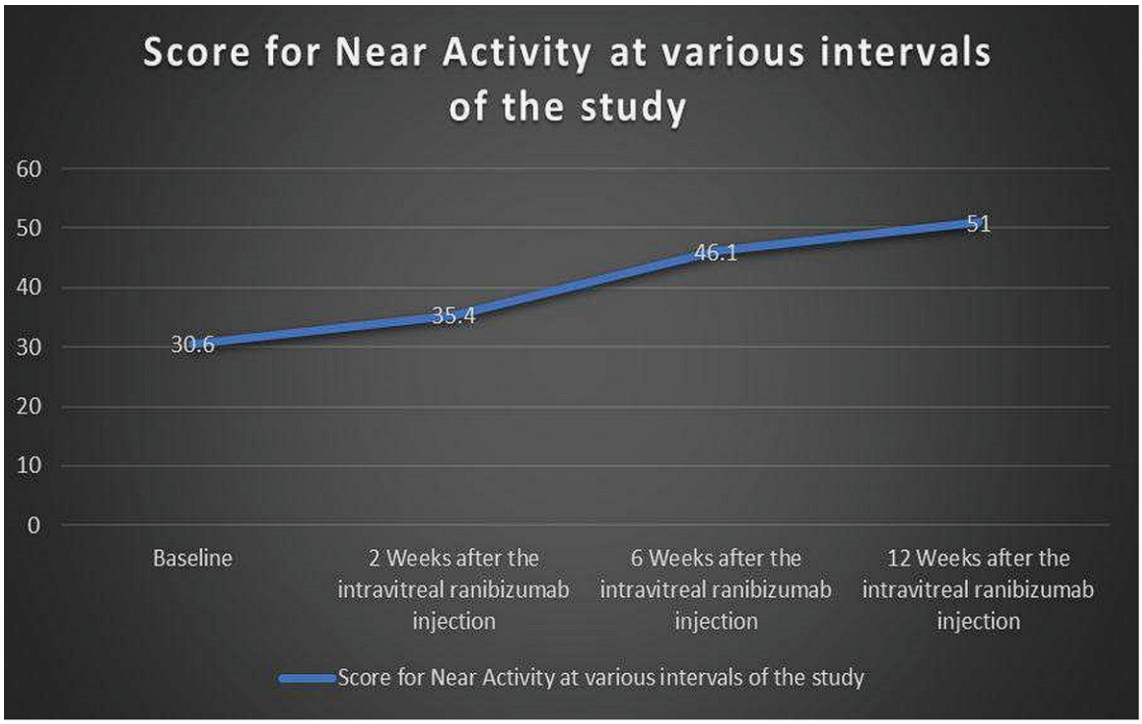

Figure 4. **Changes in the score for near activity during the period of study**

Method of Data Analysis

All statistical data collected was entered into Microsoft Excel Sheet. Qualitative variables were expressed as proportion while quantitative variables were expressed as mean with standard deviation. Analysis of data was done using Statistical Package for Social Sciences (SPSS) Version 24 software. Change in various parameters of vision related quality of life was studied using repeated measures of Analysis of Variance (ANOVA). The level of significance was determined by the p-value. A p-value less than 0.05 was considered statistically significant.

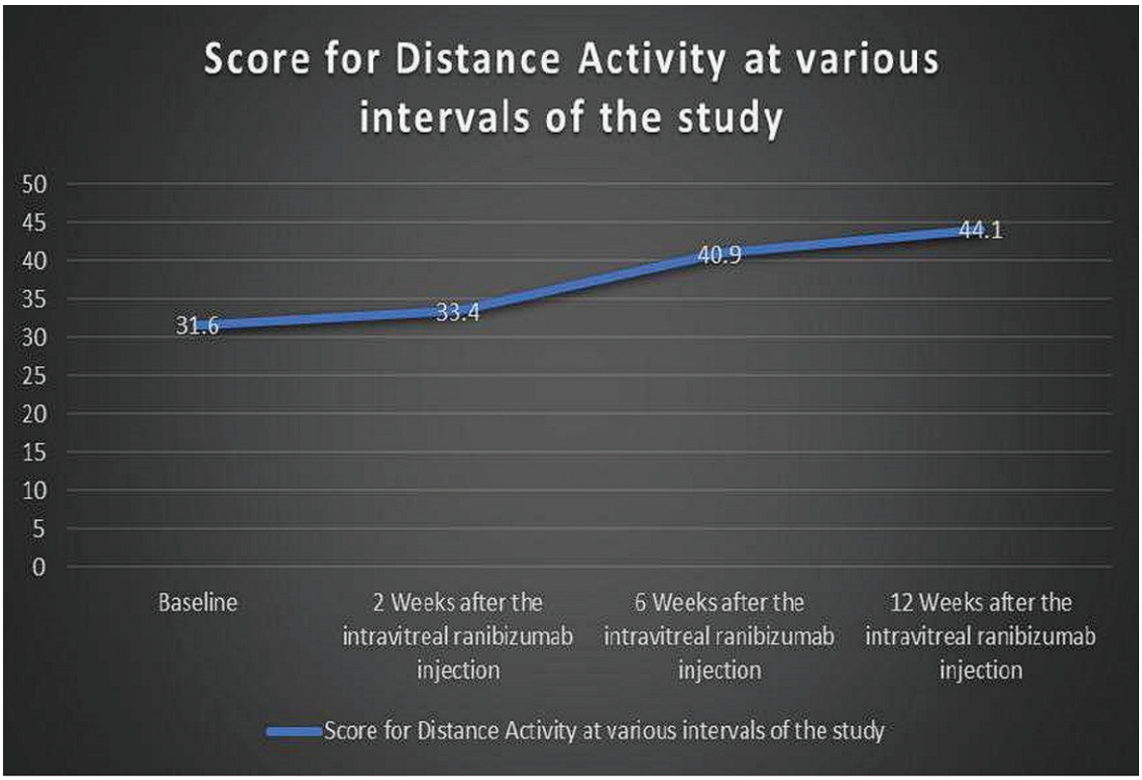

Figure 5. **Changes in the score for distance activity during the period of study**

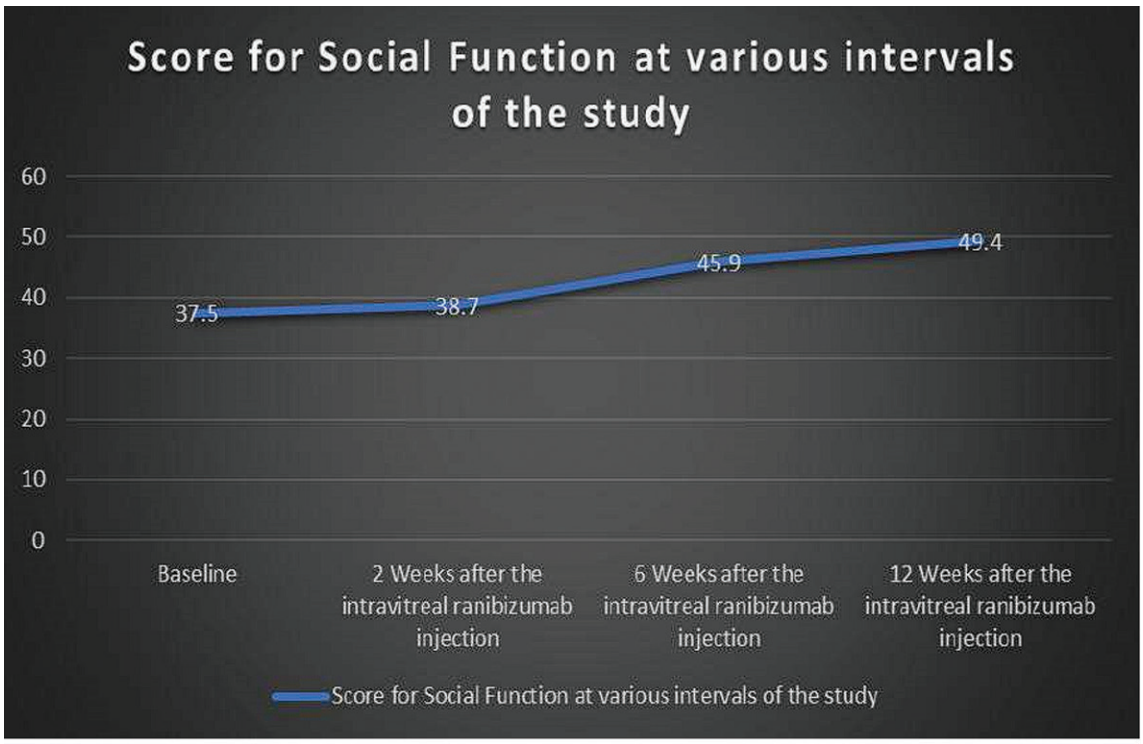

Figure 6. **Changes in the score for social function during the period of study**

RESULTS

40 patients were enrolled for the study of which 16(40%) were males and 24(60%) were females. 16(40%) of the subjects received the intravitreal Ranibizumab injection in the right eye while 24(60%) of them received the injection in the left eye. 18(45%) subjects belonged to the age group of 45 – 60 years while 22(55%) of them were aged above 60 years. 15(37.5%) of the subjects were homemaker, 10(25%) were professionals, 8(20%) were skilled workers while 7(17.5%) were clerical workers. 17 (42.5%) of the subjects had an income

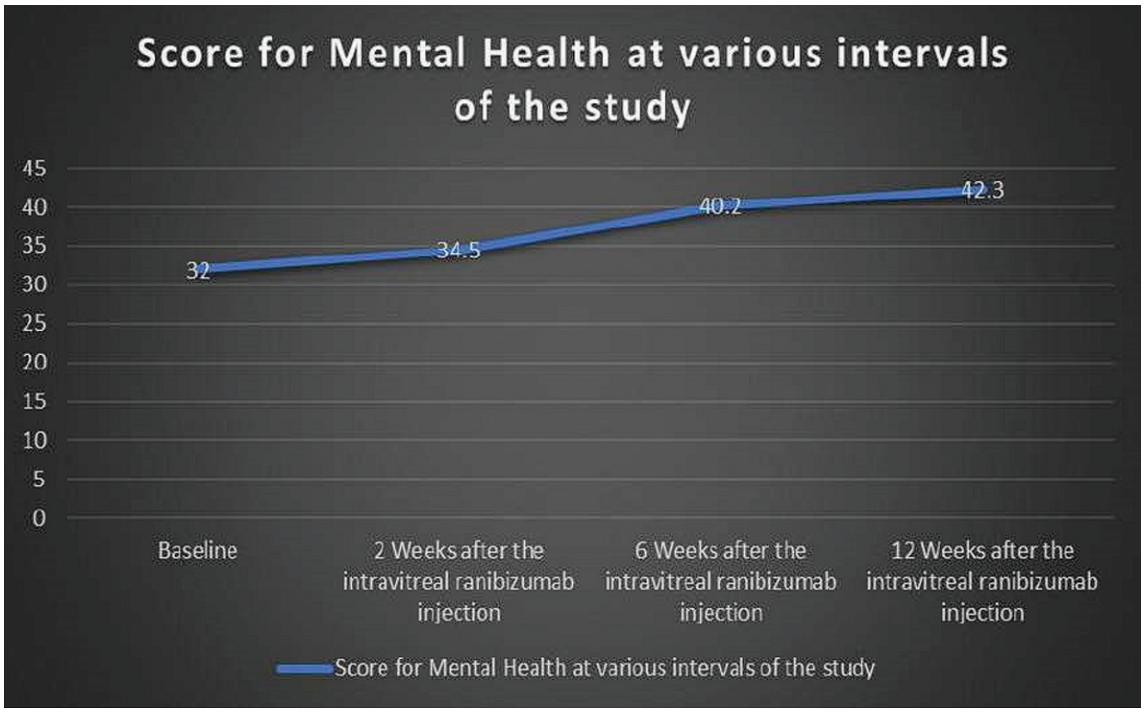

Figure 7. **Changes in the score for mental health during the period of study**

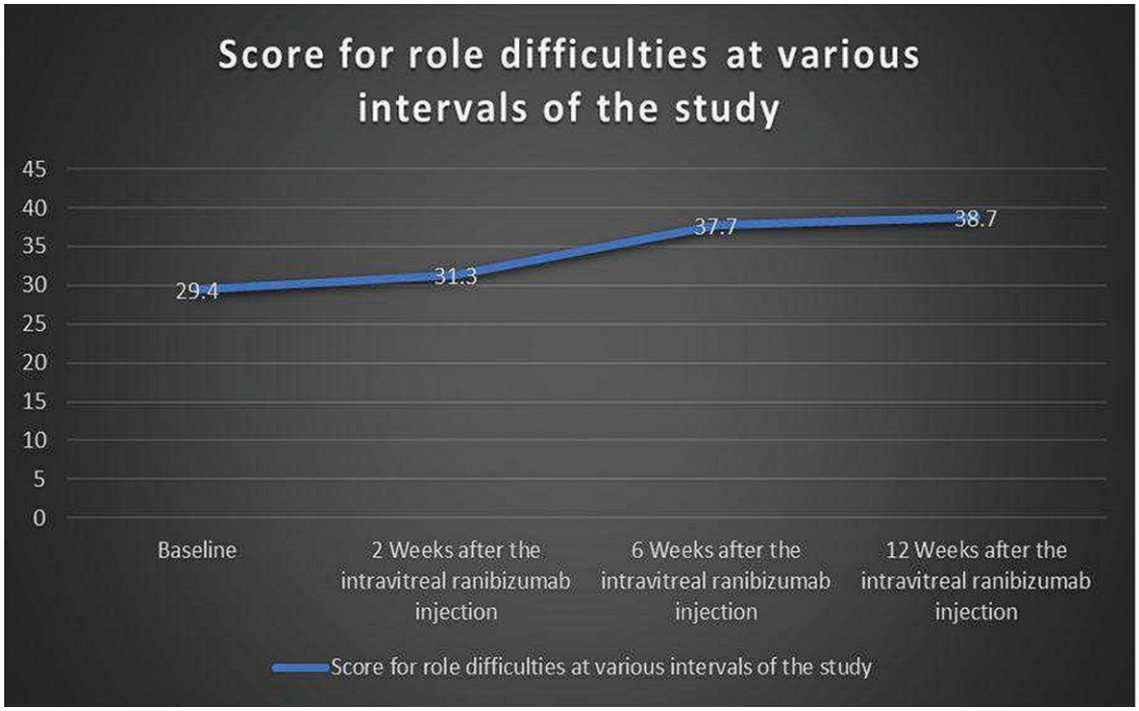

Figure 8. **Changes in the score for role difficulties during the period of study**

between 1000 to 3000 Indian Rupees, 10(25%) subjects each had an income less than 500 Indian Rupees and between 500 to 1000 Indian Rupees, and 3(7.5%) had their income between 3000 to 6000 Indian Rupees. 21(52.5%) of the study participants had a duration of diabetes mellitus between 5 to 10 years, 15(37.5%) had diabetes mellitus for a duration of more than 10 years and 4(10%) had the disease for a duration of less than 5 years. 19(47.5%) of the subjects received oral hypoglycaemic agents (OHA) alone as part of treatment for diabetes mellitus, 17(42.5%) received both insulin and OHA while 4(10%) received insulin alone. 11(27.5%) patients had a baseline central macular thickness as measured by the optical coherence tomography report of the macula to be between 600-700 micrometres, 10(25%) patients had a value of 500 – 600microme-

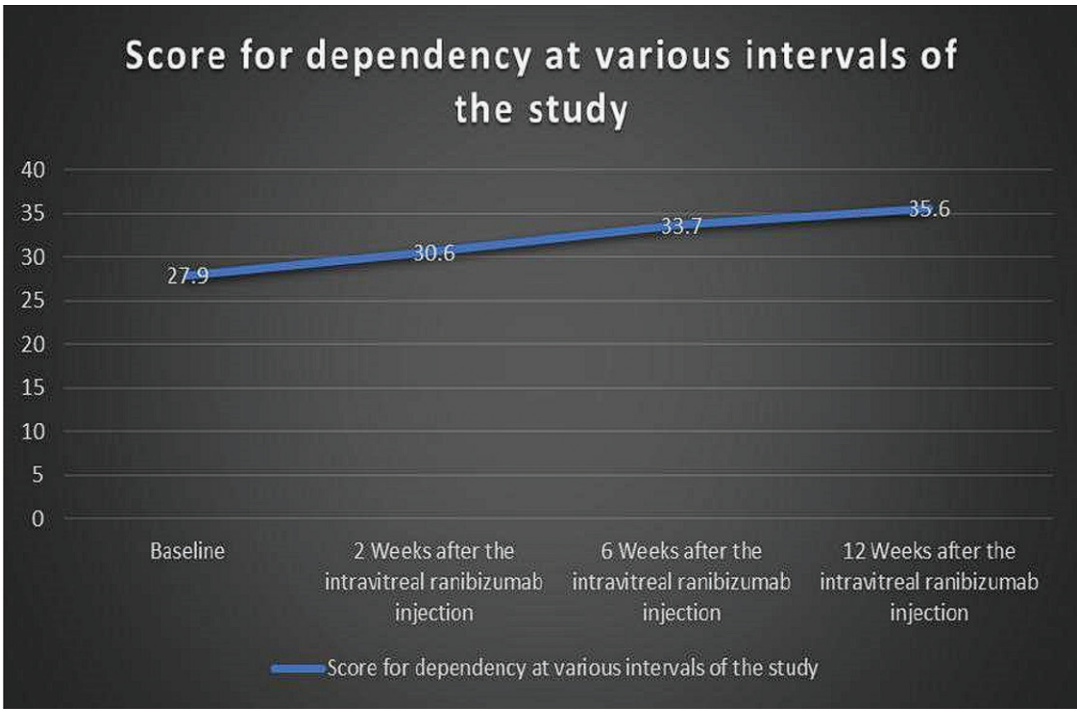

Figure 9. **Changes in the score for dependency during the period of study**

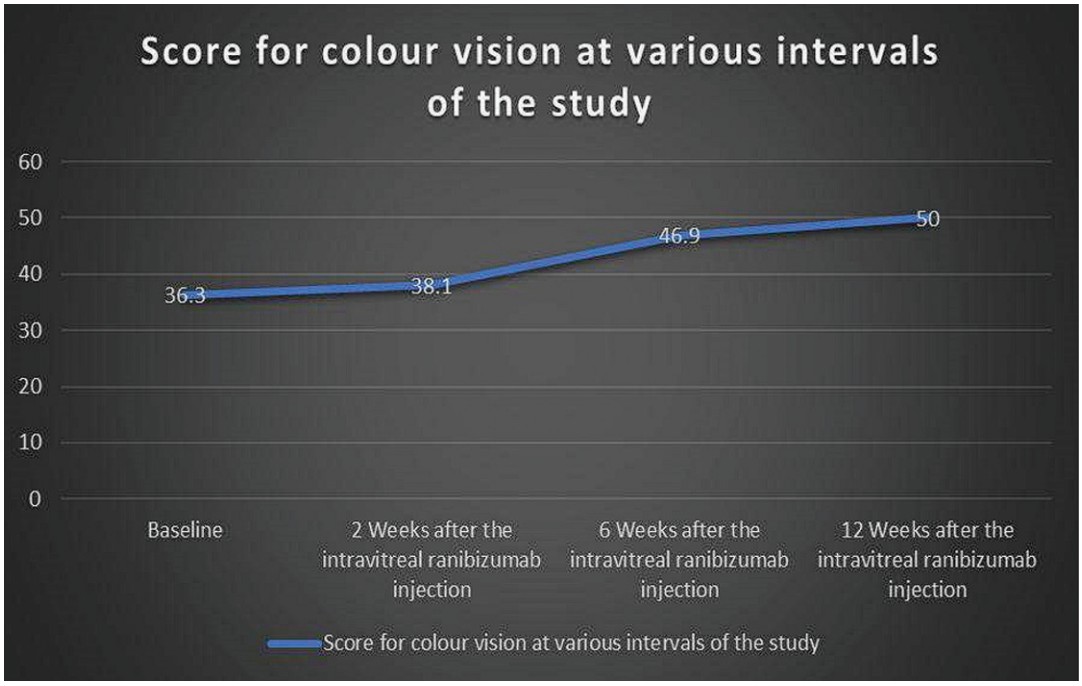

Figure 10. **Changes in the score for colour vision during the period of study**

tres, 8(20%) patients had a value of 400-500 micrometres, 7(17.5%) patients had a value between 300-400 micrometres and the remaining 4(10%) had a value more than 700 micrometres. The evaluation of the retina of the subjects, with a +20 Dioptre lens using an indirect ophthalmoscope, who were to undergo the intravitreal Ranibizumab injection showed that 14(35%) patients had severe non-proliferative diabetic retinopathy, 13(32.5%) had moderate non-proliferative diabetic retinopathy, 9(22.5%) had mild to moderate proliferative diabetic retinopathy, 3(7.5%) had mild non-proliferative diabetic retinopathy and 1(2.5%) patient had high risk proliferative diabetic retinopathy.

The following **Table 1** and **Figure 1** shows the descriptive statistics regarding the scores for the overall vision-related quality of life during the period of study.

Analysis of variance (ANOVA) for repeated measures

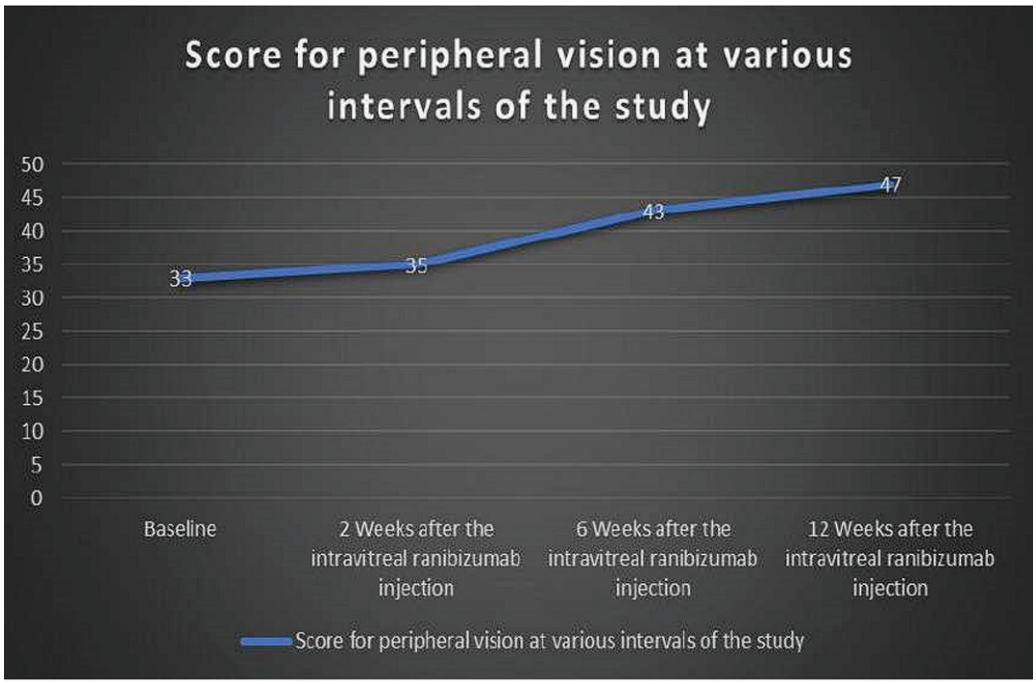

Figure 11. **Changes in the score for peripheral vision during the period of study**

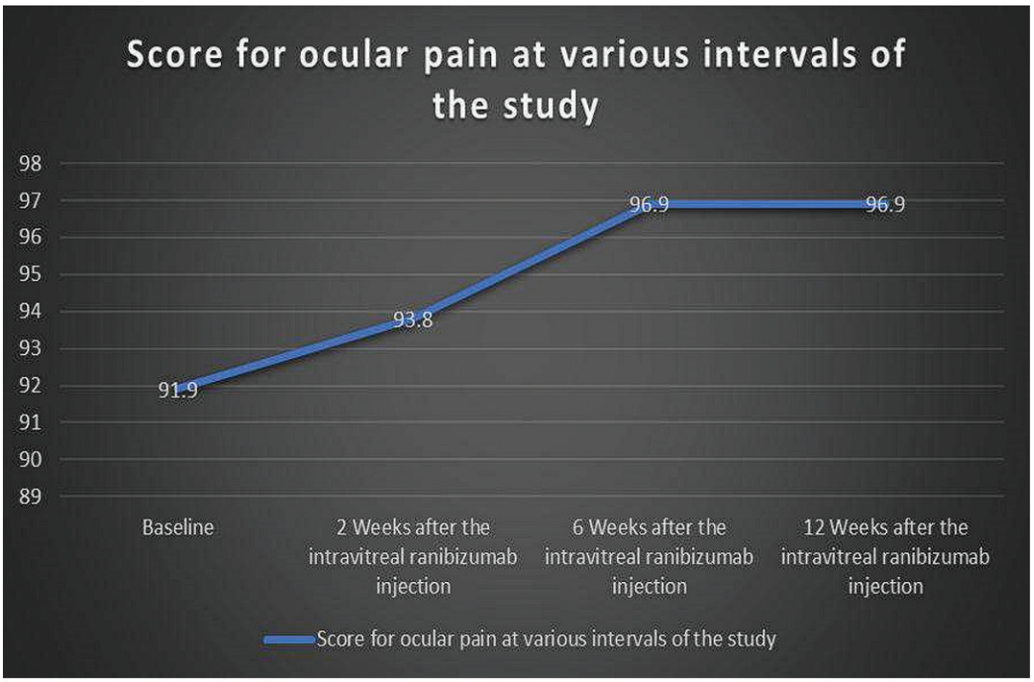

Figure 12. **Changes in the score for ocular pain during the period of study**

was utilized for the statistical analysis and the adjustment used for multiple comparisons was Sidak. The p value was kept significant at 0.05. The following tables **(Table 2 and Table 3)** depict the results of the statistical analysis.

The following figures **(Figures 2-12)** shows the descriptive statistics regarding the scores for various subdomains of vision related quality of life during the period of study.

DISCUSSION

The main objective of this study was to assess the changes in the overall vision-related quality of life among patients with diabetic macular edema who were receiving intravitreal ranibizumab injections at a tertiary eye care hospital in Trivandrum.

The mean score for the overall vision-related quality of life in the study was found to be 38.2±9.1 at baseline

which improved to 41.0±10.3 at 2 weeks, 48.2±14.0 at 6 weeks and 51.1±15.2 at 12 weeks following the single injection of intravitreal ranibizumab. Statistical analysis was done using ANOVA for repeated measures and the p-value was kept significant at a value less than 0.05. The p-value obtained on statistical analysis was 0.000 and this showed that there was a statistically significant improvement in the overall vision-related quality of life among patients with diabetic macular edema receiving intravitreal ranibizumab injection. The result obtained in this study was similar to other studies done elsewhere such as the study done by Elif Betul et al[9] where at 6 months following the intravitreal ranibizumab injection, they found the improvement in the overall vision-related quality of life scores was significantly higher for the group that received intravitreal ranibizumab than the group that received the focal or grid laser. Also, the RIDE and RISE studies showed improvement in the overall vision-related quality of life irrespective of whether 0.3mg or 0.5mg ranibizumab was used.[10]

The secondary objective of the study was to analyse the changes in the various subdomains that contribute to vision related quality of life viz general vision, general health, distance vision, near vision, peripheral vision, colour vision, ocular pain, social function, role difficulties, mental health and dependency.

All subdomains of vision related quality of life showed a statistically significant improvement except the score for general health.

The baseline score for general health was 27.5±7.6, which at 2 weeks improved to 28.8±9.0, at 6 weeks was 29.4±9.6 and at 12 weeks was 30.0±11.6. However, statistical analysis showed the improvement in scores was not statistically significant and the p-value was 0.062. In the study conducted by Elif Betul et al,[9] the baseline score for general health was 48.6 and in 6th month following intravitreal ranibizumab it was 51. The p-value in their study was 0.22. Their study also did not get any statistically significant improvements in the general health subscale following the intravitreal ranibizumab injection.

CONCLUSION

The study was undertaken to analyse what changes were being brought about in the vision-related quality of life of individuals with diabetic macular edema who were receiving intravitreal ranibizumab injections. Diabetic macular edema has been identified as the most common cause of defective vision in patients with diabetic retinopathy. Many modalities of treating the same have been identified, of which the current mainstay treatment is pharmacotherapy using intravitreal anti-VEGF agents. The study showed that the overall vision-related quality of life showed a statistically significant improvement following an injection of intravitreal ranibizumab thereby helping in decreasing the burden of the disease. This shows that the intravitreal ranibizumab injection not only brings about anatomical improvements in the thickness of the macula but also translates into better vision-related quality of life for the patients receiving the intravitreal ranibizumab injection.

The various subdomains of vision-related quality of life were also analysed in the study. All subdomains of vision-related quality of life except general health viz general vision, distance vision, near vision, peripheral vision, ocular pain, colour vision, social function, role difficulties, mental health and dependency also showed statistically significant improvement in scores during the period of study.

The general health subscale did not show any statistically significant improvement following the intravitreal ranibizumab injection in this study.

No studies were done in Kerala that analysed the qualitative changes brought about by the intravitreal ranibizumab injection in patients with diabetic macular edema and this study shows that similar to studies done elsewhere, intravitreal ranibizumab can bring about an improvement in the vision-related quality of life of individuals with diabetic macular edema.

END NOTE

Author Information

1. Dr. Allen Mathew, Department of Ophthalmology, Regional Institute of Ophthalmology, Thiruvananthapuram, Kerala, India
2. Dr. Simon George, Department of Ophthalmology, Regional Institute of Ophthalmology, Thiruvananthapuram, Kerala, India
3. Dr. S Remadevi, Department of Ophthalmology, Regional Institute of Ophthalmology, Thiruvananthapuram, Kerala, India

Conflict of Interest: None declared

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