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Research Article

ROLE OF INTRAVITREAL RANIBIZUMAB IN TREATING THE DIABETES MELLITUS TYPE-2 PATIENTS WITH SUBFOVEAL CHOROIDAL THICKNESS AND DIMINISHED VISUAL ACUITY

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ABSTRACT

Objective: This study was conducted with the objective to measure the Subfoveal Choroid thickness and correlate it with the diminished visual acuity in patients with Diabetes Mellitus Type 2, who develop macular edema and to study the effect of Intravitreal injections of Ranibizumab during follow up.

Methods: A cross sectional, interventional study conducted in 52 patients with uncontrolled Diabetes Mellitus Type-2 with macular edema by measuring the Subfoveal Choroid thickness with the help of manual caliper function present in the Heidelberg Spectralis OCT program. Patients with SFCT less than 450 microns were included. The SFCT and the corresponding visual acuity were measured before and after Intravitreal Ranibizumab injections 1.25mg (0.05mL) at monthly intervals for 3 months and correlated with age, gender, and choroid thickness.

Results: Out of 52 patients there were 31 (59.61%) females and 21 (40.38%) males. 50% of the patients were aged between 50 and 60 years and 50% patients were aged between 60 and 70 years. The patients responding to the Intravitreal injections in terms of best-corrected visual acuity (BCVA) between the reinjection and post-injection were found to be statistically important (p=0.001). The subfoveal Choroidal thickness (SFCT) variations, before and after injections were found to be statistically significant at the end of 3 months (p<0.05).

Conclusions: Injection Ranibizumab was found to have a significant role in the reduction of average SFCT and in addition clear evidence of improved BCVA.

Keywords: Visual acuity, Choroid, Subfoveal choroidal thickness, Best-corrected visual acuity and Ranibizumab.

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INTRODUCTION

The middle layer of the orbit otherwise the choroid is concerned with nutrition to the superficial layer of the sclera and the deeper retinal layer and hence consists of a rich circulatory network [1]. The basic structures of the retina consist of the retinal pigment epithelium and photoreceptors [2]. The retinal function depends on the above two cellular elements and they are crucial for visual acuity [3]. The velocity of blood flow in this layer is an essential factor and facilitated by the choriocapillaris present in the inner and outer vascular layers [4]. Hence, a healthy choroid helps in maintaining the function of the retina. Optical coherence tomography (OCT) is a very useful noninvasive imaging tool available to ophthalmologists which helps in ascertaining the high-resolution cross-sectional images of the retina [5]. The other recently added accessories of OCT are improved enhanced depth imaging (EDI) spectral-domain [6]. The latter tool is helpful in getting the cross-sectional picture of the choroid in close up to the zero delay line which helps in optimizing the sensitivity at the outer boundary of the choroid [2]. The macula of the retina becomes edematous in diabetes mellitus (DM) type 2 patients, due to retinal vascular hyper-permeability resulting in local leakage of body fluids from micro aneurysms into the surrounding tissues [7]. Such leakages in the retina both local and diffuse types are visualized by fluorescein angiography [8]. Histopathology of choroid and retina shows choroidal dysfunction among patients with diabetes [9], characterized by deprivation of the choriocapillaris, narrowing and dilatation of micro-vessels, increased tortuosity, and the development of sinusoidal-like structures among the choroidal lobules [3]. Functional investigation of DM patients showed reduced choroidal blood flow in the majority. Similarly, measurement of choroidal thickness in DM patients was reported by many authors in terms of choroidal thickening, thinning, and no change in eyes with diabetic retinopathy [5]. Such choroidal changes cause reduced visual acuity [6,7]. In the present study, an attempt was made to study the changes in the thickness of the subfoveal choroid and correlate it with the visual acuity when macular edema develops in DM patients before and after the use of intravitreal injections of ranibizumab.

METHODS

Type of study

A cross-sectional, interventional, and analytical study.

Institute of study

Government Medical College and General Hospital, Ananthapuramu, Andhra Pradesh, India.

Period of study

June 2021–December 2022.

52 patients with DM type II with diminished vision were screened for retinochoroidal changes on OCT and their visual acuity was tested. An institutional ethics committee approval was obtained before commencing the study and a committee approved consent form and pro forma were used during the study.

Inclusion criteria

Patients aged between 50 and 70 years were included. Patients of both genders were included. Patients with diminished vision and DM type II were included. Patients with hemoglobin A1C ranging from seven to eight throughout the study period were included. Patients with DME values ranging from 300 to 450 mm and mild-to-moderate DPR were included.

Exclusion criteria

Patients with controlled DM were excluded. Patients with high myopia measuring more than 6 diopters were excluded. Patients who had undergone previous organ laser surgery on the retina were excluded. Patients treated with steroidal or other injections on the retina were excluded. All the patients were elicited about their demographic details, followed by clinical history taking, and a thorough clinical examination and fundoscopy were done. Optometry assessments, like uncorrected visual acuity (UCVA), best corrected visual acuity (BCVA), fundus fluorescein angiography, slit lamp examination, and OCT using both the EDI and conventional technique were used in all the patients. The latter method was used to measure and determine the thickness subfoveal choroidal thickness (SFCT) of the macula and baseline central foveal thickness (CFT).

Procedure adopted

Injection of ranibizumab (antivascular endothelial growth factor [VEGF]) was given as three doses at an interval of 4 weeks through the intravitreal route. The procedure was undertaken under local anesthesia using 0.4% benoxinate-HCL drops used twice at an interval of 2 min. The entire procedure was performed under strict aseptic conditions taking care to disinfect the skin with iodine lotion. The lids were opened and the eyeball stabilized with a speculum followed by eye wash with 5% povidone-iodine wash for 3 min. Ranibizumab 1.25 mg (0.05 mL) was loaded in a small syringe and injected into the vitreous through pars plana 4 mm posterior to the limbus using a sharp thirty-G needle, and pressure for 1 min with microsponge was done at the site of the injection to reflux to prevent vitreous prolapsed. The follow-up consisted of monthly evaluation and repetition of injection for three doses. At each visit of follow up, visual acuity using the metrics of UCVA, BCVA, and manifest refraction were applied to assess the visual acuity. In addition, SFCT was quantified using the manual caliper tool inside the Heidelberg Spectralis OCT program**.**

Statistical analysis

The mean and standard deviation (SD) values were computed. Percentages were used to express the common variables. The normality of the data was assessed using the Kolmogorov–Smirnov and Shapiro–Wilk tests. p<0.05 was taken as significant.

RESULTS

Among the 52 patients included in this study, there were 31 (59.61%) females and 21 (40.38%) males. 26 (50%) patients were aged between 50 and 60 years and 26 (50%) patients were aged between 60 and 70 years. Patients with DM type 2 alone were 15 (28.84%), patients with DM type 2 and hypertension were 11 (21.15%), patients with DM type 2 and chronic kidney disease (CKD) were 10 (19.23%), patients with DM type 2 and liver disease were 8 (15.38%), patients with DM type 2 and cardiac disease were 5 (09.61%), and patients with DM type 2 and hypertension and hepatic disease were 3 (05.76%) (Table 1). Among the demographic data, age incidence was significant statistically with p-value at 0.001 (p significant at <0.05). However, the factors such as gender and associated co-morbid conditions were not significant statistically (p-value more than 0.05) (Table 1).

The average BCVA was 0.18±0.21 in preinjection patients and the postinjection average BCVA was 0.34±0.15 (Table 2). There was a statistically significant improvement in the study after injection with ranibizumab (p<0.05).

The mean SFCT values and their SD were noted and found that before treatment started, the mean thickness and SD were 214.56±20.15. After the first injection of ranibizumab at the end of 4 weeks, it was 203.61±20.15. At the end of 8 weeks following injection of ranibizumab in the 5th week, the mean value was 198.48±18.25 which was statistically significant. The mean values of SFCT at the end of 12 weeks after the 3rd injection of ranibizumab in the 10th week were 195.47±19.15 which was not significant statistically with p value more than 0.05 (Table 3).

The mean value of the CFT before the injection of ranibizumab was 372.65±27.68. The mean CFT value at the end of 12 weeks following three injections of ranibizumab was 322.75±15.64, and the mean baseline CFT in the studied eyes was statistically significant with p<0.05 (Table 4).

Improvement in the visual acuity in the patients at the end of 12 weeks was assessed and found that there was a definite improvement in 41 (78.84%) patients and no improvement in 11 (21.15%) patients (p<0.05) hence found to be statistically significant (Table 5).

DISCUSSION

The present study was conducted to study the changes in the thickness of the subfoveal choroid and correlate it with the visual acuity when macular edema develops in DM patients before and after the use of intravitreal injections of ranibizumab. Among the 52 patients, there were 31 (59.61%) females and 21 (40.38%) males. 26 (50%) patients were aged between 50 and 60 years and 26 (50%) patients were aged between 60 and 70 years. Patients with DM Type 2 alone were 15 (28.84%), DM

Table 1: Demographic data of the subjects (n=52)

Observation	Number	Percentage	p-value
Age			
50–60 years	26	50	0.001
60–70 years	26	50	
Gender			
Male	21	40.38	0.112
Female	31	59.61	
DM type 2			
DM type 2 alone	15	28.84	
With hypertension	11	21.15	0.231
With chronic kidney disease	10	19.23	
With liver diseases	08	15.38	
With cardiac disease	05	09.61	
With hypertension and hepatic disease	03	05.76	

DM: Diabetes mellitus

Table 2: Average BCVA among the preinjection and postinjection patients (n=52)

Treatment status	BCVA (n=52)	p-value
Pre	0.18±0.21	0.001
Post	0.34±0.15	

BCVA: Best-corrected visual acuity

Table 3: Average SFCT before and after each intravitreal injection of ranibizumab (n=52)

Status of treatment	SFCT (n=52); Mean±standard deviations	p-value
Preinjection	214.56±18.85	
Postinjection		
1	203.61±20.15	0.002
2	198.48±18.25	0.004
3	195.47±19.15	0.213

SFCT: Subfoveal choroidal thickness

Table 4: Mean CFT values in the patients before and after treatment with intravitreal injection of ranibizumab (n=52)

Stats of treatment	CFT Mean and standard deviations	p-value
Pre	372.65±27.68	
Post	322.75±15.64	0.0351

CFT: Central foveal thickness

Table 5: Final outcome in terms of improvement in visual acuity among the subjects (n=52)

Final outcome	Number	Percentage	p-value
Improved visual acuity	41	78.84	0.001
No improvement in visual acuity	11	21.15	

type 2 and hypertension were 11 (21.15%), DM type 2 and CKD were 10 (19.23%), DM type 2 and liver disease were 08 (15.38%), DM type 2 and cardiac disease were 05 (09.61%), and DM type 2 and hypertension and hepatic disease were 03 (05.76%) (Table 1). The mean SFCT values before treatment were 214.56±20.15. After the first injection of ranibizumab, at the end of 4 weeks, it was 203.61±20.15. At the end of 8 weeks following injection of ranibizumab in the 5th week, the mean value was 198.48±18.25 which was statistically significant. The mean values of SFCT at the end of 12 weeks after the 3rd injection of ranibizumab in the 10th week were 195.47±19.15 which was not significant statistically with p-value more than 0.05 **(**Table 3). Laíns *et al.* [7] and Yiu *et al.* [8] conducted a similar study and found that there was a reduction thickness choroidal layer in DM type 2 patients. However, Lee *et al.* [9] observed that there was no thinning of this layer, especially in mild and proliferative types. Shiragami *et al.* [10] on the other hand strongly suggested that there was a definite reduction in the thickness of the choroidal layer in his patients with DM type 2. The edema of the macular area of the retina occurs due to ischemia of the microvessels resulting in the release of VEGF [11] Rayess *et al.* [12] is of the opinion that patients with higher initial SFCT values usually have better preserved choriocapillaris, and hence the macular edema is also less. Consequently, the photoreceptor layer's functionality is better maintained compared to individuals with a thinner choroid. The observation made by Rayess *et al.* [12] explains the better response in patients in terms of better anatomical response and also better visual acuity gain in diabetes patients. Kang *et al.* [13] studied the correlation between initial SFCT values and gain the visual acuity after completion of the treatment in patients with neovascular age-related macular degeneration. They found that patients who had a greater baseline SFCT had better improved outcomes in thinning and improvement of visual acuity. Rayess *et al.* [12] also concluded that patients with better thinning of SFCT had more favorable acuity gain outcomes. Byeon *et al.* [14] and Latalska *et al.* [15] following their study in the years 2007 and 2013 reported a gain in the visual acuity in patients in a significant manner in all their patients who had thinning of the retinal thickness after multiple intravitreal bevacizumab injections. Rayess *et al.* [12] presumed that the failure to achieve a gain in the visual acuity in their study could be due to the rapid development of cataracts, retinal detachment, detachment of other layers of the choroid, subfoveal hard exudate, and disruption of Muller's fibers to large extent. Soman *et al.* [16] suggested that the presence of systemic co-morbidities along with DM might be the cause for the decreased response. Hence, they suggested a thorough investigation of the co-morbidities and their early treatment to achieve visual acuity.

Limitations to the study

The limitations of the study are small sample size and short duration study. The studies with longer duration of follow-up and increased number of injections of ranibizumab would allow us to effectively evaluate the role of this drug.

CONCLUSION

Ranibizumab is effective in treating the SFCT observed in DM type 2 patients with high values of SFCT, CFT, and loss of visual acuity. The final outcome is not only anatomical thinning of the choroid but also gain in the BCVA.

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