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Original Article

Ophthalmology Section

Effect of Intravitreal Injection of Ranibizumab on Diabetic Macular Oedema at a Tertiary Centre in West Bengal: A Prospective Study

VYSAKH BALAN[1], ATANU BISWAS[2]

ABSTRACT

Introduction: Diabetic Retinopathy (DR) is one among the many causes of visual loss in people all over the world. Diabetic Macular Oedema (DME) is the most common among vision threatening complications of DR, with a major impact on quality of life of the patient. The intravitreal ranibizumab injection (anti Vascular Endothelial Growth Factor (VEGF), which prevents neovascularisation, is given monthly with approved dose of 0.3/0.5 mg with or without laser in the option of choice for all cases of central involving macular oedema.

Aim: To find out the effectiveness of injection ranibizumab on patients with DME and to provide the better line of treatment for DME patients.

Materials and Methods: This prospective study with quasi-experimental design constituted all the Type I and II Diabetic patients attending Out Patient Department (OPD) in College of Medicine and JNM Hospital, West Bengal, India from December 2019 to January 2021. Spectral Domain Optical Coherence Tomography (SD-OCT) images were obtained and used to diagnose macular oedema. Intravitreal injection ranibizumab (0.5 mg) was given as a standard treatment protocol with a dose interval of one month to all the DME patients. Foveal Thickness (FT) and Visual Acuity (VA) were evaluated before and after one month of injection. The t-test was used to compare the mean value of Central Macular Thickness (CMT) before and after intervention, $p<0.05$ was considered for statistical significance.

Results: In the current study, (n=105), mean age of the population was 55.1 years and gender distribution being: females- 54 (51.4%) and males- 51 (48.6%). Mean duration of diabetes was 10.7 years. CMT value significantly decreased from mean of 416.0095 to 383.8667 after injection. The mean LogMAR value significantly decreased from 1.0350 to 0.8625 after injection. Positive correlation was found between LogMAR after treatment with CMT (r-0.857; p-value <0.0001).

Conclusion: Single dose of 0.5mg of intravitreal injection of ranibizumab is effective in decreasing the CMT and improving VA in patients with DME.

Keywords: Central macular thickness, Diabetes mellitus, Diabetic retinopathy, Foveal thickness

INTRODUCTION

Diabetes Mellitus (DM) is a well-established risk factor for macrovascular and microvascular complications [1]. In 2019, DM affected 463 million people globally and is expected to raise to 578 million by the year 2030 [2]. DR is a complication that causes decreased vision in diabetics and it includes diabetic macular ischaemia, DME, tractional retinal detachment, and vitreous haemorrhage [3]. Of all these, DME is the most common complication which causes foremost impact on the quality of life of the patient [4]. The main molecular mechanism primarily causing DME is disruption of the blood retinal barrier by phosphorylation of the junctional proteins [5]. Researchers raised a possibility of a chemical that promotes vasoproliferation and this led to the hypothesis that some chemical substances could be the causative agents of DME [6]. It is confirmed by the discovery of VEGF, which was shown by sequencing analysis to be identical molecules. Angiogenesis throughout the body and eye is promoted by this biochemical signal protein, VEGF, thus setting up the stage to inhibit the single molecular target which was putatively responsible for the formation of DME [7,8]. The first anti-VEGF agent to be approved by the US Food and Drug Administration (USFDA) is intravitreal ranibizumab. It is manufactured in the US by Gentech\Roche and is a recombinant humanised IgG monoclonal antibody fragment which attaches to and inhibits VEGF. It thus prevents the subsequent growth of new blood vessels by interrupting the interface of VEGF with its receptors [9].

It was first approved by Food and Drug Administration (FDA) in 2006 for wet Age-Related Macular Degeneration (ARMD) since then it has been approved for the treatment of macular oedema following Retinal Vein Occlusion (RVO) and DME. In 2015, it was approved for patients with DR [10]. The sanctioned dose of intravitreal ranibizumab is either 0.3/0.5 mg in 0.05 mL with dosing recommendation varying according to indications [9]. However, actual treatment protocols vary but include strict monthly administration as needed. Injection intervals vary including treat and extend regimen, and depends on disease patient and physician.

The aim of the study was to evaluate the effect of a single dose of intravitreal injection of ranibizumab on patients with DME. The study also aimed to evaluate the impact of the intravitreal injection of ranibizumab on Best Corrected Visual Acuity (BCVA) and on CMT/FT in SD-OCT.

MATERIALS AND METHODS

This prospective study with quasi-experimental design was conducted at College of Medicine and JNM Hospital, Kalyani, West Bengal, India, from December 2019 to January 2021. The study protocol included administration of single dose of intravitreal injection of ranibizumab (0.5mg) in those with DME and the effect at the end of one month. The study has been approved by Institute Ethics Committee (IEC) vide letter number (CM-JNM-2019-095).

Inclusion criteria: Those with centre involving DME secondary to DM (Type 1 or 2), willingness to provide written informed consent

as applicable, age ≥18 years, retinal thickening secondary to DME involving centre of the fovea with CMT ≥250 μm in the centre subfield as assessed on OCT, decrease in vision determined to be primarily the result of DME and not to other causes and ability and willing to return for all scheduled visits and undergo assessments were included in the study.

Exclusion criteria: Those with history of vitreoretinal surgery in the study eye, with Pan-Retinal Photocoagulation (PRP) or macular laser photocoagulation and previous use of intraocular corticosteroids within three months of screening, those with previous use of intraocular corticosteroids in the study eye {e.g., Triamcinolone Acetate (TA)} within three months of screening, those with previous treatment with antiangiogenic drugs in either eye (pegaptanib sodium, anecortave acetate, bevacizumab, ranibizumab, etc.,) within three months of the day 0 (first day of treatment) visit, those with Proliferative DR (PDR) in the study eye, iris neovascularisation, vitreous haemorrhage, traction retinal detachment, or preretinal fibrosis involving the macula in the study eye and those patients with mature cataract or media opacities due to poor quality OCT images were all excluded from the study.

Sample size estimation: The study by Raman R et al., found that the incidence of DME was 2.6% [11]. So, considering p=0.026, the number of patients required for this study was 105.07~105 with power 87%. Formula used for sample size calculation:

$$n = 4pq / (L^2)$$

Where, n = required sample size, p= 0.026

q = 1–p,

L = Loss % (Loss of information)

Here p= 0.026,

q=1-p = 1- 0.026 = 0.974,

4pq = 4 x 0.026 x 0.974 = 0.101296

L^2 = 0.000964

L= 0.0310

Loss of information percentage= 3.10%

n =4pq/(L^2)= 0.101296/0.000964= 105.07= 105

All the relevant examinations were done, including VA, slit lamp, indirect and direct ophthalmoscopy. SD-OCT images were obtained. Patients were prepared for intravitreal injection ranibizumab. Intravitreal injection of ranibizumab (0.5 mg) was given as per standard treatment protocol. Follow-up was done with SD-OCT and VA test and were repeated after one month.

Outcome: Assessed by comparing SD-OCT images and VA before and after one month of injection ranibizumab. CMT: First, line scan was done and taken for subjective analysis with fovea centred at 0° angle. Then, macular cube scan 200 × 200 was taken and the macula was mapped on fast macular thickness map. It comprises three concentric circles centred on the fovea; the fovea (<1 mm diameter), the inner macula (1-3 mm), and the outer macula (3-6 mm). These zones were further divided into nine early treatment DR study regions. Since CMT was highly correlated between the right and left eyes among the 170 participants, the average CMT between both eyes was taken as the value.

LogMAR value in the measurement of VA is measured as follows: Each letter in LogMAR chart has a score value of 0.02 log units. Since there are five letters per line, the total score for a line on the LogMAR chart represents a change of 0.1 log units. The formula used in calculating the score is:

LogMAR VA = 0.1 + LogMAR value of the best line read – 0.02 X (number of optotypes read)

STATISTICAL ANALYSIS

For statistical analysis data were entered in Microsoft excel spreadsheet and then analysed by Statistical Package for the Social Sciences (SPSS) (version 27.0; SPSS Inc., Chicago, IL, US) and GraphPad Prism version 5. Two-sample t-tests for a difference in mean involved unpaired samples or independent samples. T-test was used to compare the mean value of CMT and VA before and after intervention, p<0.05 was considered for statistical significance. Correlation between CMT and VA was tested using Pearson's Correlation Coefficient Test.

RESULTS

In all 105 patients in the study, single eye was affected. The mean age was 55.1143 years ranging from 38 to 80 years; 54 (51.4%) patients were females and 51 (48.6%) patients were males [Table/Fig-1].

Variables	Frequency	%
Age in group (years)		
≤50	38	36.2
51-60	33	31.4
61-70	26	24.8
71-80	8	7.6
Gender		
Female	54	51.4
Male	51	48.6

[Table/Fig-1]: Distribution of age and gender.

A total of 50 (47.6%) patients had DME in the left eye and 55 (52.4%) had DME in the right eye.

Mean CMT before injection was 416.0095 and after injection was 383.8667 with median of 407 and 372 respectively. Mean logMAR before injection was 1.0350 and after injection was 0.8625 with median of 1 and 0.78, respectively [Table/Fig-2].

Parameters	Mean±SD	Minimum	Maximum	Median	p-value (Paired t-test)
CMT before injection Ranibizumab (μm)	416.0095±93.33	280.0000	640.0000	407.0000	<0.0001
CMT after injection Ranibizumab (μm)	383.8667±90.22	260.0000	580.0000	372.0000	
logMAR before injection Ranibizumab (log units)	1.0350±0.5	0.2000	2.4000	1.0000	<0.0001
logMAR after injection Ranibizumab (log units)	0.8625±0.48	0.2000	2.4000	0.7800	

[Table/Fig-2]: Distribution of mean CMT and logMAR (Visual Acuity) before and after injection ranibizumab.

A positive correlation was found between CMT before and after injection ranibizumab vs age but result was not statistically significant [Table/Fig-3].

The value of Pearson Correlation Coefficient (r) was 0.845. A high positive correlation was found between logMAR before injection ranibizumab vs CMT before injection ranibizumab [Table/Fig-4].

The correlation between VA and CMT after injection ranibizumab was high and statistically significant. The value of Pearson Correlation Coefficient (r) was 0.857. High positive correlation was found between logMAR after injection ranibizumab vs CMT after injection ranibizumab [Table/Fig-5].

		Age
CMT before injection ranibizumab	Pearson Correlation Coefficient (r)	0.061
	p-value	0.5340
	Number	105
CMT after injection ranibizumab	Pearson Correlation Coefficient (r)	0.052
	p-value	0.6010
	Number	105
logMAR before injection ranibizumab	Pearson Correlation Coefficient (r)	0.072
	p-value	0.4660
	Number	105
logMAR after injection ranibizumab	Pearson Correlation Coefficient (r)	0.047
	p-value	0.6350
	Number	105

[Table/Fig-3]: Correlation of CMT and logMAR (Visual Acuity) before and after injection Ranibizumab.

		CMT before injection ranibizumab
logMAR before injection	Pearson Correlation Coefficient (r)	0.845**
	p-value	<0.0001
	Number	105

[Table/Fig-4]: Correlation between logMAR before injection ranibizumab vs CMT before injection ranibizumab.

		CMT after Injection ranibizu mab
logMAR after injection	Pearson Correlation Coefficient (r)	0.857**
	p-value	<0.0001
	Number	105

[Table/Fig-5]: Correlation between logMAR after injection ranibizumab vs CMT after injection ranibizumab.

DISCUSSION

Patients included in study were with centre-involving DME secondary to DM. Retinal thickening secondary to DME involving the centre of the fovea with CMT ≥275 µm in the centre subfield as assessed on OCT. Decrease in vision was determined to be primarily the result of DME and not to other causes. Ability (in the opinion of the investigator) and willingness to return for all scheduled visits and assessments. Total 105 patients were included in this study. Inagaki K et al., showed that the mean logMAR VA had improved from 0.52±0.34 at baseline to 0.44±0.32 at one month after treatment. The mean CMT decreased significantly by one month [12].

Minami Y et al., showed mean FT decreased significantly from 452±77 to 429±65 µm after two hours. Significant improvement in mean logarithm of the minimum angle of resolution BCVA was noted. The ΔFT after two hour significantly correlated with the ΔFT after one month. The ΔVA after 1 day significantly correlated with the ΔVA after 1 month [13]. It was reported by Campochiaro et al., that between macular oedema after Branch Retinal Vein Occlusion (BRVO) and DME there are several cytokines whose levels in the aqueous humour differed [14]. The authors are of the opinion that by measuring the short-term intravitreal injection ranibizumab effects will be useful to consider the difference in the mechanisms of macular oedema between BRVO and DME by additional measurement of the intraocular cytokine levels in eyes and also aid to predict efficacy of the drug.

Sharaf A et al., in their study found that at one month CMT was 341.0±88.66 µm with 17.96% improvement with mean pre-injection CMT being 432.0±144.0 µm [15]. In the current study, CMT preinjection was 416.0095±93.3345 µm and one month postinjection was 383.8667±90.2228 µm, with Pearson Correlation Coefficient being 0.061 and 0.052 suggesting a positive correlation.

Welch DE et al., in the past reported that 1 to 2 hour after intravitreal injection of bevacizumab (IVB) the FT decreased significantly in two patients with exudative Age-related Macular Degeneration (AMD) and seven patients with DME, in their study [16]. They reported that within two hour after injection a significant decrease in OCT thickness. Although a different anti-VEGF drug (bevacizumab) was used in patients with DME and AMD, the current findings match the results of their study. It was stated that baseline FT may envisage the structural result in response to IVR treatment [17]. Also, between the baseline BCVA and the BCVA at one month, there was a significant correlation. Baseline BCVA may predict the functional outcome after IVR treatment, as reported previously [18,19]. However, no significant correlation between the ΔVA-one month and the baseline BCVA was found. As previously reported in the study, eyes with a low baseline VA tend to have a large increase in the ΔVA-one month [20].

The study showed that the mean logMAR before injection ranibizumab (mean±SD) of patients was 1.0350±0.5096 and the mean logMAR after injection ranibizumab (mean±sd) of patients was 0.8625±0.4863.

It was examined that the value of Pearson Correlation Coefficient (r) was 0.072. A positive correlation was found between logMAR before injection ranibizumab vs age. The study showed that the value of Pearson Correlation Coefficient (r) was 0.047. The positive correlation was found between logMAR after injection ranibizumab vs age.

Limitation(s)

It was a monocentric study and the ongoing COVID-19 pandemic and lockdown limiting the logistics of patients and visits for follow-up were done only in the emergency cases.

CONCLUSION(S)

This study concludes that a single dose of 0.5 mg of intravitreal injection of ranibizumab seems to be effective in decreasing the CMT and improving VA in patients with DME. The need for this study was to evaluate the effect of single dose injection ranibizumab in patients with DME which was achieved. However, this study also recommends large scale multicentric studies with larger sample size to further validate the findings of the present study.

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PARTICULARS OF CONTRIBUTORS:
1. Senior Resident, Department of Ophthalmology, College of Medicine and JNM Hospital, Kalyani, West Bengal, India.
2. Associate Professor, Department of Ophthalmology, College of Medicine and JNM Hospital, Kalyani, West Bengal, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Atanu Biswas,
B-12/95, Kalyani-741235, West Bengal, India.
E-mail: biswasatanudr@gmail.com

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