Suez Canal University Medical Journal Vol. 25 (2), 2022
Pages 7-11

Correlation between Diabetic Cystoid Macular Edema and Best Corrected Visual Acuity after Intravitreal Injection of Ranibizumab

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Abstract

Background: **Diabetic macular edema is a general term defined as retinal thickening within two-disc diameters of the foveal center; it can be either focal or diffuse in distribution. Intravitreal injection of anti-vascular endothelial growth factor (Ranibizumab) was approved for the treatment of diabetic macular edema.** ***Objective:*** **Assessment of correlation between diabetic cystoid macular edema and best-corrected visual acuity (BCVA) after intravitreal injection of Ranibizumab.** ***Patients and Methods:*** **Quasi-experimental interventional study was undertaken at Suez Canal University Hospital, Ophthalmology Department on patients who were diagnosed as having diabetic cystoid macular edema (CME) by optical coherence topography. A total of 60 participants were evaluated by taking a complete ophthalmologic history, examination, and investigations using a pre-designed checklist, and intravitreal injection of anti-VEGF was done.** ***Results:*** **Our study showed that the study group consisted of 71.4% females and 28.3% males. In our study group, we found that the Mean ± SD. In CME 3.50 ± 0.50 pre-VEGF injection, 2.0 ± 0.82 post VEGF injection with improvement1.50±0.50 (44.44%). The mean of BCVA in decimal among participants was 0.15 ± 0.06 pre-VEGF injection while 0.25 ± 0.07 post-VEGF injection with an improvement of 0.10 ± 0.03 (25.0%). There was strong relation and statistically significant.** ***Conclusion:*** **Intravitreal injection of anti-VEGF was very effective in diabetic macular edema. Improvement of diabetic macular edema was associated with improvement in best-corrected visual acuity.**

Keywords: Anti-VEGF, CME, BCVA, Optical coherence tomography (OCT)

Introduction

Approximately 347 million people worldwide have diabetes mellitus (DM)[1]. The worldwide prevalence of DM is predicted to grow to 430 million patients by 2030[2]. Diabetic macular edema is a general term defined as retinal thickening within two-disc diameters of the foveal center The diagnosis of macular edema is based on binocular slit-lamp biomicroscopy, leakage on FA, and recently on the qualitative and quantitative information on retinal structure and thickness offered by OCT[3]. The pathway that results in DME is the disruption of the BRB[4]. Several clinical studies suggest that the inner barrier is the prima-

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ry site of vascular leakage that results in DME. The disruption of the BRB leads to an abnormal inflow of fluid into the neurosensory retina that can exceed the outflow and cause the accumulation of fluid in the intraretinal layers of the macula[5-7]. Isoforms of VEGF-A have been shown to be the most important promoters of intraocular neovascularization and hyper permeability. At the cellular level, the VEGFR-2 receptor regulates the blood–retinal barrier and controls endothelial cell mitogenesis[8]. VEGF is produced by several different cells within the retina (capillary endothelial cells, pericytes, pigment epithelial cells, neurons, and astrocytes). Although all retinal cell types respond to VEGF, the capillary endothelial cell represents the VEGF primary target. Hypoxia-induced upregulation of VEGF breaks down the blood-retinal barrier and increases capillary permeability[9]. Intravitreal Ranibizumab injection was first approved by the FDA in 2006 for wet age-related macular degeneration. Since then, it has been approved for the treatment of macular edema following retinal vein occlusion and diabetic macular edema. Most recently, it was approved in 2015 for patients with diabetic retinopathy[10].

Patients and Methods

Quasi experimental interventional study was undertaken at Suez Canal University hospitals, Ophthalmology Department on patients who were diagnosed as having diabetic cystoid macular edema. We excluded patients with type 1 diabetes, history of vitreoretinal surgery, intravitreal injection of any drugs, macular edema not due to diabetes, presence of media opacities such as vitreous hemorrhage or cataract, cases with motion artifacts preventing the accurate analysis of the microvascularization, and patients' refusal of intravitreal injection of anti-VEGF. Enrolled patients were evaluated by taking a complete ophthalmologic history, examination, and investigations using a predesigned checklist in conjunction with a designed database computerized program for data entry and analysis.

1-Examination

i) Visual acuity assessment, ii) Slit-Lamp biomicroscopic examination (SL-D7 Topcon, Tokyo, Japan), iii) Intra-ocular pressure measurement, iv) Fundus examination: Indirect ophthalmoscope

2-Investigations

Optical coherence tomography (OCT): We classified patients into four groups based on the ratio of the vertical size of the largest macular cyst in relation to the size of maximum macular thickness, with the use of OCT: CME I: Patients with cysts less than (30%) of macular thickness. CME II: Patients with cysts between 30% and 60% of macular thickness. CME III: Patients with cysts between 60% and 90% of macular thickness. CME IV: Patients with cyst became more than 90% of the macular thickness.

Preparation and administration of IVT treatment

We applied a single-use topical anesthetic to the eye. We instilled 5% povidone iodide onto the ocular surface and allow adequate time (3-5 minutes) prior to injection. We marked the scleral injection site using the mm gauge (the entry site of the needle should be 3.0-3.5 mm from the limbus in aphakic/pseudophakic patients, and 3.5-4.0 mm in phakic patients). We injected an appropriate volume (maximum 0.1 ml) of therapeutic agent slowly and carefully.

Post-operative follow-up:

OCT scanning was done for all the patients after one month from the injection.

We Compared finding pre and post-injection.

Statistical Analysis

Collected data were coded, entered, and analyzed using Microsoft Office Excel (2007) software. Data were then imported into Statistical Package for the Social Sciences (SPSS) version 20.0 (IBM SPSS Ver. 20.0) and MedCalc version 12.1.3.0 software for (SPSS INC. CHICAGO IL USA) analysis. Baseline characteristics of the study populations were presented as frequencies and percentages (%) in qualitative data or mean values and standard deviations (SD) in quantitative data.

Results

Sixty participants (60 eyes) were 71.4% (43) females and 28.3% (17) males. The mean age of the group was 46.95 ± 7.82 years (range: 32- 63), The mean DM duration in the group was 10.48 ± 4.70 years (range: 5 – 20) (Table 1).

Table 1: Demographic data of the study cases (n= 60)

Variables		No.	%
Gender	Male	17	28.3
	Female	43	71.7
Age (years)	Min. – Max.	32.0 – 63.0	
	Mean ± SD.	46.95 ± 7.82	
	Median (IQR)	46.50(40.0 – 52.0)	
Duration (years)	Min. – Max.	5.0 – 20.0	
	Mean ± SD.	10.48 ± 4.70	
	Median (IQR)	10.0(6.0 – 14.50)	

In CME, the mean ± SD was 3.50 ± 0.50 pre-VEGF injection, and 2.0 ± 0.82 post-VEGF injections with an improvement of 1.50 ±0.50 (44.44%) There was a statistically significant. (Table 2). The mean of BCVA in decimal among participants was 0.15 ± 0.06 pre-VEGF injection while 0.25 ± 0.07 post-VEGF injection with an improvement 0.10 ± 0.03 (25.0%). There was statistically significant. (Table 3). By comparing correlations between BCVA, CME pre, and post-intravitreal injection. There was a strong correlation between improvement in BCVA and CME (Pearson coefficient 0.601). There was statistically significant (Table 4).

Table 2: Values of pre and post-VEGF injection according to CME (n= 60)

CME	Pre VEGF injection	Post VEGF injection	Improvement (%)	T	p
Min. – Max.	3.0 – 4.0	1.0 – 3.0	1.50 ± 0.50 (44.44%)	23.043*	<0.001*
Mean ± SD.	3.50 ± 0.50	2.0 ± 0.82			

*t: Paired t-test, p: p-value for comparing between pre and post, *: Statistically significant at p ≤ 0.05*

Discussion

In our study group, we found that the Mean ± SD. In CME 3.50 ± 0.50 pre-VEGF injection, 2.0 ± 0.82 post-VEGF injections with the improvement of 1.50 ±0.50 (44.44%, p<0.001). The mean of BCVA among participants was 0.15 ± 0.06 pre-VEGF injection while 0.25 ± 0.07 post-VEGF injection with an improvement of 0.10 ± 0.03 (25.0%). Statistically significant correlations were found between BCVA, CME pre, and post-intravitreal injection. There was a strong correlation between improvement in BCVA and CME. The presence of cystoid spaces in chronic diabetic macular edema may resemble areas of capillary nonperfusion on enface OCTA since both may appear as black or grey areas[11,12]. Cystoid spaces seen on OCT were also found to colocalize with areas of nonperfusion on OCTA[11-13]. It is possible that these cystoid spaces may result in lateral displacement of capillaries or preferentially occur in areas of capillary nonperfusion due to the development of nearby leaky micro aneurysms[11-14]. The disappearance of these cystoid spaces following treatment with resultant capillary reperfusion may be another mechanism for an increase in vascular density following treatment[13].

Table 3: values of pre- and post-VEGF injection according to BCVA (decimal) (n= 60)

BCVA	Pre VEGF injection	Post VEGF injection	Improvement (%)	t	p
Min. – Max.	0.08 – 0.25	0.17 – 0.25	0.10 ± 0.03 (25.0%)	20.510*	<0.001*
Mean ± SD.	0.15 ± 0.06	0.25 ± 0.07			

*t: Paired t-test, p: p-value for comparing between pre and post, *: Statistically significant at p ≤ 0.05*

Table 4: Correlation between BCVA and CME (improvement)

	CME Improvement	BCVA (improvement)	R	P
Pre VEGF injection	3.50 ± 0.50	0.15 ± 0.06	*0.601*	<0.001*
POST VEGF injection	2.0 ± 0.82	0.25 ± 0.07		

*r: Pearson coefficient, *: Statistically significant at p ≤ 0.05*

In one study analyzing the effect of treatment on these spaces, however, no reperfusion occurred in nonperfusion areas following resolution of the cystoid spaces[11]. This, however, may have been due to the chronic nature of edema in these cases which requires further validation in cases with the earlier stages of the disease. The effects of repeated intravitreal injections of different VEGF inhibitors for DME on the macular perfusion of diabetic patients have been recently evaluated in several studies that used the relatively new OCT technology. Originally, this evaluation has depended on the use of FA and expert human graders[15-18].

Conclusion

Improvement of macular perfusion and cystoid macular edema associated with improvement in best-corrected visual acu-

ity. Anti-VEGF treatment was very effective in DME.

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