Original Article

Role of Intravitreal Bevacizumab (Avastin) in Diffuse Diabetic Macular Edema

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Purpose: To observe the changes in best corrected Visual Acuity (VA) and central macular thickness after intravitreal injection of Bevacizumab (Avastin) in patients suffering from diffuse macular edema.

Study Design: Observational study.

Place and Duration of Study: Sindh Institute of Ophthalmology and Visual Sciences, Hyderabad, Sindh. From July 2017 to December 2017.

Material and Methods: 50 eyes from 29 patients suffering from diffuse Diabetic Macular Edema (DME) were given intravitreal bevacizumab. Patients with VA ≤ 20/60, HBA1C ≤ 7.5 % were included. While, patients with high diabetic profile, high blood pressure, increased blood urea and creatinine level and past history of stroke were excluded. Slit-lamp examination was performed to observe the number of anterior chamber cells. Best corrected VA investigated by early treatment diabetic retinopathy study (ETDRS) chart and complete ocular examination was performed on each patient. Swept source Optical Coherence Tomography (OCT) was used for the measurement of Central Macular Thickness (CMT).

Results: 50 eyes of 29 patients between 35 and 75 years of age (mean 49.28 ± 8.16 years) were given Intravitreal injection of Bevacizumab. The Base line VA & central macular thickness mean were noted, significant increase in VA & decrease in macular thickness after 3 months of 3rd administration of injection Avastin was confirmed by OCT. Two way ANOVA was used to analyze the data.

Conclusion: Bevacizumab plays an important role in reducing diabetic macular edema and improving vision. Stability and increase in VA was observed and CMT in diabetic macular edema was decreased after intravitreal injection of bevacizumab.

Key Words: Bevacizumab, Diabetic macular edema, Vascular endothelial Growth Factor.

Diabetic retinopathy (DR) is one of the major causes of visual disorders in actively working population in the world[1]. Moreover, in developing countries DR has been demonstrated as a chief cause of blindness. Leakage of macular capillaries results in Diabetic macular edema (DME) which is the main reason of visual impairment in proliferative and non-proliferative DR[2,3].

Vascular permeability factor, also known as Vascular Endothelial Growth Factor (VEGF), is a single protein which causes the phosphorylation of tight proteins that stimulates the formation of blood vessels and hence increases the permeability of retinal vessels[4]. Similarly, VEGF gene is known to induce its transcription by hypoxia and has been reported to be a major inducer of VEGF gene transcription[5,6]. Patients suffering from proliferative diabetic retinopathy (PDR) have been found with higher levels of VEGF in ocular

fluids[7]. In addition, when normal eyes of experimental animals were inoculated with VEGF, they resulted with micro aneurysm formation and higher vascular permeability which are the same pathological conditions seen in the patients of diabetic retinopathy[8,9]. Retinal neovascularization and macular edema have also been shown to be affected by VEGF[10,11]. Treatments with anti VEGF drugs have been proved as a substitute for the management of diffuse Diabetic Macular Edema (DME)[12]and Retinal Neovascularization (RN)[13].

Bevacizumab (Avastin) is a drug used in the treatment of diabetic eye diseases, age related macular degeneration (AMD) and other retinal disorders. It is a full length protein which binds to all families of VEGF and has been used systemically in tumor therapy[14]. Intravitreal injection of Avastin has been reported as a useful drug in the suppression of choroidal neovascularization, macular edema due to central retinal vein occlusion (CRVO), vascular permeability and fibro-vascular proliferation. Furthermore, intravitreal injection of Avastin does not seem to be harmful at high concentration in the retina of albino rabbit[18].

Compared with laser, Anti VEGF drugs have been reported more effective. Avastin is extensively used off-label as an intravitreal management of macular edema due to other causes[10]. In the following study, we investigated the role of anti VEGF Bevacizumab (Avastin) in patients suffering from DME wherein, VEGF is the main mediator of vascular permeability and plays a key role in the catabolism of retinal blood barrier.

MATERIAL AND METHODS

50 eyes of 29 patients of diffuse DME were recruited in this study. It was accepted by Institutional Review Board (IRB) of SIOVS. The diagnosis of diffuse DME was investigated by swept source OCT.

Inclusion criteria comprised of best-corrected VA ≤ 20/60, Glycated Hemoglobin ≤ 7.5%, any gender, patients with type 2 Diabetes Mellitus, aging between 35 to 75 years. Diffuse DME criteria was defined as hard retinal exudates within 500µm of the macular center, 1 disc diameter or greater retinal edema, any part of which was under the limit of 1 disc diameter of center of macular area. Exclusion criteria comprised of patients with bleeding disorders, any infection of cornea, former treatment of Avastin, recent history of heart attack, hypertension and former history of laser either focal or grid.

All patients were selected through retina clinic of Sindh Institute of ophthalmology & visual science (SIOVS), Hyderabad, after fulfilling the inclusion criteria. Objectives and methods of study were explained and then consent form was signed from each individual.

Slit lamp examination was done in each patient. Swept source OCT was performed for assessment of macular thickness before administration of Avastin. Anti VEGF Bevacizumab (Avastin, 1.25 mg/ 0.05 mL) was injected intravitreal by monthly interval for three months. It was injected after local anesthesia, 3.5 mm in pseudophakic and 4 mm in phakic patients away from limbus. Swept source OCT was performed on all patients 3 months after anti VEGF injection. Outcome was observed on the basis of decrease in central macular thickness (CMT) and improvement in visual acuity. Swept source OCT was performed to confirm the effect of anti VEGF (Avastin) in diffuse DME. Data was analyzed using SPSS version 24.

RESULTS

A total of 50 eyes of 29 patients were selected during this study. Among whom, 32 eyes were from males and 18 from females. Avastin was injected intravitreal in all 50 eyes of 29 patients. Patients' ages ranged between 35 and 75 years (mean 49.28 ± 8.16 years). All patients selected in this study were Non-Insulin Dependent Diabetic (NIDDM), had diffuse DME, which was confirmed by swept source OCT.

The baseline VA mean & CMT mean were noted, significant increase in VA & decrease in macular thickness after 3 months of 3rd administration of injection Avastin was confirmed by OCT. During this 3 months study, there were no complains of intraocular irritation, endophthalmitis, enhanced IOP and detachment of retina.

Statistical analysis of OCT and visual acuity (VA) are described in table1 and table 2, respectively.

Table1: Descriptive statistics of OCT at baseline and after 3 months of intravitreal injection of Avastin.

	N	CMT (μM) Minimum	CMT (μM) Maximum	Mean	SD
Baseline	50	300	595	372.14	77.60
1 Month	50	250	389	323.19	73.82
3 Months	50	166	498	278.94	75.86
P Value				0.03904*	

CMT – Central macular thickness
SD – Standard Deviation
Analysis was performed in SPSS version 24.0
*Represents a significant difference

Table 2: Descriptive statistics of Visual Acuity (VA) at baseline and after 3 months of intravitreal injection of Avastin.

	N	Minimum	Maximum	Mean	SD
VA pre	50	0.3	1.0	0.692	0.1915
Et1	50	0.2	1.0	0.540	0.2306
Et3	50	0.2	1.0	0.438	0.2423
P Value				0.02804*	

VA Pre – Baseline ETDRS Visual Acuity, Et1 – ETDRS Visual Acuity at one month, Et3 – ETDRS Visual Acuity after three months
SD – Standard Deviation
Analysis was performed in SPSS version 24.0
* Represents a significant difference

DISCUSSION

The most frequent complication in diabetic patients is diffuse DME, which is a significant cause of visual impairment in these patients. Due to increase in extracellular fluid, the level of vision decrease, as a result barriers within the retinal blood vessels due to accumulation of this extracellular fluid.

It has been reported that DME and VEGF are affected by retinal hypoxia, which increases vascular permeability of macula, leads to DME in patients of diabetes. Bevacizumab is known to produce quick result in recovery of macular edema.

As demonstrated in the section 'results', a total of 50 eyes from 29 patients were examined during this research. All the eyes were given Intravitreal injection of Avastin, which lead to functional and physiological betterment. Central macular thickness (CMT) before administration of injection Avastin ranged from 300 to 595 μm with a mean of 372.14 μm.

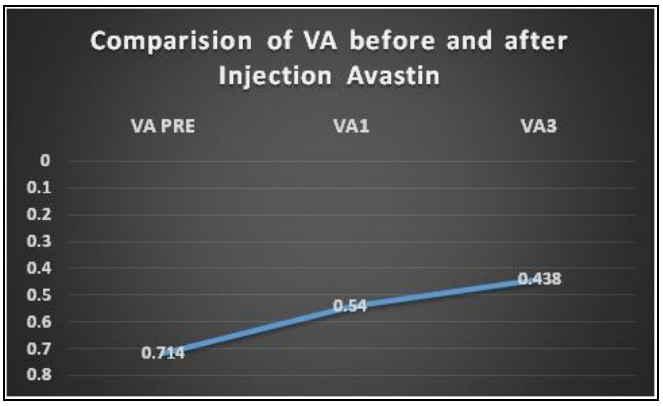

Fig. 1: Comparison of Visual Acuity (VA); VA PRE – at baseline. VA1 – VA after 1 month, VA3 – VA after 3 months.

As shown in figure 1, after one month of administration of Avastin, significant decrease in visual acuity was observed with a mean of 0.540 μm. On the other hand, mean CMT decreased noteworthy up to 323.19 ± 32.58 μm ranging from 250.78 to 389.76 μm. 46 eyes showed increased in VA, while 4 eyes showed no difference in VA.

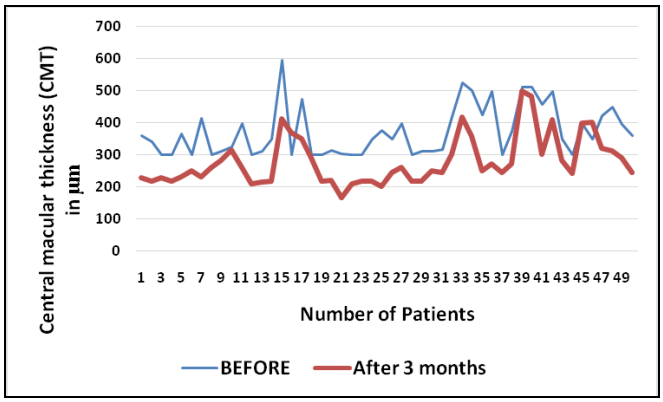

Fig. 2: Comparison of Central Macular Thickness at baseline (Before) and after three months of injection Avastin.

After three months of the treatment with injection Avastin, there was a noteworthy decrease in CMT, ranging from 166 to 498 µm in all 50 patients with a mean of 278µm measured from swept source OCT (Fig. 2). 47 eyes showed reduction in macular thickness and only 3 eyes showed minor increase in macular thickness. Mean VA before injected injection Avastin was 0.692. During this study, no systemic side effects were noticed and bevacizumab was well tolerated. There was no evidence of ocular inflammation, correspondingly, Optical tolerance was also good. As compared with the study reported by Haritoglou *et al.*[20] our research proved noteworthy decease in CMT and improvement in Visual Acuity.

Recently, Chen et al described the mechanism and degenerative effects of intravitreal Ranibizumab in 10 different eyes in patients suffering from macular edema[21]. On the other hand, our study showed improvement in OCT findings and VA in comparatively more patients (Fig. 3).

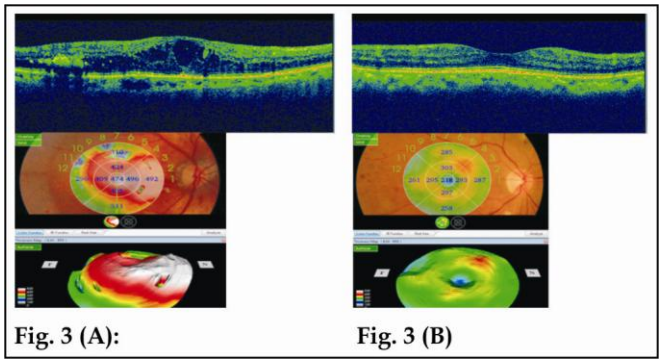

Fig. 3(A): Central macular thickness before injection Avastin 474µm, measured by swept source 3D Optical Coherence Tomography.

Fig. 3(B): Central macular thickness after 3rd intravitreal injection of AVASTIN was 218 µm showing significant improvement.

CONCLUSION

Anti VEGF injection of bevacizumab (Avastin) proved to be capable for the management of diabetic macular edema and improving vision. At the doses of 1.25 mg/0.05 mL, it provided significant increase in VA and helps in decreasing CMT in DME. We may assume without any harm that the rate of visual complications were managed with no significant side effects.

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Conflict of Interest

There are no conflicts of interest

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