Original Article

To Compare the Effect of Intravitreal Bevacizumab on the Resolution of Macular Edema Secondary to Diabetic Retinopathy and Branch Retinal Vein Occlusion

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Purpose: To assess the efficacy of intravitreal bevacizumab in treating patients with macular edema secondary to diabetic retinopathy and retinal vein occlusion.

Material and Methods: This comparative study was carried out in LRBT Free Base Eye Hospital, Karachi from 1st March 2010 to 28th February 2011. Total 60 patients were recruited for the study among which 32 (53.33%) were male and 28 (46.66%) were female, with age ranging from 40-65 years. Out of the 60 patients, 35 (58.33%) were diagnosed with macular edema secondary to diabetic retinopathy, and 25 (41.66%) with macular edema secondary to branch retinal vein occlusion. They were classified into Group A and Group B respectively. Informed written consent was obtained from all the patients before their participation in the study. Detailed medical and ophthalmic history was recorded. Baseline assessment of patients included best-corrected visual acuity (BCVA) on snellen chart, slit lamp examination of anterior segment and posterior segment (using 78D/90D lens), indirect fundoscopy with 20D lens, intraocular pressure measurement, colour fundus photography, fundus fluoresein angiography and optical coherence tomography. All the patients were treated with 2 injections of intravitreal bevacizumab 1.25 mg/0.05 ml, at an interval of 6 weeks, and assessment was carried out at 6 weeks and 12 weeks. Efficacy of intravitreal bevacizumab was assessed in terms of improvement in BCVA and reduction of macular thickness.

Results: 60 patients were enrolled in this study and were followed for a period of 3 months. Group A: at the end of three months, 27 (77.14%) out of 35 patients showed improvement in BCVA of 2 snellen lines from baseline, and the mean central macular thickness (CMT) reduced from 502µm to 384µm. Group B: At the end of three months, 17 (68%) out of 25 patients showed improvement of BCVA of up to 2 snellen lines and mean CMT reduced from 510µm to 370µm.

No serious adverse effects were observed in both the groups such as inflammation, increased intraocular pressure, endophthalmitis or thromboembolic event.

Conclusion: Intravitreal bevacizumab injection for macular edema caused by branch retinal vein occlusion and diabetic macular edema was safe and effective for improving visual acuity and reducing central retinal thickness.

Macular edema associated with vascular diseases, such as diabetic retinopathy, vascular occlusions and choroidal neovascularization, can have different etiopathologies[1].

Diabetic retinopathy is a significant public health problem[2]. Diabetic retinopathy occurs due to abnormal retinal blood vessels either due to their proliferation (proliferative retinopathy) or due to the fact that the vessels are functionally incompetent and leak fluid and lipid in to the retina. Visual impairment occurs when edema affects the central retina or macula (diabetic macular edema)[3].

Retinal vein occlusion (RVO) is the most common retinal vascular disease after diabetic retinopathy[4]. The most common sequelae of branch retinal vein occlusion (BRVO) is the development of macular edema (ME) with a consecutive deterioration in vision. The major stimulus for the formation of macular edema and neovascularization in patients with RVO seems to be hypoxia-induced production of vascular endothelial growth factor (VEGF), an angiogenic factor that promotes angiogenesis and increases vascular permeability[5].

VEGF has been implicated as an important factor in the breakdown of the blood-retinal barrier, with increased vascular permeability resulting in retinal edema in diabetic patients by affecting the endothelial tight junction proteins[6]. VEGF levels are significantly elevated in eyes with diabetic macular edema[7]. Therefore, anti-VEGF treatments have been proposed as an alternative adjunctive treatment for diabetic maculae edema (DME) [8].

While several studies have been conducted assessing the role of bevacizumab in the management of diabetic macular edema and macular edema secondary to retinal vein occlusion, there are no studies available comparing the efficacy of bevacizumab in both diabetic retinopathy and macular edema secondary to retinal vein occlusion.

MATERIAL AND METHODS

This study was carried out in LRBT Free Base Eye Hospital, Karachi from 1st March 2010 to 28th February 2011. Study included 60 patients, 32 (53.33%) were males and 28 (46.66%) females with age ranging from 40 to 65 years. Out of 60 patients, 35 (58.33%) were diagnosed with macular edema secondary to diabetic retinopathy, 25 (41.66%) were secondary to branch retinal vein occlusion, all were divided into two groups. Group A included 35 patients with diabetic macular edema and Group B included 25 patients with macular edema secondary to BRVO. Informed written consent was obtained from all patients before their participation in the study. Detailed medical and ophthalmic history was noted. Base line assessment of patients included best corrected visual acuity on snellen chart, Amsler grid chart was used to detect any metamorphosis, slit lamp examination of anterior segment, intraocular pressure was recorded, posterior segment examination was carried out by slit lamp biomicroscopy with 78D/90D lens as well as indirect fundoscopy with 20 D lens. Color fundus photograph was taken, Fundus fluorescein angiography was performed to observe leakage and to ascertain the limits of macular edema. Central macular thickness was assessed with optical coherence tomography (figure 1 and 2). Systemic investigations include blood pressure recording, laboratory test for urea, creatinine and electrolytes and glycosylated hemoglobin (HbA1c) was checked to determine diabetic control over the last three months. Those patients having any evidence of other macula pathology like age related macular degeneration (AMD), glaucoma, previous pan retinal photocoagulation or grid laser within the past six months, evidence of vitreomacular traction, any irregularity or widening of the foveal avascular zone (FAZ) on fundus fluorescein angiography, glycosylated hemoglobin >8 mg/dl, uncontrolled hypertension, chronic renal failure or recent history of cerebrovascular accident, were excluded from the study.

The administration of intravitreal Bevacizumab (Avastin) was approved by the hospital ethics committee. The dose of intravitreal Bevacizumab (Avastin) delivered was 1.25 mg/0.05 ml. Two injections were given at an interval of 6 weeks under strict aseptic conditions. Prophylactic antibiotics were given for 4 days after the procedure. Patients were followed on the 1stpost operative day to check for any elevation of intraocular pressure, subconjunctival hemorrhage or any signs of infection. The next followup was scheduled on the 6th week to assess any improvement in best corrected visual acuity, central macular thickness on optical coherence tomography and extent of edema on fundus flourescein angiography. After recording these findings, patients were administered the second injection of bevacizumab 1.25 mg/0.05 ml. The last follow up was done 6 weeks later (12 weeks after the first injection) and the results were tabulated.

Data was analysed in SPSS (version 13). Frequency and percentages were calculated for categorical variables like visual acuity and central macular thickness. McNemar's test was applied pre and post injection changes in visual acuity and central macular thickness within each group; and chi-square test was applied to compare these changes between the two groups.

RESULTS

60 patients, 32 (53.33%) males and 28 (46.66%) females with age ranging between 40-65 years were enrolled in the study. Among them Group A consisted of 35 (58.33%) patients who were diagnosed with diabetic macular edema whereas, Group B consisted of 25 (41.66%) patients diagnosed with macular edema secondary to BRVO. Patients in both the groups received two doses of intravitreal bevacizumab (Avastin) 1.25 mg/0.05 ml.

Group A: On the first post-injection evaluation at 6 weeks, 12 (34.28%) out of 35 patients had visual improvement from 6/60 to 6/36, 6 (17.14%) out of 35 patients had visual improvement from 6/36 to 6/24, 2 (5.71%) out of 35 patients had visual improvement from 6/24 to 6/18, 2 (5.71%) out of 35 patients had visual improvement from 6/18 to 6/9 and2 (5.71%) out of 35 patients had visual improvement from 6/12 to 6/6. Average decrease in macular thickness was 71μm. On final evaluation after 3 months, 12 (34.28%) out of 35 patients had visual improvement from 6/36 to 6/24, 6 (17.14%) out of 35 patients had visual improvement from 6/24 to 6/18, 2 (5.71%) out of 35 patients had visual improvement from 6/18 to 6/9, 2 (5.71%) out of 35 patients had visual improvement from6/9 to 6/6. Thus, overall 24 (68.57%) patients showed an improvement of 2 lines of vision on the snellen chart, whereas, in 8 (22.85%) patients visual acuity remained unchanged. In 3 (8.57%) patients, vision deteriorated despite decrease in macular thickness. Mean decrease in central macular thickness was 118μm at 12 weeks follow up and 10 (28.5%) out of 35 patients showed a decrease in focal and diffuse leakage.

Group B: Six weeks after the first injection, 2 (8%) out of 25 patients had visual improvement from counting finger at 3 feet to 6/60, 10 (40%) out of 25 had visual improvement from 6/60 to 6/36, 4 (16%)out of 25 had visual improvement from 6/36 to 6/24, 2 (8%) out of 25 had visual improvement from 6/24 to 6/18 and 1 (4%) out of 25 had visual improvement from 6/18 to 6/12. Mean reduction in macular thickness was 80 μm. On final assessment after 3 months (i.e. 6 weeks after the 2nd injection), 2 (8%)out of 25 had visual improvement from 6/60 to 6/24 partial, 10 (40%) out of 25 had visual improvement from 6/36 to 6/24, 4 (16%) out of 25 had visual improvement from 6/24 to 6/18, 2 (8%) out of 25 had visual improvement from6/18 to 6/12, 1(4%) out of 25 had visual improvement from 6/12 to 6/9. Thus, overall 19 (76%) patients showed an improvement of up to 2 lines of vision on snellen chart, whereas in 4 (16%) patients, visual acuity remained unchanged. In 2 (8%) patients, vision deteriorated despite the decrease in macular edema. Mean decrease in central macular thickness was 140 μm at 12 weeks follow up.

On comparing the visual acuity at final assessment at 12months, no statistical difference was found between the two groups (p=0.794). Similarly, on comparing the central macular thickness values at 12 months, no statistical difference was found (p=0.355).

Figure 3 and 4 indicate the post operative improvement in visual acuity and macular edema in both the groups.

DISCUSSION

Macular edema can result from a variety of retinal diseases and can cause varying degrees of visual loss. The most common cause of macular edema is diabetic macular edema (DME), and ME within one disc diameter of the fovea occurs in 9% of patients with diabetic retinopathy (DR)[9]. Retinal vascular occlusion (RVO) is the second most common cause of macular edema and often has devastating visual consequences[10].

Diabetic macular edema is a manifestation of diabetic retinopathy that produces loss of central vision. Macular edema affects approximately 29% of diabetic patients with disease duration of 20 years or more and main reason for reduced vision in this population[11]. Diabetic macular edema is now the principle cause of vision loss in people with diabetes[12]. Diabetic macular edema has been characterized by inflammation, including intravenous induction of proinflammatory cytokines[13] and intraretinal expression of proinflammatory responses[14].

Retinal vein occlusion is a frequent vascular disease that often leads to visual impairment. One of the main reasons for visual loss is the development of macular edema[15]. An impaired microcirculation and

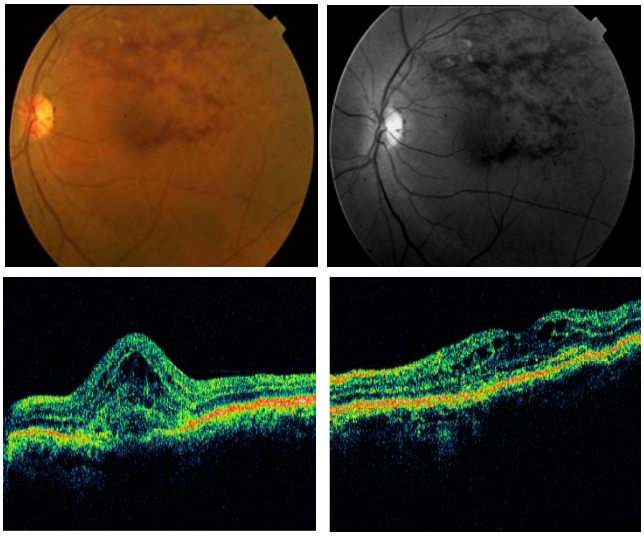

Fig. 1: Illustrates the coloured photograph and red-free photograph of a patient with superior branch retinal vein occlusion with macular edema. The images at the bottom show the optical coherence tomographic pictures. The image on the left was taken before the injection Bevacizumab (Avastin) was administered and the image on the right was taken 3 months post-injection.

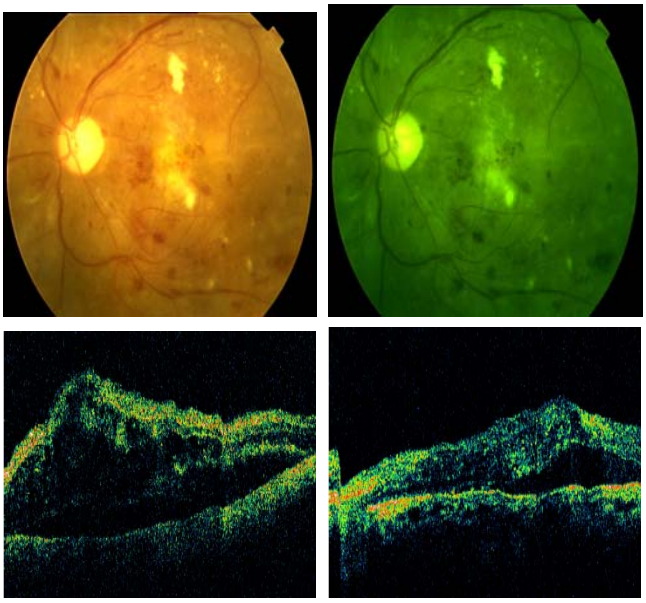

Fig. 2: Illustrates the coloured photograph and red-free photograph of a patient with diabetic macular edema. The images at the bottom show the optical coherence tomographic pictures. The image on the left was taken before the injection Bevacizumab (Avastin) was administered and the image on the right was taken 3 months post-injection.

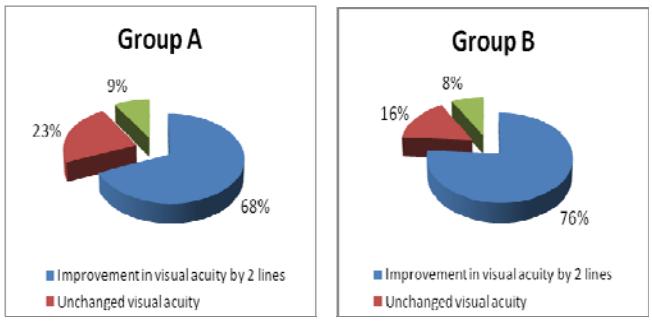

Fig. 3: Indicates the post injection best corrected visual acuity at 3 months (on Snellen chart) in the two groups. It also indicates the p-value which shows that statistically there is no difference between the two groups.
P = 0.794 (insignificant difference)

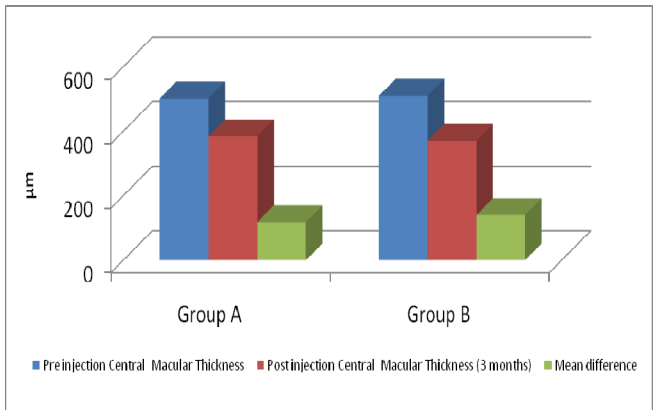

Fig. 4: Indicated the central macular thickness pre-injection and at final follow up at 3 months in Group A and Group B. it also gives the mean difference of central macular thickness in the two groups. It also indicates the p-value which shows that statistically there is no difference between the two groups.
P = 0.355 (statistically insignificant)

reduced blood flow lead to a dysfunction of the endothelial blood-retinal barrier with increase permeability and plasma exudation into the central retina. Efforts are required to reduce macular edema as soon as possible as irreversible damage of the photoreceptors occurs as early as 3 months after the development of macular edema[16].

Bevacizumab was initially studied for the treatment of exudative age-related macular degeneration (AMD) with intravenous delivery with promising results[17]. In this study we compared data of

baseline values and after treatment with two injections of intravitreal Bevacizumab (Avastin) 1.25mg/0.05ml in patients with macular edema secondary to diabetic retinopathy and branch retinal vein occlusion. In group A, 68.57% (24/35) showed visual improvement up to two lines of snellen chart, and on average; macular thickness was reduced up to 118µ at the end of 12 weeks. Whereas Seo WJ[18] in 2009, showed improvement of best corrected visual acuity ≥2lines and macular thickness reduction was 139µ on three months follow up. Nagasawa et al[19] did not observe any change in best visual acuity and retinal thickness in the short term observation up to 4 weeks after the intravitreal injection of Bevacizumab. Shen et al[20] in 2011, observed mean BCVA improved from 41.76 ± 15.59 to 48.41 ± 17.90, and macular thickness up to 123µ on three months of follow up. In group B, 76% (19/25) showed visual improvement of up to two lines of snellen chart, and on average; macular thickness was reduced up to 140µ at the end of 12 weeks. Whereas Hoeh et al[21] in 2009, showed visual acuity improved by 1.8 ± 2.6 lines on (ETDRS), and mean central retinal thickness decreased 215µ on 25 weeks follow up. Abegg et al[22] in 2008, showed improvement of visual acuity from 0.7 ± 0.3 to 0.5 ± 0.3 (logMAR), and decrease in central retinal thickness was 149µ on 6 weeks after intravitreal injection of bevacizumab. Astem et al[23] in 2009 observed that intravitreal Bevacizumab seems to be more effective for macular edema due to retinal vein occlusion than diabetic macular edema. But in this study, no statistically significant difference was observed regarding the efficacy of avastin on the resolution of macular edema between the two groups in terms of visual acuity (p=0.794) and central macular thickness (p=0.355).

CONCLUSION

For macular edema caused by retinal vein occlusion and diabetic macular edema, Bevacizumab administration intravitreally improved visual acuity and central retinal thickness at each time point through to 12 weeks and although the follow up period was short with limited number of patients, it was observed that intravitreal bevacizumab was more effective in eyes with branch retinal vein occlusion than those with diabetic macular edema. Further larger control trials as well as longer duration of follow up are required to establish the efficacy of intravitreal bevacizumab in resolving macular edema in these two vascular diseases.

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