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Original Article

Visual Outcome of Intravitreal Bevacizumab in Treatment of Diabetic Retinopathy

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Abstract

Background :To evaluate the efficacy of monthly intravitreal bevacizumab injections (1.25 mg/.05 ml) in improving or stabilizing visual acuity measured by Snellen's visual acuity charts for diabetic retinopathy.

Methods: This was a prospective Quasi experimental study of 59 diabetic patients having diabetic retinopathy with indication of intravitreal anti VEGF,Bevacizumab. Patients diagnosed of having fresh vitreous haemorrhage and diabetic macular edema were included. Maximum three intravitreal bevacizumab injections were given, each with a dose of 1.25mg in 0.05ml(at 0month, 1 month, 2 months) with final follow up at the period of 3 months. The criteria for improvement was a gain of at least one line on Snellen's visual acuity chart, compared to the baseline while stabilization was considered if the visual acuity was unchanged relative to the baseline.

Results: A total of 59 patients, 25 (49.1%) males and 34 (50.84%) females , having age range 40-65 years,were given intravitreal injection. Twenty six eyes (44.06%) with diabetic macular edema showed improvement while visual acuity was stabilized in 4 eyes (6.7%). In patient with vitreous hemorrhage, 27 eyes (45.76%) showed improvement while stabilization of visual acuity was noted in 2 eyes (3.3%). No patient with worsening of visual acuity was noted.

Conclusion: Intravitreal Bevacizumab is very effective in improving the visual outcome in diabetic patients having macular edema and vitreous hemorrhage.

Key Words: Visual Outcome, Intravitreal, Bevacizumab, Diabetic Retinopathy

Introduction

As the prevalence of diabetes is increasing in the world, Diabetic retinopathy (DR) is becoming a most important public health problem and threat to sight in the working-age population.[1, 2] It is also a major cause of blindness in developing countries. According to the Diabetic Association of Pakistan – World Health Organization (DAP-WHO) survey (1994-1998), overall prevalence of diabetes in Pakistani population is 11.47%.[1]In diabetic retinopathy there are abnormal retinal blood vessels which can be either due to the proliferation of new vessels (proliferative retinopathy) or due to functionally incompetent and leaky vessels. The vascular endothelial growth factor (VEGF) has been suggested as a main factor, firstly in proliferation of new weak vessels which can rupture causing vitreous hemorrhage and resulting in decrease visual acuity, and secondly it causes the breakdown of the blood-retinal barrier causing increased vascular permeability which results in retinal edema by disturbing the endothelial tight junction proteins. This retinal edema in macular area is called diabetic macular edema and when it fulfills a certain clinical criteria, it is known as clinically significant macular edema.[2, 3]

Most of the adults became blind due to proliferative diabetic retinopathy (PDR) and principally treated by pars plana vitrectomy and Argon laser but the bleeding from fibrovascular membrane (FVM) is still a risk to be considered. A humanized vascular endothelial growth factor (VEGF) antibody known as Bevacizumab (Avastin Genetech Inc, South San Francisco, California, USA) previously used for metastatic colorectal carcinoma but recent reports have showed its effectiveness in the treatment of neovascular disorder in the eye like proliferative diabetic retinopathy and in diabetic macular edema.[4]

Though the normal human retina contains VEGF, its levels are considerably raised in eyes with diabetic macular edema(DME) and proliferative diabetic retinopathy(PDR). Therefore, intravitreal anti-VEGF treatments have been recommended as an adjunctive treatment for DME.[3] The drug acts by decreasing the size and number of new vessels and also helps in resolving the vitreous hemorrhage . Currently, some

anti-VEGF drugs, including pegaptanib, ranibizumab, bevacizumab, and aflibercept, are available.[5]

Bevacizumab (Avastin, Genentech Inc., San Francisco, CA) is a complete full-length humanized antibody, it binds to and competitively inhibits all isoforms of the VEGF-A family. While bevacizumab is presently FDA approved for the treatment of metastatic colorectal cancer, metastatic breast cancer, and non-small cell lung cancer , it is widely used off-label for treatment of ocular diseases like retinal vein occlusion, neovascular age-related macular degeneration, DME, proliferative diabetic retinopathy, rubeosis irides, and retinopathy of prematurity[5].

Although intravitreal use of bevacizumab is an off-label option, its use has increased exponentially in the past few years primarily due to its efficacy and cost effectiveness.[5] The purpose of this study was to evaluate the efficacy of monthly intravitreal bevacizumab injections (1.25 mg/.05 ml) in improving or stabilizing visual outcomes (best corrected visual acuity (BCVA)), as measured by snellen's visual acuity charts, for diabetic retinopathy.

Patients and Methods

This prospective study which was conducted at Benazir Bhutto Hospital, Rawalpindi from July to June 2015.A total number of 59 eyes of 59 patients were selected on the basis of non-probability, purposive sampling. Inclusion criteria was diabetic patients with vitreous hemorrhage (associated with proliferative diabetic retinopathy) with absence of tractional retinal detachment on B-scan ultrasonography,diabetic macular edema with any stage of non proliferative diabetic retinopathy and diabetic macular edema with proloferative diabetic retinopathy but without vitreous hemorrhage. Diabetic patients who had received prior treatments with other modalities like laser photocoagulation, intravitreal Ranibizumab, intravitreal or posterior subtenon triamcinolone, patients with anterior segment diseases, diseases affecting the vision like corneal opacity, uveitis, glaucoma, visually significant cataract, etc. due to which exact role of bevacizumab, regarding visual outcome, cannot be assessed .Patients with other associated posterior segment diseases affecting the vision like age related macular degeneration, central retinal vein occlusion, central retinal artery occlusion, retinal detachment (rhegmatogenous, tractional, serous, all type of), opic nerve disease, etc and patients who developed any complications of intravitreal Bevacizumab which can affect the visual acuity , were excluded. Pre-operatively visual acuity was measured using snellen's acuity chart, complete anterior segment and posterior segment examination was done using slit lamp, +90D lens, indirect ophthalmoscopy. Intraocular pressure (IOP) was measured using Goldman applanation tonometer. Fundus Fluorescein Angiography and B-scan ultrasound examinations were done where necessary. The risks and benefits of treatment were discussed and informed consent was taken .All the patients included in the study received intravitreal bevacizumab with a dose of 1.25mg in 0.05ml and given by the same surgeon. Topical anesthetic proparacaine was given before injection and repeated as necessary. All the injections were given with strict sterile technique (cleaning conjunctival sac with diluted povidone iodine) under full aseptic conditions in operation theatre. Injection was given 4mm, 3.5mm, 3mm posterior to the limbus in phakic, psuedophakic and aphakic eyes respectively through the infero-temporal pars plana with a 30-gauge needle . The injection site was compressed for several seconds to avoid reflux of avastin when the needle was removed. Patients were advised to use antibiotic and steroid combination eye drops for 07 days after the intravitreal injection. Follow up was scheduled after 1 week, 4 weeks and every month till the end of follow up at 3 months. Follow up visits included checking visual acuity by snellen's chart and complete ocular examination. At each visit complications like endophthalmitis, vitreous hemorrhage (not present pre-injection , in case of macular edema), traumatic cataract, uveitis, retinal detachment which can affect the visual acuity, were evaluated . The primary end point of the treatment was a change in best corrected visual acuity from baseline over 03 months. The maximum number of injections given was three for each eye and they were given four weeks apart.The criteria for improvement was a gain of at least one line on snellen's visual acuity chart , compared to the baseline while stabilization was considered if the visual acuity on the snellen's chart was unchanged relative to the baseline.

Results

Out of 59 diabetic patients, 42.4% were males and 57.6% were females. The age range was from 45 to 67 years with a mean of 53.02 ± 9.79. (Table 1). All patients completed 1 month of follow-up after the last injection. The glycosylated hemoglobin (HbA1c) was 6.0 ± 1.3 at baseline. Pre-injection, there were 16 (27%) eyes with best corrected visual acuity (BCVA) better than or equal to 6/15, 27 eyes (45%) with VA between 6/24 and 6/60 and 16 (27%) with VA below 6/60. At

the end of 1 month of follow up after 3rd injection, 37 (62.7%) eyes had BCVA better than or equal to 6/15; 18 (30.50%) between 6/24 and 6/60 and in 4 (6.7%) eyes the vision was worse than 6/60. Two (10%) eyes had BCVA better than or equal to 6/18. So, the final assessment was 1 month after the 3rd injection.A total number of 59 patients, 25 males and 34 females with an age range of 40-65 years, mean age 53.02 (± SD 9.79) were subjected to intravitreal injection of bevacizumab (Table 1). Out of the total 59 eyes, 30 (50.84%) had diabetic macular edema and 29 (49.16%) with diabetic vitreous hemorrhage (DVH) (Table 2).

Table 1: Patient's characteristics

Age range	40-65
Males	25 (42.4%)
Females	34 (57.6%)
No. of patients	59
Duration of study	1 year
Average follow up	3 months

Table 2: frequency of DME and vitreous hemorrhage

Total number of eyes	59
DME	30 (50.84%)
Vitreous hemorrhage	29 (49.16%)

Table 3: Baseline visual acuity (preinjection)

Baseline visual acuity	DME(No. of eyes)	DVH(No. of eyes)
6/300	10	5
6/150	1	-
6/60	1	-
6/30	8	5
6/24	7	6
6/15	3	11
6/12	-	2

Twenty six eyes (44.06%) with diabetic macular edema showed improvement while visual acuity was stabilized in 4 eyes (6.7%). In patients with diabetic vitreous hemorrhage associated with proliferative diabetic retinopathy (PDR) with vitreous hemorrhage, 45.76%eyes showed improvement while stabilization of visual acuity was noted in 2 eyes (3.3%). No patient with worsening of visual acuity was noted. A significant outcome in visual acuity was noted (Table 3-5; Figure 1). The Wilcoxon test was used for comparison of preoperative and postoperative BCVA (Table 6). For all statistical tests a p value of <0.05 was considered statistically significant and in our study it is <0.05 which is statistically significant. Snellen visual acuity was converted to Log MAR for data analysis.No systemic side effects of the given treatment were observed.However amongst the local side effects, sub-conjunctival hemorrhage was the most frequent; occured in 20 eyes (19.6%). Complications like endophthalmitis, retinal detachment or traumatic cataracts were not seen in any case.

Table 4: Visual outcomes of IVB: Post injection improvement at 3 months

Post Injection visual acuity	DME(No. of eyes)	DVH(No. of eyes)
6/6	-	2
6/7.5	3	11
6/12	2	3
6/15	8	8
6/24	2	2
6/30	3	3
6/60	8	-
6/300	4	-

Table 5: Pre and post injection visual acuities
(taking all diseases in account)

Visual acuity	PreInjection, no. of eyes	Post injection, no. of eyes
6/6 – 6/15	16	37
6/24 – 6/60	27	18
< 6/60	16	4

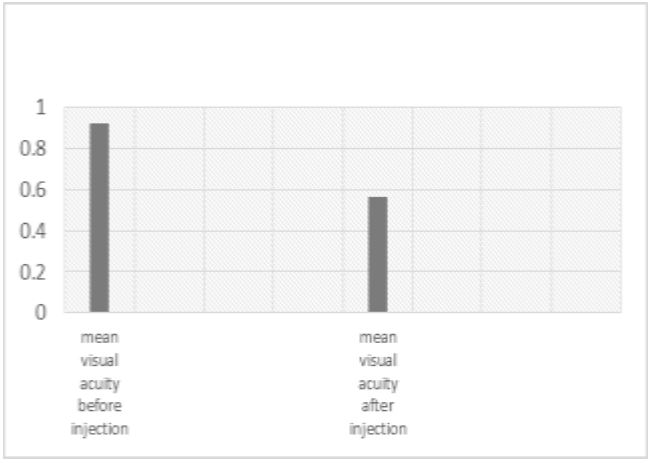

Figure 1. Mean visual acuity before and after injection

Table 6: Wilcoxon test:

Mean Visual Acuity Before Injection	Mean Visual Acuity After Injection	p-Value
0.921	0.562	0.001

Discussion

Common causes of visual loss in patients of diabetic retinopathy are macular edema, vitreous haemorrhage and tractional retinal detachment. In patients of diabetic retinopathy, angiogenic mediators such as insulin like growth factor-1, erythropoietin, fibroblast growth factor and endothelial growth factor (VEGF) are released as a result of retinal ischemia and lead to the formation of new vessels in the retina. Vitreous hemorrhage occurs as a result of these neovascular growths and by precluding the retinal view, prevents panretinal photocoagulation, the gold standard treatment in proliferative diabetic retinopathy. The clinical use of anti-angiogenic agents has developed new opportunities for the treatment of retinal vascular disorders. Considering the antiangiogenic therapy, it accelerates the resolution of hemorrhage and facilitates PRP. So, it's a good choice for patients with vitreous hemorrhage.[6]

Diabetic macular edema is the main cause of decreased central vision in patients with diabetic retinopathy. It can be diffuse or localized. Clinically significant macular edema includes retinal thickening within 500 µm of the center of the fovea, hard exudates within 500 µm of the center with associated retinal thickening (which may be outside the 500 µm) and at least one disc diameter of retinal thickening, any part of which is within one disc diameter of the center of the fovea. [7] Diagnosis of macular edema is clinical but we also confirmed our diagnosis by fundus fluorescein angiography, the available investigation in our department. Anti-angiogenic agents have been proved to be effective in resolving this macular edema. The agent which we used was Bevacizumab.

Bevacizumab was first approved by the US Food and Drug Administration (FDA), for the treatment of carcinomas[8]. Bevacizumab is used as an off-label treatment intravitrealy for ocular diseases with high levels of VEGF, such as choroidal neovascularization (CNV), proliferative diabetic retinopathy, diabetic maculopathy and retinal vein occlusion.[8]

VEGF, was first documented in 1989 by Napoleon Ferrara.[8]VEGF inhibition induces several effects on endothelial cells including inhibition of proliferation.[8] Bevacizumab has been used on "off-label" basis since 2005. It is used as first line treatment in macular degeneration because of its cost effectiveness as compared to other drugs like Lucentis and Macugen (FDA approved antiVEGF).[9,10] The most common indications of Bevacizumab shown in one paper by Lihteh Wu et al were diabetic retinopathy and CNV of several etiologies.[11] Similarly in our study, the main indications were diabetic retinopathy, with diabetic macular edema (50.84%) and PDR with vitreous hemorrhage(49.1%).

In diseases like diabetic retinopathy, diabetic maculopathy, and retinal vein occlusions, increased levels of VEGF were found in vitreous. Regardless of a large antibody, bevacizumab confirmed full penetration of retina[12]. No evidence of a noxious effect was observed in patients treated with 1.25mg of bevacizumab measured by full field and multifocal ERG.[13]

In a prospective study of patients with proliferative diabetic retinopathy treated with intravitreal injections of bevacizumab, a rapid regression of actively leaking neovascularization, as well as significant improvement in mean visual acuity from 20/160 to 20/125 at three months follow up, was found.[14] In our prospective study, out of 59 patients with diabetic macular edema and PDR, 53 patients showed significant improvement (89.8%), however, 6 patients (10.2%), shows no change in BCVA , and there was no patient with worsening of visual acuity. It is comparable to a local study by Jahangir T, et al which also showed significant improvement in visual acuity in patients with diabetic macular edema after intravitreal Avastin.[15]

In a study by Tareen IFH, the mean BCVA at base line was 0.42±0.14 Log Mar units. [16] This improved to 0.34±0.13, 0.25±0.12, 0.17±0.12 and 0.16±0.14 Log Mar units at 1 month after 1st, 2nd 3rd injections and at final visit at 6 months respectively, a difference that was statistically significant (P>0.0001) from base line. The mean 1mm central macular thickness measurement was 452.9 ± 143.1 µm at base line, improving to 279.8 ± 65.2 µm (P<0.0001) on final visit.In a study of Bahoo MLA , Overall improvement rate was 11 (15.7%) with signifcant improvement from 1.028 log MAR at baseline to 0.99 at 12 weeks. [17]In a study of Bokhari SA,mean central macular thickness (CMT) reduced from 502µm to 384µm. [18]In a study of Shaikh FF, mean central macular thickness was 520.40±139.1 µm at baseline, which decreased to 385.90±98.30 µm (p<0.0001) at one month and to 427.40±112.6 µm (p=<0.0001) at three months.[19]

Conclusion

1.Anti-VEGF therapy is the mainstay for the treatment of many retinal diseases.

2.Treatment with Bevacizumab is beneficial in improving and stabilizing visual acuity in diabetic retinopathy.

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