# CHANGES IN VISUAL ACUITY AND MACULAR THICKNESS AFTER INTRAVITREAL BEVACIZUMAB IN VASCULAR RETINOPATHIES

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## ABSTRACT

***Objective:*** To determine the effect of intravitreal Bevacizumab (Avastin) on visual acuity and central foveal thickness in patients with vascular retinopathies.

***Study Design:*** Quasi experimental study.

***Place and Duration of Study:*** Armed Forces Institute of Ophthalmology (AFIO) Rawalpindi, from 1 June 2011 to 31 May 2012.

***Patients and Methods:*** Forty four eyes of 36 patients with macular oedema and/or retinal neovascularization due to retinal vascular diseases were included in final analysis. Each patient underwent complete ophthalmic examination including best corrected logMAR visual acuity (logMAR BCVA), slit lamp biomicroscopy, intraocular pressure measurement, and central foveal thickness (CFT) measurement. Intravitreal Bevacizumab (Avastin) was given in a dose of 1.25 mg/ 0.05 ml under topical anesthesia. Primary outcome measures were logMAR BCVA and CFT values on optical coherence tomography (OCT). Secondary outcome measures were IOP at 1st hour after intravitreal Bevacizumab (IVB) and ocular complications of IVB. These study parameters (excluding IOP) were recorded at 2 weeks, 4 weeks, 8 weeks, 12 weeks and 24 weeks after IVB injection.

***Results:*** Mean age of the study population was 55.36 ± 14.01 years with 78% male patients. Total of 58 IVB injections were given with sub conjunctival hemorrhage (22%), IOP > 21 mm Hg (28%), corneal erosion (7%) and lens injury (3%) were the main complications. Baseline mean logMAR BCVA was 1.24 ± 0.69 and mean CFT was 486.61 ± 145.29 microns that changed to 0.71 ± 0.65 and 310.98 ± 72.90 microns respectively at 2 weeks after IVB injection. Significant visual improvement and reduction in CFT observed at 2 weeks after IVB remained stable throughout the follow up period.

***Conclusion:*** Intravitreal Bevacizumab results in significant visual improvement and reduction in macular oedema in patients with various proliferative retinopathies.

**Keywords:** Bevacizumab, Vascular endothelial growth factor, Intravitreal Injection, Avastin, Retinal Neovascularization.

## INTRODUCTION

Vascular endothelial growth factor (VEGF) is associated with ocular neovascularization and increased vascular permeability that plays a major role in both normal and pathologic angiogenesis. Retinal vaso occlusive diseases are associated with elevated intravitreal levels of VEGF[1]. A number of structurally related growth factors namely VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E and placenta growth factor belong to VEGF family; out of which, VEGF-A is the primary modulator of angiogenesis and increases vascular permeability[2]. Consequently, anti-VEGF agents play an important role in the treatment of retinal vasoocclusive diseases by causing regression of existing micro vessels, normalization of surviving mature vasculature and inhibition of vessel growth and neovascularization[3]. Anti-VEGF agents currently in use are Ranibizumab (Lucentis), Bevacizumab (Avastin) and Pegaptanib (Macugen).

Bevacizumab (Avastin) is a 149 K Da full length humanized murine monoclonal antibody that binds all biologically active isoforms of VEGF-A, thereby inhibiting angiogenesis[2,4,5]. Off label use of intravitreal Bevacizumab has shown promising results in retinal vascular diseases like wet age related macular degeneration (ARMD), Diabetic Macular Edema (DME), Proliferative

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Diabetic Retinopathy (PDR) with or without vitreous hemorrhage, Retinal Vein Occlusion (RVO), Eale's disease, Retinopathy of Prematurity (ROP), Coat's disease and neovascular glaucoma[4,6,7]. Serious systemic side effects like thromboembolism, systemic hypertension and gastrointestinal hemorrhage can occur with intravenous use of Bevacizumab. However, intravitreal dose of Bevacizumab (1.25 mg/ 0.05 ml) is 400 times less than the systemic dose that is well tolerated by patients[8,9]. Despite being used as off label treatment, cost effectiveness of the agent merits its use in various retinal vascular pathologies with favorable functional and anatomical results.

The aim of this study was to determine the changes in best corrected logMAR visual acuity (logMAR BCVA) and central foveal thickness (CFT) after intravitreal Bevacizumab (IVB) injection in patients with retinal vascular disorders. This study further aimed to determine the efficacy of IVB in maintaining visual acuity and macular thickness and requirement of repeat dose of IVB over a period of six month follow up.

## MATERIAL AND METHODS

A quasi experimental study was conducted at Armed Forces Institute of Ophthalmology (AFIO) Rawalpindi from 1st June 2011 to 31th May 2012. Forty one patients of more than 18 years of age with macular oedema and/or retinal neovascularization due to retinal vascular diseases were enrolled in this study through non probability convenient sampling. Inclusion criteria further incorporated patients with fluorescien angiography proven neovascular ARMD, patients of CRVO/BRVO presenting within 3 months of onset of symptoms, and patients of proliferative / non proliferative diabetic retinopathy with macular odema. Patients with uncontrolled hypertension or glaucoma, pregnancy, vitreomacular traction, any other ocular disease secondarily compromising visual acuity, history of vitreoretinal surgery in last one year and history of intravitreal injection during the last 3 months were excluded.

Written informed consent was taken from each patient after discussing pros and cons of treatment and off label use of the drug and its potential side effects. Prior approval of hospital ethical committee was obtained. Each patient underwent complete ophthalmic examination including best corrected logMAR visual acuity (logMAR BCVA) using ETDRS vision chart, slit lamp biomicroscopy with non contact super 66 D lens, intraocular pressure (IOP) measurement, and central foveal thickness (CFT) measurement using spectral domain Topcon 3 D-1000 Mark-II optical coherence tomography (OCT) machine. All the relevant details including patient's demography, diagnosis, timing and number of IVB injections, ocular examination findings, CFT measurements and post injection complications were endorsed on a pre designed proforma. Line scoring method for measurement of logMAR BCVA was used in this study[10].

**Table-1: Best corrected visual acuity (BCVA) and macular thickness at various intervals in the study population after intravitreal bevacizumab in vascular retinopathies.**

| | Log MAR BCVA | | | Central foveal thickness (μ) | | |
|---|---|---|---|---|---|---|
| | Mean ± sd | 95% CI | *p* value * | Mean ± sd | 95% CI | *p* value* |
| Baseline | 1.24 ± 0.69 | 1.04 - 1.45 | | 486.61 ± 145.29 | 443.68 – 529.54 | |
| 2nd week | 0.71 ± 0.65 | 0.52 – 0.9 | < 0.001 | 310.98 ± 72.90 | 289.44 – 332.52 | < 0.001 |
| 4th week | 0.61 ± 0.58 | 0.44 – 0.79 | < 0.001 | 287.23 ± 61.82 | 268.96 – 305.5 | < 0.001 |
| 8th week | 0.61 ± 0.55 | 0.46 – 0.78 | < 0.001 | 309.89 ± 90.96 | 283.01 – 336.77 | < 0.001 |
| 12th week | 0.59 ± 0.55 | 0.43 – 0.76 | < 0.001 | 300.02 ± 83.72 | 275.28 – 324.76 | < 0.001 |
| 24th week | 0.60 ± 0.59 | 0.43 – 0.78 | < 0.001 | 314.68 ± 85.01 | 289.56 – 339.8 | < 0.001 |

* *p* value is based on comparison of BCVA and CFT at various intervals with baseline values using Wilcoxon signed ranks test. CI = Confidence Interval, sd= standard deviation

All intravitreal injections were given under topical anesthesia. Strict asepsis was maintained by using pre and post injection 0.5% Moxifloxacin eye drops, 5% Povidone-Iodine for eyelids and conjunctival fornices and application of sterile eye drape. Intravitreal Bevacizumab (Avastin) was given in a dose of 1.25 mg/ 0.05 ml through supra temporal or supra nasal pars plana approach 3.5-4.0 mm posterior to limbus using a 29 G tuberculin syringe. Topical tobramycin /dexamethasone eye drops four times a day was prescribed for one week after each injection. Primary outcome measures were logMAR BCVA and CFT values on OCT. These study parameters were recorded at 2 weeks, 4 weeks, 8 weeks, 12 weeks and 24 weeks after IVB injection. Forty four eyes of 36 patients were included in final analysis as 5 patients did not complete the entire follow up.

Statistical analysis of the data was done using SPSS version 13.0. Descriptive statistics i.e. mean ± standard deviation for numerical values and frequencies along with percentages for categorical variables were used to describe the data. Wilcoxon signed ranked test was used for comparison of pre and post injection best corrected log MAR visual acuity and central foveal thickness and a $p$ value of <0.05 was considered statistically significant.

## RESULTS

Forty four eyes of 36 eligible patients were included in final analysis. There were 78% males in this study and right eye was involved in 50% of cases. Mean age of the study population was 55.36 ± 14.01 years with 42% of the patients in 7th decade of life. Most frequent diseases in the study were DME 45%, and RVO 32% (Figure-1). Total of 58 intravitreal bevacizumab (IVB) injections were given with a mean of 1.32 ± 0.561 injections. Ocular complications observed after IVB injections included sub conjunctival hemorrhage (22%), IOP > 21 mm Hg (28%), corneal erosion (7%) and lens injury (3%). 10% of the injections were associated with mild to moderate ocular pain that subsided after some time without any treatment. Mean IOP of 19.64 ± 6.17 at 1 hour after injection was significantly higher than pre injection baseline IOP of 15.93 ± 3.39 mm Hg ($p$ < 0.001).

Baseline mean logMAR BCVA was 1.24 ± 0.69 (Range: 0.3 – 3.0) that improved significantly to 0.71 ± 0.65 (Range: 0.02 – 3.0) at 2 weeks after IVB. Baseline mean central foveal thickness (CFT) was 486.61 ± 145.29 microns (μ) that had reduced significantly after IVB when measured at various time intervals (Table-1). Significant improvement in BCVA logMAR and reduction in CFT was observed at 2 weeks after IVB that remained stable throughout the follow up period.

## DISCUSSION

High levels of VEGF is normally expressed in retinal pigment epithelium (RPE) playing an important role in maintaining adequate blood flow to RPE and photoreceptors[2]. Hypoxic stimulus in retinal vaso occlusive diseases results in over expression of VEGF that promotes angiogenesis. Intravitreal injection of anti VEGF agents like Bevacizumab has shown positive visual and anatomical outcome in various neovascular ocular diseases[6]. Disease pattern of our study population is shown in figure-1. In a study conducted on 200 patients of choroidal and retinal neovascularization disorders, common indications of IVB were diabetic retinopathy (55%), age related macular degeneration (ARMD) (26%), RVO (10%) and Eale's disease (3%)[11]. Mean age of our study population was 55.36 ± 14.01 years with 78% of patients being male. Mean age range from 50.66–59.2 years quoted in various Pakistani studies very much corresponds with our results suggesting that neovascular ocular diseases have propensity to cause visually significant problems in older age group[4,7,8,11-14]. Gender distribution in various Pakistani studies on retinovascular diseases and use of IVB showed a varied frequency of male patients ranging from 38%-70%[7,8,11-14]. Mean number of IVB injections given in our study were 1.32 per eye, whereas a mean of 2.35–3.28 injections were given in various settings depending upon the nature of

disease and follow up duration[8,14-16]. Fewer injections given in this study are attributed to the follow up protocol that was aimed at repeating the injections on required basis as indicated by the OCT findings and visual acuity on each follow up visit.

Short term rise of IOP following intravitreal injections is one of the major concerns for the treating surgeon. IOP > 21 mm Hg at the end of 1st hour after IVB injection was found in 28% of eyes in our study with a mean pre injection IOP of 15.93 mm hg and post injection IOP (at 1st hr after IVB) of 19.64 mm Hg. Jan S et al found IOP > 21 mm Hg within one hour of IVB in 29% of patients that returned to normal next day[14]. Falkenstein IA et al concluded that IVB caused volume related rise in IOP that spontaneously fell to less than 30 mm Hg within 15 minutes[17].

IVB is an effective treatment modality for various retinal vascular diseases causing significant reduction in macular oedema and improvement in visual acuity. Significant reduction in mean CFT and improvement in logMAR BCVA was observed form 2nd week onward after IVB injection in our study. Hypoxia induced VEGF up regulation plays an important role in the pathogenesis of DME. Recently, Anti VEGF agents have been used for the treatment of DME with promising anatomical and functional outcome. Baseline mean logMAR BCVA in patients with DME in our study was 1.02 ± 0.46 with mean CFT of 494.5 ± 121.7 µ that had changed to 0.57 ± 0.39 and 342.4 ± 89.33 µ respectively at final follow up. Baseline mean logMAR BCVA ranging from 0.87-1.21 reported in various studies that had improved to 0.6 – 0.77 at final follow up visit[12,18-19].

The ocular morbidity due to RVO is related to macular oedema, ischemic retinopathy and anterior/posterior segment neovascularization. Owing to raised intravitreal VEGF levels in patients with RVO, introduction of anti VEGF agents has added a new dimension in the treatment of RVO. Baseline mean logMAR BCVA was 1.69 and mean CFT was 510.5 µ in our study sub group of RVO patients that had changed to 0.75 and 315.9 µ respectively at 24 weeks follow up visit. Baseline mean logMAR BCVA ranging from 1.13–1.48 and mean CFT ranging from 536.4 – 887 µ was observed in studies on central retinal vein occlusion (CRVO) patients, that had improved to 0.83–0.84 logMAR BCVA and 326.17 – 372 µ of CFT at final follow up after IVB injection[16,20]. Jan S et al and Hassan M et al in their studies on use of IVB in CRVO reported a

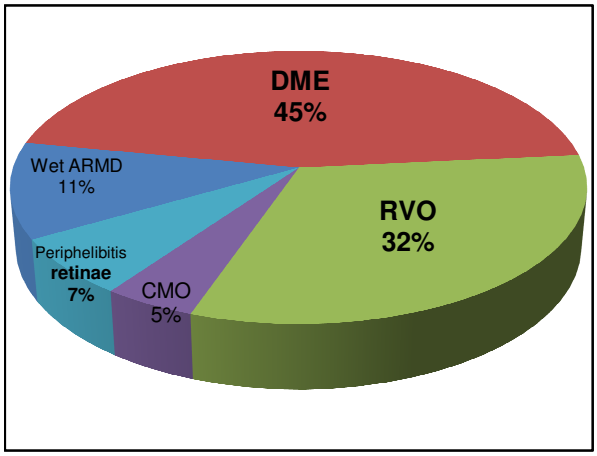


**Figure-1: Frequency of retinal diseases in the study population.**
DME: Diabetic macular edema, RVO: Retinal vein occlusion, CMO: Cystoid macular oedema, ARMD: Age related macular degeneration

baseline Snellen BCVA of 6/60 or better in 12% and 54% of subjects respectively that had improved to 6/60 or better in 59% and 80% of cases at final follow up[13,14]. Similar improvement in BCVA and reduction in CFT was observed following use of IVB in cases of branch retinal vein occlusion[15,20].

ARMD sub group of our study population had baseline mean logMAR BCVA of 1.15 ± 0.57 and mean CFT of 312 ± 122.4 µ that had changed to 0.73 ± 0.67 and 260.6 ± 46.53 µ at final follow up visit. Iqbal K et al reported a mean visual improvement from 0.21 to 0.43 (letter scoring method) and decrease in mean CFT by 99 µ at final follow up after IVB injection in patients of neovascular ARMD[8]. Anti VEGF agents have been tried in various other retinal vascular disorders like cystoid macular oedema (CMO),

Eale's disease, Coat's disease and CNV due to causes other than ARMD with favorable functional and anatomical outcome. Two of our patients with CMO had mean logMAR BCVA of 0.74 and mean CFT of 571 µ that had improved to 0.05 and 264 µ respectively after IVB. Barone A et al reported a baseline mean BCVA of 0.60 and mean CFT of 546.8 µ in patients of refractory pseudoaphakic CMO that had changed to 0.20 and 228.7 µ respectively at final follow up after IVB injection[21].

There is growing evidence that anti VEGF agents have a definite role in the management of proliferative retinopathies. Their use in isolation or in combination with other treatment modalities like laser photocoagulation, photodynamic therapy and intravitreal steroids have resulted in early visual rehabilitation and long term stable functional and anatomical outcome.

## CONCLUSION

During the last decade anti VEGF therapy has become the main stay of treatment in various neovascular retinopathies. Off label use of intravitreal Bevacizumab in various vascular retinopathies results in significant visual improvement and reduction in macular oedema, making it first choice anti VEGF agent in our country.

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