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*Original Research Article*

# A Multivariate Analysis of Intravitreal Injection of Anti-VEGF Bevacizumab in the Treatment of Retinal and Choroidal Neovascularization

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## ABSTRACT

**Aim:** To investigate the safety and efficacy of intravitreal bevacizumab for the treatment of neovascular age related macular degeneration, and as an adjunct to proliferative diabetic retinopathy and retinal vein occlusion cases with progressing neovascularization in spite of complete panretinal photocoagulation and to assess the improvement in visual acuity, decrease in macular thickness in optical coherence topography.

**Materials And Methods:** A prospective non-randomized clinical study was carried out in 34 eyes in which 28 patients having CNVM, 4 patients with PDR and 2 patients having retinal vein occlusion were tested for visual acuity and macular thickness were checked before and after intravitreal injection of anti VEGF bevacizumab.

**Results:** There were 2 line improvements in visual acuity by Snellen chart in CNVM patients and one line improvement in PDR and retinal vein occlusion at 12 weeks. Macular thickness was reduced 100µ at 8 weeks in CNVM and 12 weeks in PDR and 50 % reduction in retinal vein occlusion.

**Conclusion:** Intravitreal bevacizumab (1.25 mg) treatment was well tolerated over 3 months with significant safety and efficacy.

***Key Words:*** bevacizumab, Choroidal neovasculaisation, proliferative diabetic retinopathy, VEGF

## INTRODUCTION

Vitreous haemorrhage is the most common cause of blindness in middle age group which is due to abnormal Neovascularization in retina and choroid. Retinal arteries are end arteries in which abnormal Neovascularization is caused by various pathologies among which diabetic retinopathy is the leading cause. [1] Diabetics have a 20-25 times greater risk of blindness compared to normal people**.** [2] According to various studies around 40-60 percent of untreated diabetic patients are losing their vision due to retinal neovascularization. Around 30-40 % patients are refractory to pan retinal photocoagulation. [3,4] Recent

studies show they were effectively managed with anti VEGF agents. The National Eye Institute estimated that there may be more than 16,000 new cases of legal blindness yearly from this disease. Wisconsin beaver dam study shows that incidence of choroidal Neovascularization caused by age related macular degeneration is 1.2%. another study conducted by wisconin beaver dam showed that incidence of central retinal vein occlusion is 0.1% and it can be treated with anti VEGF agents. [5,6] Retinal hypoxic status release vascular endothelial growth factor which binds with flt1 and KDR receptors present in endothelial cells and increased vascular permeability and induces abnormal angiogenesis. [7]

## MATERIALS AND METHODS

It is an Interventional, Prospective, Non-randomized clinical study done in tertiary eye care center over period of one year. The study was approved by institutional human ethical committee and consent obtained after explaining the study procedure to the patient.Patients with CNV attributable to AMD diagnosed by FFA and OCT with BCVA of less than 6/24, patients with PDR and progression despite complete PRP and patients with CRVO with neovascularization not responding to laser photocoagulation were included in this study. Patients who were treated for CNV, tractional retinal detachment in a case of high risk PDR, with History of uveitis, vitrectomy, uncontrolled hypertension, recent myocardial infarction and recent cerebral vascular accident were excluded from the study. Patients who were referred to Retina clinic with provisional diagnosis of AMD, PDR, and CRVO were screened and selected for the study. All the patients were taken a brief history, and subjected to detailed systemic and ophthalmic evaluation. Anterior segment examination with Slit lamp biomicroscope and posterior segment examination using 90D, binocular indirect ophthalmoscope and a detailed fundus drawings were done and Fundus photograph was also taken for documentation. Fundus fluorescein angiography and Optical coherence tomography were done for all the patients. Twenty eight eyes of 28 patients with neovascular AMD, four eyes of 4 patients with proliferative diabetic retinopathy with post laser status and two eyes of 2 patients with retinal vein occlusion were included. The off-label use of the drug and its potential risks and benefits were discussed extensively with all patients. All patients signed a comprehensive consent form before administration of the intravitreal bevacizumab.

A commercially available bevacizumab (1.25mg/0.05ml) was prepared for each patient and placed in a tuberculin syringe using aseptic techniques. After the eye had been prepared in a standard fashion using 5% povidone iodine and topical antibiotics, 1.25 mg (0.05 ml) of bevacizumab was injected intravitreally via the pars plana. After the injection, intraocular pressure and retinal artery perfusion were checked, and patients were instructed to administer topical antibiotics for 3 days. Patients were called 2 to 3 days after injection and were re examined within 1 week.

Patients received reinjections on a monthly basis until macular edema, /or pigment epithelial detachment (PED) / or neovascularization resolved.

Main outcome measures looked for were Best corrected visual acuity (Snellen's chart) and Macular thickness by OCT (SPECTRAL). All the patients were asked for regular follow-up at 2weeks, 8weeks, 12 weeks. At each visit patients were checked for intra-ocular pressure, BCVA were checked and Fundus photographand OCT were recorded.

## RESULTS

In our study, total number of patients were 34 in which male patients were 20 (59%) and females 14(41%) most of the patients were in the age group of 50-60 yrs. among 34 patients 28 patients(82%) were having choroidal neovascularization and 4 patients(12%) proliferative diabetic retinopathy and 2 patients (6%) had retinal vain occlusion. Before giving injection patients number of patients with visual acuity between hand movements to 1/60 were 16 patients, between 2/60 to 4/60 were 13 patients and between 5/60 to 6/24 were 5 patients. Macular thickness by OCT before injection between 150-200 there were 5 patients and 201-250 9 patients 251-350 12 patients and more than 350 there were 8 patients. After giving injection bevacizumab patient was reviewed at 2 weeks 8 weeks and 12 weeks. After giving injection avastin there was no improvement in 24 patients at 2 weeks. Maximum 2 line improvement in Snellen's chart was seen at 12 weeks in cnvm patients which is correlated with the previous study by Geitzenauer W et al, KlinMonatsblAugenheilkd. [8,9] In PDR there was no improvement in2 patients and 1 line improvement in 2 patients at 12 weeks. In retinal vein occlusion there was one line improvement at 12 weeks in one patient. Post injection macular thickness was reduced upto 100µ in 24 patients and no change in thickness at 2 weeks. Maximum thickness reduction seen at 12 weeks.1 patient showed no improvement and he was found to have CNVM with scar formation.

Table 1: visual acuity by snellens chart prior to injection Bevazumab

| Visual Acuity | CNVM | PDR | RVO | Total |
|---|---|---|---|---|
| HM – 1/60 | 11 | 3 | 2 | 16 |
| 2/60 – 4/60 | 12 | 1 | - | 13 |
| 5/60 – 6/24 | 5 | - | - | 5 |

Table 2: macular thickness by stratus OCT before injection Bevazumab

| OCT | CNVM | PDR | RVO | Total |
|---|---|---|---|---|
| 150 - 200 | 3 | 2 | - | 5 |
| 201- 250 | 6 | 1 | 2 | 9 |
| 251 - 350 | 12 | - | - | 12 |
| >350 | 7 | 1 | - | 8 |

Table : 3 vision improvement after injection Bevazumab

| Vision improvement | 2 weeks | 8 weeks | 12 weeks |
|---|---|---|---|
| No change | 24 | 4 | 1 |
| 1 line improvement | 3 | 14 | 9 |
| 2 line improvement | 1 | 8 | 16 |
| >2 line improvement | - | 2 | 2 |

Table : 4 reduction of macular thickness after injection Bevazumab

| Macular thickness reduction | 2weeks | 8weeks | 12weeks |
|---|---|---|---|
| No change | 3 | 2 | 1 |
| Upto 100µm | 24 | 22 | 18 |
| Upto 200 µm | 1 | 4 | 9 |
| >200 µm | - | - | - |

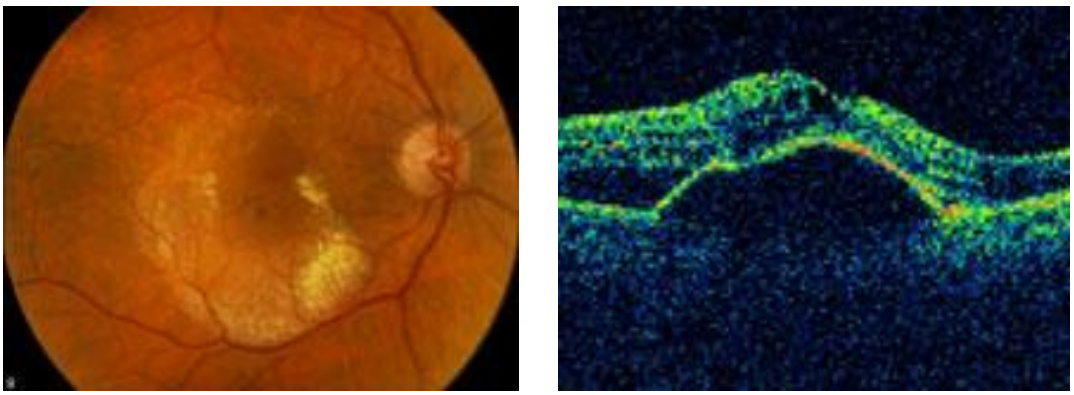


Figure : 1. CNVM before giving injection Bevazumab

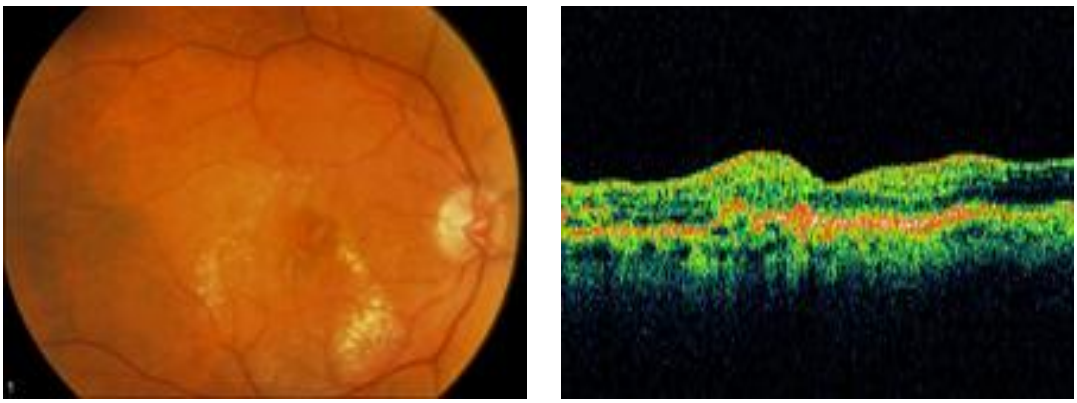
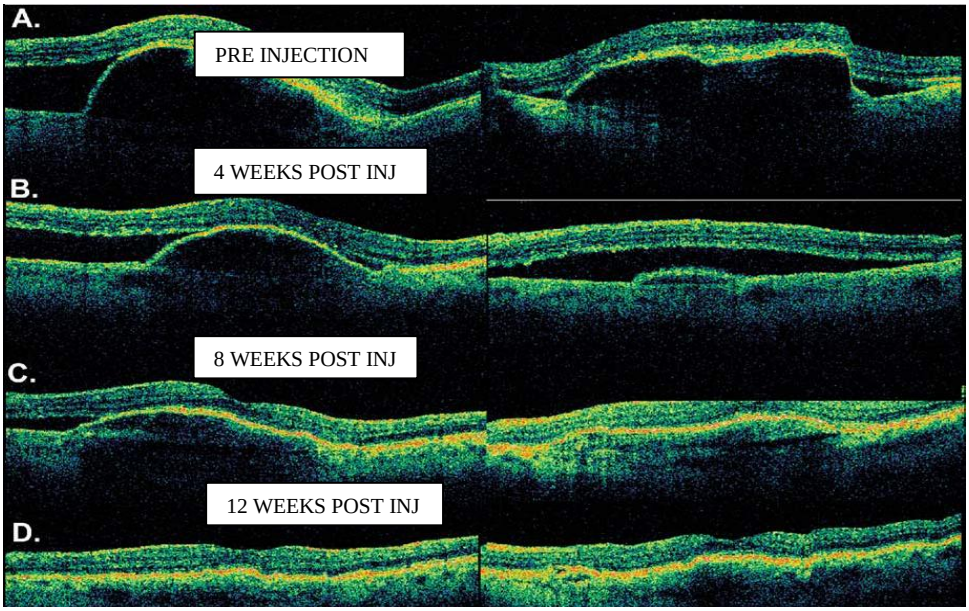


figure :2. 8weeks after giving injection Bevazumab




## DISCUSSION

International age related maculopathy epidemiological study group defines early ARMD is characterized by drusens, RPE pigmentation and advanced ARMD characterized by geographic atrophy and CNVM. [9] Smoking, hypertension, high fat intake, female sex and unlight exposure are some risk factors for ARMD. Exudative ARMD can be treated with anti VEGF agents, photodynamic therapy and argon laser photocoagulation. [10] Among these treatment modalities anti VEGF agents plays an important role. This is a 6 months prospective, non-randomized clinical study to investigate the safety and efficacy of intravitreal bevacizumab for the treatment of neovascular AMD, and as an adjunct to PDR and CRVO cases with progressing neovascularization in spite of complete PRP. [11] The main aim was to evaluate the improvement in visual acuity, decrease in macular thickness in the above said conditions following intravitreal injection. Of the 34 patients who met the inclusion criteria for the study, 20 were male and 14 were female, the ratio being 1.5:1. The mean age was 55 years. Out of 34 eyes, 82% of

cases were with CNV, 12%cases were PDR and 6% were CRVO. The mean baseline pre-procedure V/A considered was 3/60, the least V/A being HM, and the highest V/A being 6/24. The baseline mean macular thickness was 356µ.All the patients were given 1.25mg of Bevacizumab intravitreally under aseptic precautions after explaining the procedure who then signed a consent form. Follow-up ranged from 2 to 12 weeks. All 34 patients completed a 12-week follow-up visit. During each follow-up, patients were checked for improvement in V/A, decrease in macular thickness and Fundus photographs were taken for documentation. After intravitreal bevacizumab a significant visual improvement in 4weeks of about 50% and by the end of 12 weeks 60% improvement by Snellen's chart. 1 case of CNVM showed no improvement because of macular scarring. The response of Bevacizumab to Proliferative diabetic retinopathy is less when compared to other conditions because of associated systemic factors. The mean V/A improves by 50% (1 line improvement) by the end of 8weeks which remained the same by the end of the study in 50% of cases. 1 case dropped vision after 12 weeks because of cystoid macular oedema with vitreo-macular traction and he underwent repeat injection. Out of 2 cases of CRVO, 1 case (50%) started showing 1 line improvement by 8 week and he maintained it till the end of the study, 1case showed no improvement because of optic atrophy. This study shows that the vast majority of patients demonstrated stability or improvement of the VA. Of those few patients with a visual decline, the change was felt to be due to disease progression rather than drug toxicity. The base line mean macular thickness in CNV cases was 345µand showed reduction in macular thickness of 50µ at the end of 2weeks, and 50% reduction of 100µ at the end of 8 weeks. 1 case of CNV showed no improvement till the end of the study because of macular scarring. In PDR cases, 50% (2cases) showed improvement of 50µ reduction at the end of 1month post injection, 50% showed reduction of upto 100µ at the end of 12weeks and 25% (1case) showed no change because of non-resolving cystoid macular oedema associated with vitreo-macular traction. In CRVO, out of 2 cases, 1case showed reduction of macular thickness by the end of 2 months, both showed 50% reduction by the end of the study and this is because of vascular perfusion factor associated with Anti VEGF Bevacizumab.

## CONCLUSIONS

Intravitreal bevacizumab (1.25 mg) treatment was well tolerated over 6 months with significant safety and efficacy. Among anti – VEGF agents bevacizumab was selected because which was the only drug got FDA approval and less expensive. [12] Nevertheless, this is a small interventional study, with no comparison arm to quantify the actual magnitude of benefit of this treatment modality compared with other therapies. This would have to be studied subsequently in larger studies and also needs to be compared with other VEGF inhibitors regarding safety and efficacy.

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