# **Original Research Article**

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# Evaluation of effect of intravitreal injection bevacizumab in treatment of choroidal neovascualr membrane of the eye

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## **ABSTRACT**

**Background:** Age-related macular degeneration (ARMD) is the leading cause of irreversible blindness in individuals over 50 years in developed countries. The objective was to study the effect of intravitreal bevacizumab in patients of choroidal neovascular membrane of eye by visual acuity and fluorescence angiography photograph.

**Methods:** Non-randomized, open label, prospective analysis of 30 eyes in 30 patients with choroidal neovascualr diagnosed by direct ophthalmoscope and slit lamp 90D biomicroscopy. Visual acuity of the clinically diagnosed patient was taken by ETDRS (early treatment diabetic retinopathy system) visual acuity chart. Fundus fluorescence angiography was done by topcon retinal camera. Now all patients regardless of type were given 3 injections of 0.05 ml of injection bevacizumab intravitreally at infratemporal site 3.5 mm and 4 mm away from the limbus in pseudophakic and phakic eye repectively at interval of 1 month. After 1 month of last dose, patient was assessed with ETDRS chart for visual acuity, FFA for anatomical changes. FFA was done before and after giving 3 injection of bevacizumab at monthly interval. Patients were asked for regular follow-up and patients were examined after 6 hours, 48 hours and 7 days for any early and late complications.

**Results:** There was significant improvement of visual acuity after intravitreal bevacizumab treatment (before 1.196 log MAR and after 0.95067 log MAR with p value is 0.0001, paired t-test with t=6.333 with 29 degree of freedom) in cases of choroidal neovascular membrane. Gain in visual acuity was accompanied by a significant decrease in leakage in fluorescein angiography (FFA)

**Conclusions:** We present evidence that intravitreal bevacizumab is an effective treatment for choroidal neovascular membrane.

Keywords: ARMD, Anti-VEGF, ETDRS, FFA

### INTRODUCTION

Retina is a multilayer inner most layer of eye which represents visual function of eye. Any disturbance or disruption of retinal layer and sub retinal layer may lead to visual problem. Age-related macular degeneration (AMD) is the leading cause of visual loss in people over 50 years of age, approximately 50-60% of the patient

with age related macular degeneration develop loss of visual acuity within 5 yr. 1,2

Most AMD patients have macular drusen or retinal pigment epithelial abnormalities or both.<sup>3</sup> Approximately 10% of AMD patients manifest the neovascular form of the disease.<sup>4</sup> Neovascular includes choroidal neovascularization (CNV) and associated manifestations such as retinal pigment epithelial detachment (PED),

retinal pigment epithelial tears, fibro vascular disciform scarring, and vitreous hemorrhage.<sup>3</sup>

In choroidal neovascular membrane, neovascular sprout growing under or through the RPE through breaks in Bruch's membrane.<sup>5</sup> Usually this occurs in association with evidence of fibroblasts, myofibroblasts, lymphocytes, and macrophages.<sup>6</sup> Various growth factors are suspected to be involved in the development of this CNV, such as vascular endothelial growth factor (VEGF) which cause the new vessels formation.<sup>7</sup>

Following penetration of the inner aspect of Bruch's membrane, the new vessels proliferate laterally between the Retinal Pigment epithelium (RPE) and Bruch's membrane. As these neovascular twigs mature, they develop a more organized vascular system stemming from a trunk of feeder vessels off the choroid, as well as proliferation of fibrous tissue.<sup>8</sup>

The endothelial cells in the arborizing neovascular tufts lack the barrier function of more mature endothelial cells. Hence these new vessels can leak fluid (and fluorescein) in the neurosensory, subsensory, and RPE layers of the retina. Proteins and lipids may accompany this process and precipitate in any layer of the retina.

In addition, the fragile vessels are prone to hemorrhage. Occasionally, blood may extend through all the layers of the retina, breaking through into the vitreous cavity. Ultimately, a fibro-vascular scar results, usually causing disruption and death of the overlying sensory retinal tissue accompanied by severe visual loss.

# Risk factors 9,10

- Genetic
- Gender: Choroidal neovascular membrane is more common in females rather than males
- Age: Choroidal neovascular membrane is more common after 50 years of age.
- Systemic illness: Hypertension, Diabetes
- Refractive error: Myopic patient have greater chances of development of choroidal neovascular membrane.
- Sun exposure
- Tobacco smoking

Micronutrient deficiency as measured in blood serum levels or by dietary history.

# **METHODS**

A non-randomised, open label, prospective study was carried out in department of ophthalmology, government medical college and Sir Takhtsinhji general hospital, bhavnagar to evaluate the effect of intravitreal bevacizumab injection in treatment of choroidal neovascualr membrane (CNVM).

The protocol was approved by the Institutional Review Board, Human Ethics Committee, Government Medical College; Bhavnagar [approval no. IRB (HEC) no. 563/2015]. And all patients gave written informed consent.

For the study, patients attending ophthalmology department in Sir T. Hospital diagnosed of having Membrane choroidal Neovascular by ophthalmoscope and slit lamp 90D biomicroscopy. Visual acuity of the clinically diagnosed patient was taken by ETDRS visual acuity chart. Fundus fluorescence angiography was done by Topcon Retinal Camera. Now all patient regardless of type were given 3 injections of 0.05 ml of injection bevacizumab intravitreally at infratemporal site 3.5 mm and 4 mm away from the limbus in pseudophakic and phakic eye repectively at interval of 1 month. After 1 month of last dose, patient was assessed with ETDRS chart for visual acuity, FFA for anatomical changes.

For fluorescence angiography, we used fluorescence sodium U.S.P. 200 mg in 1 ml. After giving test dose and Avil, dexona injection (to prevent adverse reaction) we inject 2cc fluorescence dye after that we will take fundus photograph in early, intermediate and late phase.

#### Inclusion criteria

• Any type of choroidal neovascular membrane

### Exclusion criteria

- Known patient of diabetes.
- Pre-existing pathology e.g. corneal macular or optic nerve disorders and glaucoma.
- Any other choroidal pathology

# Intervention

Intravitreal injection of bevacizumab (Avastin; Genentech inc. (Roche group), South San Francisco, California) from a vial of 100 mg/4ml, without any filtration or purification procedure in the operating room under sterile aseptic condition, on outpatient basis.

All 30 patients were given injection at same time from one vial with aseptic precaution. Informed written consent was obtained.

Patient was prepared and pupil dilated with 0.8% tropicamide and 5% Phenylephrine eye drops. After sterilization of the peripalpapebral region with 7.5% povidon iodine and conjunctiva with 5% povidone iodine solution, proparacaine 0.5% eye drops was instilled into the conjunctival fornix for topical anaesthesia two to three times before injection.

The injection Avastin containing bevacizumab (1.25mg/0.05 ml) was given through the pars plana route

in the inferotemporal quadrant (4mm post limbus in phakics; 3.5 mm post limbus in pesudophakics) using a 30-gauze needle and tuberculin syringe.

While removing the needle, the injection site was grasped with one toothed Lims' forceps and a cotton bud soaked in 5% povidone iodine solution to prevent reflux of the injected drug.

Then one drop of topical antibiotic moxifloxacin 0.5% eye drops and anti-glaucoma drug timolol 0.5% eye drops was instilled. Immediately fundus was examined with direct ophthalmoscope to check for the central retinal arterial pulsation.

Paracentasis was done if CRA pulsation was present or if the globe felt very tense. Eye was patched and IOP measured after a six hour with NCT.

Antibiotic moxifloxacin 0.5% Eye drops q.i.d were continued for a week. Patients were examined after 6 h ours, 48 hours and 7 days for any early and late complications.

Then all patients given three monthly interval injection bevacizumab and routine follow up done and after one month of last injection visual acuity and FFA was done.

## Outcome measures and statistical analysis

Adverse effect and complication (monitored throught the study period). Data was collected and entered in Microsoft Excel 2010.

Data was interpreted and analysed using statistical paired-t test.

# **RESULTS**

This study includes 30 eyes of 30 patients as per the inclusion and exclusion criteria mentioned previously. This study was undertaken to assess the effect of injection bevacizumab in patients of choroidal neovascular membrane (CNVM). To assess this effect we had used two parameters – FFA Visual Acuity (ETDRS Chart). FFA studied the leakage. ETDRS visual acuity was measured in log MAR units.

In present study predominant age group involved was between 60-70 years (Table 1). And 16 male and 14 female patient sex distribution (Figure 1). There is involvement of 20 right eye and 10 left eye in 30 patients (Figure 2).

We measure improvement in visual acuity and recorded at 2 month and 4 month and result is display in Table 2.

In our study there is 9 patients had CNVM with hypertension in which there is 2 patients shows no improvement in visual acuity and 7 patients show one

line improvement of visual acuity after treatment (Table-3)

Table 1: Age distribution.

Age (years)	No of patients
≤50	3 (10%)
51-60	7 (23.33%)
61-70	19 (63.33%)
71-80	1 (3.33%)

Also there is 12 patients had history of smoking in which there 7 patients shows one line improvement of visual acuity and 5 patients show 2 line improvement of visual acuity after treatment (Table 3).

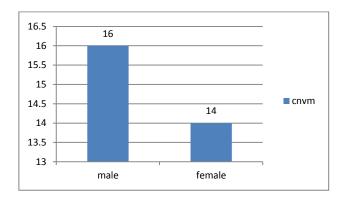


Figure 1: Sex distribution in CNVM.

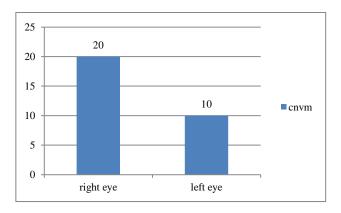


Figure 2: Involvement of eye.

Table 2: Visual acuity.

Improvement of	At 2 month	At 4 month
visual acuity	n (%)	n (%)
No change	02 (06%)	02 (06)
1 line improvement	16 (54%)	12 (40%)
2 line improvement	10 (34%)	14 (48%)
>2 line improvement	02 (06%)	02 (06%)
Total	30 (100%)	30 (100%)

There were 7 patients who have both association hypertension and smoking in which there is only one line improvement of visual acuity after treatment (Table 3).

Table 3: Association of CNVM with risk factor and visual improvement after treatment.

History	Hyperte nsion	Smoking	Both	No history
	9 (30%)	12 (40%)	7	9 (30%)
No improvement	2	-	-	-
One line improvement	7	5	7	-
Two line improvement	-	7		9

Total 9 patients in our study who have not association with any kind of history and they show 2 line improvement of visual acuity. This data suggest that there is significant relation between CNVM alone and CNVM with other risk factor. Presence of other risk factor affect the final outcome of treatment.

The mean value of pre treatment vision was 1.196 log MAR and after treatment mean value of vision was 0.95067 log MAR with two tailed p value= 0.0001 which is statistically significant with t=6.333 with 29 degree of freedom. (P value<0.005) which indicate that there is greater difference between Mean of pre treatment vision log MAR and post treatment Log MAR (Figure 3). Correlation coefficient is r=0.8738 with effective pairing result in a significant correlation between columns. With this data paring appears to be effective. Also there is significant reduction of leakage in FFA in all patients having CNVM except 2 patients who have no change in appearance in FFA. This two patient was occult CNVM and scar CNVM.

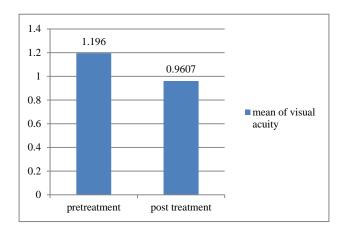


Figure 3: Mean of visual acuity.

Table 4: Mean of standard deviation.

	Standard deviation
Pre treatment	0.2368
Post treament	0.3851

Table 5: Data parameters.

Parameter	Pre treatment	Post treatment	Difference
Mean	1.196	0.9607	0.2043
# of points	30	30	30
Std deviation	0.23680	0.3851	0.2122
Std error	0.04323	0.07031	0.03874
Minimum	0.7800	0.3600	0.000
Maximum	1.780	1.780	0.7200
Median	1.220	1.000	0.2100
Lower 95% CI	1.108	0.8069	0.1661
Maximum 95% CI	1.284	1.094	0.3246

#### **DISCUSSION**

This study includes 30 eyes of 30 patients as per the inclusion and exclusion criteria mentioned previously. This study was undertaken to evaluate the effect of injection bevacizumab in patients of choroidal neovascular membrane (CNVM). To evaluate this effect we had used two parameters – FFA, visual acuity (ETDRS Chart). FFA studied the leakage. ETDRS visual acuity was measured in log MAR units.

In present study of 30 patients, 14 females and 16 males were included. Predominant age group involved was between 60-70 years.

A total of 30 patients were studied during 27 October 2015 to 26 march 2016. Among them, 10% patients were <50 years, 23.33% were 51-60 year of age, 63.33% were 61-70 year of age and the remaining 3.33% were 71-80 years of age (Figure 1). The ratio of male to female in our study was 1.14:1. There is 30% patients having CNVM with hypertension and 40 patients were CNVM with smoking. FFA showed 90% of patients were with classical angiographic type with CNVM, 10% patients were occult and disciform scar type with some leakage.

Choroidal neovascularization (CNV) is a distinct clinical entity and may account for 10% of all age related macular degeneration cases with CNV in patients between 50-70-years old.

Various treatments such as, intravitreal and subtenons steroids, transpupillary thermotherapy, surgical removal and photodynamic therapy with verteporfin have been attempted with varying success in preventing visual loss in patients with CNV. Recently, intravitreal anti-VEGF treatment has proved very effective and beneficial in patients with CNV.

Our study we have 30 patients who have CNVM which is diagnosed by Fluorescence angiography method. From 30 patient 28 patients showed classic CNVM appearance in which there is early angiogram show fine discrete,

well-demarcated focal area of hyper fluorescence which is increase in hyper fluorescence increases in intensity and extends beyond the boundaries of the hyper fluorescent area identified in earlier phases of the angiogram through mid- and late-phase frames. And 2 patients have appearance of Occult CNVM in which they develop fine often stippled with hyper fluorescent dots which not increase in size and intensity in all phase.

Then all patients given 3 monthly Injection of Intravitreal Bevacizumab in one sitting (all 30 patients given injection simultaneously).

We recorded data of visual acuity and intro ocular pressure on follow up examination

On examine data and measure on excel pair T test is apply and we found that The mean value of pre-treatment vision was 1.196 log MAR and after treatment mean value of vision was 0.95067 log MAR with a p value= 0.0001 which is statistically significant. (P value <0.005) which indicate that there is greater difference between Mean of pre-treatment vision log MAR and Post Treatment Log MAR.

In our study there is 9 patients had CNVM with hypertension in which there is 2 patients shows no improvement in visual acuity and 7 patients show one line improvement of visual acuity after treatment (Table 3).

Also there is 12 patients had history of smoking in which there 7 patients shows one line improvement of visual acuity and 5 patients show 2 line improvement of visual acuity after treatment (Table 3).

There were 7 patients who have both association hypertension and smoking in which there is only one line improvent of visual acuity after treatment.

Total 9 patients in our study who have not association with any kind of history and they show 2 line improvement of visual acuity. This data suggest that there is significant relation between CNVM alone and CNVM with other risk factor. Presence of other risk factor affects the final outcome of treatment.

The mean number of intravitreal bevacizumab injections received by patients in our study was 3. After three monthly injections there is significantly reduction of leakage in FFA and improvement of visual acuity.

Intravitreal bevacizumab also used in branch retinal vein occlusion for prevention of neovascularization and to treat macular oedema. There are lots of studies which suggest that there is marked improvement of vision and reduction in macular thickness after used of intravitreal Bevacizumab and prevents visual loss and neovascularization.

A total 278 patients were included in the study according to the inclusion and exclusion criteria. Mean age of the patients was 54.28 years (SD=5.62). Out of 278 patients included in the study, 132 had BRVO, 141 had CRVO while 5 had HRVO. Mean visual acuity before injection was 2.309 lines of Snellen's acuity chart read, with minimum of 1 line read and maximum of 4 lines read (standard deviation=1.00). After 12 weeks post injection, 92 patients read 7 lines (6/6) of Snellen's visual acuity chart. Mean visual acuity was 4.75 lines of Snellen's acuity chart read, with minimum of 1 line read and maximum of 7 lines read (standard deviation=1.00). 77% of the patients had visual improvement after injection (p<0.05). 11

Our study of use of intravitreal Bevacizumab in choroidal Vascular Membrane support this study and indicate that there is highly efficacy of intravitreal Bevacizumab use to prevent choroidal neovascularization with mean value of pre-treatment vision was 1.196 log MAR and after treatment mean value of vision was 0.95067 log MAR with a p value=0.0001 which is statistically significant (P value<0.005).

Another study clinical ophthalmol (clinical utilization of anti-vascular endothelial growth-factor agents and patient monitoring in retinal vein occlusion and diabetic macular oedema). During the study period (2008-2011), bevacizumab was the main anti-VEGF therapy used in clinical practice for BRVO, CRVO, and DME. Patients treated with bevacizumab were monitored less frequently and received fewer injections than patients in major clinical trials of ranibizumab.<sup>12</sup>

This study suggest that inspite of ranicizumab, bevacizumab can be used in treatment for prevention of neovascularization with same efficacy as ranicizumab and low cost of therapy.

Our study also supports this data and suggests that intravitreal use of bevacizumab is highly efficacious to treat choroidal neovascualr membrane.

Another study of intravitreal use of bevacizumab for idiopathic choroidal neovascular membrane long term outcome and effect on visual acuity. This study show following result.

The mean follow-up period after diagnosis was 33.9±10.6 months. During this period, a mean of 2.5±1.7 bevacizumab injections were administered. The mean logarithm of the minimal angle of resolution (logMAR) BCVAs at diagnosis, 6 months, 12 months, and final follow-up was 0.48±0.38, 0.28±0.36, 0.25±0.35, and 0.20±0.26, respectively. The final BCVA was significantly improved over the baseline value. CNV recurred in 8 patients (30.8%), 3 of whom experienced 2 recurrences; the mean timing of recurrence was 19.7±15.5 months after diagnosis. 13

This study also suggest that intravitreal bevacizumab highly efficacious for treatment of choroidal neovascular membrane which support our study which is statistical significant.

#### Limitations

- Small sample size
- Only patients with choroidal neovascular membrane not other like BRVO, Diabetic macular oedema.
- Not availability of OCT, so we can't measure central macular thickness which is most important clinical tool for CNVM study for improvement.

# **CONCLUSION**

On the basis of our present study, we can conclude that in patients of choroidal neovascular membrane injection bevacizumab is beneficial as it leads to improvement of vision and reduction of new vessels formation.

We have observed that; in patients having, choroidal neovascular membrane injection bevacizumab helps to stabilize the disease and to inhibit neovascularization.

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Ethical approval: The study was approved by the

Institutional Ethics Committee

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