

**TO ASSESS THE SHORT TERM AND LONG TERM VARIATION IN INTRA-OCULAR PRESSURE AFTER INTRAVITREAL INJECTION OF ANTI-VEGF**

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**ABSTRACT**

**Purpose:** To assess the short term and long term fluctuations in IOP variations after intravitreal injection of anti-VEGF (Bevacizumab). **Design:** A prospective hospital based clinical study. **Method:** 100 patients were screened and 65 patients were selected with indication of intravitreal anti-VEGF for the study. Baseline IOP was measured before injection, half hour after injection and at various follow up visits at 1 week, 3 week, 3 months and 6 months using applanation tonometer. IOP at 6 months was compared to baseline and to the number of injections received. **Results:** At 30 min, out of 65 patients, 59 had normalised IOP (<21mmHg) after receiving intravitreal anti-VEGF (96.1%) which was clinically significant (p value <0.001) and 6 patients had persistent IOP elevation of >30mmHg. At the end of 6 months, 10 patients had persistently elevated IOP (>21mmHg, p value <0.001) and rest had achieved normal IOP. **Conclusion:** Though majority of patients achieve normal IOP, monitoring is necessary to identify high risk patients who have delayed normalization of IOP immediately after receiving injection and also during long term follow up visits.

**KEYWORDS:** IOP, Bevacizumab, Prospective Study.**INTRODUCTION**

Vascular endothelial growth factor (VEGF) have revolutionized the treatment of various retinal diseases including neovascular age-related macular degeneration (AMD), retinal vein occlusion and diabetic macular edema, where over expression of VEGF, vascular leakage, and neovascularization have been identified as pathogenic mechanisms that may be addressed with anti-VEGF therapy. Anti-VEGF agents have been shown to be efficacious and to have a good safety profile. Since the patients undergo frequent injections over the course of disease, there are reports of long-term risks and hence the patient safety profile has to be taken into account. Intraocular pressure elevation is a significant concern both in short term and long term after anti-VEGF.<sup>[1-3]</sup>

**VEGF and ANTI-VEGF**

The vascular endothelial growth factor (VEGF) is a signal protein produced by muller cells that stimulates vasculogenesis and angiogenesis. It belongs to a sub-family of the platelet-derived growth factor. They are important signalling proteins involved in both vasculogenesis and angiogenesis.

The most important member is VEGF-A. Other members are Placenta derived growth factor (PGF), VEGF-B, VEGF-C and VEGF-D. The latter ones were discovered

later than VEGF-A, and before their discovery, VEGF-A was called just VEGF. VEGF-A stimulates endothelial cell mitogenesis and cell migration. It acts as vasodilator and increases microvascular permeability. All members of the VEGF act by binding to tyrosine kinase receptors (the VEGFRs) on the cell surface, causing them to dimerize and become activated through transphosphorylation, although to different sites, times and extents.

Structurally the VEGF receptors have an extracellular portion consisting of 7 immunoglobulin-like domains, a single transmembrane spanning region, and an intracellular portion containing a split tyrosine-kinase domain VEGF-A binds to VEGFR-1(Flt-1) and VEGFR-2 (KDR/Flk-1). VEGFR-2 appears to mediate almost all of the known cellular responses to VEGF. The function of VEGFR-1 is less well-defined, although it is thought to modulate VEGFR-2 signalling. VEGFR-1 may act as a dummy/decoy receptor, sequestering VEGF from VEGFR-2 binding (this appears to be particularly important during vasculogenesis in the embryo).

Anti- VEGF agents Ranibizumab and Bevacizumab were derived from the same murine antibody to VEGF. Bevacizumab is the humanized full-length antibody, whereas Ranibizumab is the Fab fragment that is humanized and affinity matured, so that its binding

affinity is approximately 20 times that of Bevacizumab. Studies have shown that the Bevacizumab being full-length antibody penetrated the retina poorly,<sup>4</sup> and the high-affinity Fab fragment Ranibizumab penetrated the neurosensory retina. Other additional advantages of Ranibizumab being higher affinity binding and potentially less immunogenicity as it lacks the Fc portion of a full-length antibody.

## MATERIAL AND METHOD

In our study, a total of 100 patients were screened and out of them 65 were chosen for the study.

**Inclusion criteria-** all cases with indication of intravitreal Bevacizumab.

**Exclusion criteria-** history of glaucoma, long term steroids, corneal abnormalities, past history of intra-ocular surgeries.

For every patient included in the study, a written consent was taken. Data collected included patients' age, gender, detailed history including previous ocular history, systemic disorder, surgical history were noted. Baseline IOP was noted using applanation tonometry at the first visit.

All patients underwent detailed ocular assessment including uncorrected and BCVA, slit lamp biomicroscopy, applanation tonometry, direct and indirect ophthalmoscopy using 20D lens, slit lamp examination using 78D lens, A-Scan for axial length and anterior chamber depth, OCT and FFA.

Ocular normotension was defined as IOP less than 21mmHg on all earlier evaluation. Sustained increase in IOP was defined as an IOP >21mmHg detected during at least 2 consecutive visits and/or an elevation in IOP requiring treatment. All IOPs were measured by applanation tonometry. No eyes received IOP lowering medications or anterior chamber paracentesis before or after intravitreal injection.

Paired t- test was used to compare the baseline IOP and IOP at various intervals of follow up. P-value <0.05 was considered as statistically significant.

**Procedure:** 1.25 mg of bevacizumab in 0.05 ml was injected intravitreally into the eye through pars plana route using insulin syringe with 30G needle under full aseptic precautions in the main operating room.

**Post Injection Care:** The patient was put on topical medications in the form of antibiotic eye drops (Moxifloxacin). Oral Carbonic anhydrase inhibitor was given if the IOP persisted above 30mmHg at the end of ½ hour.

## OBSERVATION AND RESULTS

Out of 65 patients, 55.4% (36) were males and 44.6% (29) were females. The mean age group was 58.68yrs with a SD of 8.3 yrs (range 36-78yrs). The frequency of age distribution showed patients were mostly in the age group of 51-60yrs (37 patients,56.9%) followed by 61-70yrs (15 patients ,23.1%) , ≤50yrs (8 patients,12.3%) and ≥70yrs (5 patients,7.7%).The mean (mean ±SD) anterior chamber depth of patients were 2.63±0.13.

Majority of patients included in the study were diagnosed to have diabetic retinopathy (26 cases, 40%). Seventeen patients were diagnosed with age related macular degeneration (26.15%),12 patients with branch vein retinal occlusion (18.46%) and 10 patients with central retinal vein occlusion (15.38%).Thirty five patients received intravitreal bevacizumab injection in right eye (53.8%) and 30 patients received in left eye (46.2%).

Intra-ocular pressure was measured at 1/2 hr with applanation tonometer and the patients were followed up at 1 week, 3weeks, 3 months and 6 month visits for IOP measurement. Any complications, adverse events were documented, treated and followed up.

For the purpose of study, the patients were grouped based on number of injections received. Group-1 received 1-2 injections, Group-2 received 3 injections and Group-3 received >4 injections.

Our study showed that majority of patients experienced short-term pressure spikes soon after injection that normalized within 30 minutes without further intervention. The mean baseline IOP of 65 patients was 14.94mmHg with a SD of ±2.86mmHg (range 9.4mmHg to 20mmHg). Mean IOP measured at the end of half hour was 25.29±3.32mmHg (range 21mmHg to 34mmHg) with a t-value of 18.431 and a significant p-value (<0.001).There were 6 patients whose IOP persisted >30mmHg who required intervention in the form of oral acetazolamide and a topical anti-glaucoma agent.

At the end of 6 months, the patients who received 1 to 2 injections had a mean IOP of 15.44 ±2.175mmHg (baseline IOP 14.63 ± 2.7mmHg), those who received 3 injections had a mean IOP of 16.5 ± 3.53 mmHg (baseline IOP 15.00 ± 2.02mmHg) and those who received ≥4 injections had a mean IOP of 18.24 ± 2.4mmHG (baseline IOP 15.14 ± 3.79mmHg), all with a significant p- value. It shows that though all patients had IOP within normotensive range after receiving injections, they also showed a rise in IOP of upto 1 to 3 mmHg as compared to their baseline IOP. IOP within normotensive range, had a rise in IOP of upto 1 to 3 mmHg as compared to the baseline IOP.

There were 10 such patients(5 were from vascular occlusion,3 from DR and 2 from AMD group) who had persistently elevated IOP at the end of 6 months with

IOP measuring >21mmHg. The mean baseline IOP in these patients was 15.00±5.142 mmHg and mean IOP at 6 mon was 24.30±2.541 mmHg (t-value -5.253 and significant p value .001). Out of 10 only 1 patient had shallow anterior chamber depth, however we are unable to find any correlation between raised IOP and anterior chamber depth in these patients. These patients had received ≥ 3 injections during the six months which suggests that, more the number of injections received, higher is the chance of sustained elevation of IOP.

## DISCUSSION

The main purpose of this study was to identify the patients who are at risk of developing acute rise in IOP immediately following intravitreal injection of bevacizumab and also to identify patients who might develop sustained elevation in IOP due to repeated injections and adequately treat such high risk patients.

### Short term changes in IOP after anti-VEGF

There have been reports on IOP elevation in both short term as well as long term in the setting of anti-VEGF therapy. Several works have reported that patients experience short-term pressure spikes after injection that normalize within 30 minutes without any intervention in the majority of cases.<sup>[5,6]</sup>

Judy Kim *et al.*,<sup>[7]</sup> conducted a study to assess short-term trends and the need to monitor intraocular pressure (IOP) changes immediately after intravitreal injections of ranibizumab, bevacizumab, pegaptanib and triamcinolone acetonide. IOP was reduced to less than 30 mm Hg in 96% of injections by 15 minutes and in 100% by 30 minutes. Eyes with a history of glaucoma took longer to normalize the IOP.

The explanation of IOP elevation is related to the increased intraocular volume following the injection. The volume of the vitreous cavity in the human eye is approximately 4 ml, and the volume of medication injected into the vitreous ranges from 0.05 to 0.1 ml. Therefore, depending on the volume infused, the increase in fluid volume within the vitreous cavity is approximately 1.25%–2.5%. In clinical practice this frequently translates into short-term elevation of IOP.

The incidence of IOP elevation immediately after injection as shown in some studies was significantly higher with smaller bore needle size, despite the smaller volume injected with these needles. This is most likely because of less reflux through a smaller injection opening, whereas larger-bore needles allowing more reflux. In the absence of variable of reflux, other factors which are factors for IOP rise are hyperopia, size of globe and scleral rigidity, no of injections,<sup>[5,6]</sup> and short intervals between injections.

### Long term changes in iop after anti-vegf

The manner in which intravitreal anti-VEGF therapy contributes to sustained IOP elevation has been

associated to short intervals between injections, previous history of glaucoma, total number of injections. The drugs may have a direct effect on aqueous outflow via the trabecular meshwork, uveoscleral pathway or schlemm canal. Reports have varied as to whether ranibizumab or bevacizumab is toxic to anterior segment cells at pharmacological doses.<sup>[8,9]</sup> Chronic inflammation or trabeculitis related to repeated intravitreal injections could theoretically contribute to sustained IOP elevation.<sup>[10]</sup>

Nicolas A. Yannuzzi *et al.*,<sup>[11]</sup> in his report showed that serial injections of anti-VEGF agents may lead to persistent IOP elevations that require glaucoma therapy. In their study, after a mean of 20.0 anti-VEGF injections (range, 8-40 injections), the mean IOP was 29.8mm Hg (range, 22-58mm Hg), compared with a baseline of 16.9mm Hg.

Mechanical obstruction to outflow, either by the anti-VEGF agent or by-products of pharmacologic compounding or storage have also been implicated.

Kahook *et al.*,<sup>[12]</sup> found varying levels of high-molecular weight protein aggregates when comparing different samples of compounded preparations of bevacizumab and hypothesized that this large particulate matter could lead to elevated IOP by obstructing aqueous outflow. The syringe used to inject the drugs contains silicone oil droplets which can mechanically obstruct trabecular meshwork,<sup>[13,14]</sup>

Hussein Hollands *et al.*,<sup>[15]</sup> Edward W. Lee *et al.*,<sup>[16]</sup> Kahook *et al.*,<sup>[17]</sup> Bakri *et al.*,<sup>[18]</sup> have published various articles on the study conducted regarding short term and long term elevation of IOP post intravitreal injection.

**Table 1: IOP variation in all the patients (N=65).**

	Mean± SD	t-value	p-value
Baseline IOP	14.94 ±2.86	--	--
IOP ½ hr	25.29±3.32	18.431	<0.001
IOP 1 week	17.40±3.99	4.694	<0.001
IOP 3 week	16.32±3.20	3.271	0.002
IOP 3 month	17.31±4.90	3.863	<0.001
IOP_6 month	16.77±3.84	3.623	0.001

**Table 2: IOP variation seen in patients with persistently elevated IOP at 6 mon (N=10).**

Time interval	IOP(Mean ±SD)	t-value	P-value
Baseline_IOP	15.00±5.142	--	--
IOP_1hr	28.40±4.300	-5.154	.001
IOP_1_week	23.30±3.466	-4.028	.003
IOP_3_week	20.70±3.199	-2.796	.021
IOP_3_month	25.20±4.917	-4.446	.002
IOP_6_month	24.30±2.541	-5.253	.001

## CONCLUSION

The necessity of post-injection intraocular pressure (IOP) monitoring is to identify patients at high risk for delayed normalization and those who develop sustained elevation of IOP after injection. Recent guidelines for intravitreal injections recommend “monitoring of IOP after injection and provide[ing] therapy when elevated IOP warrants intervention.” But at what intervals and for how long the IOP monitoring has to be done is not recommended.

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