

## The intraocular pressure changes following intravitreal bevacizumab injections in an Indian population

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### Abstract

**Aim:** To assess the changes in Intraocular pressure (IOP) after intravitreal bevacizumab therapy.

**Design:** Prospective, Observational, Tertiary care hospital based study.

**Participants:** 95 patients receiving intravitreal bevacizumab, for varying indications, were included.

**Materials and Methods:** A study of the change in intraocular pressure of 95 patient eyes receiving intravitreal injection of bevacizumab for varying indications was performed at 4hours, 2 weeks and 6 weeks post injection.

**Results:** There was a statistically significant increase in IOP 4 hours post injection [p value= .000; 95% confidence limits of -2.07 to -1.11; mean difference of -1.59]. There was no statistical significance in IOP rise at 2 weeks (p= 0.32; 95 % confidence limits of -1.13 and 0.18; mean difference of -0.47) or at 6 weeks (p= 1.00; 95% confidence limits of -0.86 to 0.44; mean difference of -0.21). The endpoint IOP in the single injection and multiple injection groups was statistically insignificant (t=-0.32, df = 92, significance value=0.749, 95% confidence interval -1.48 to 1.07).

**Conclusion:** Although a statistically significant short-term rise in IOP was observed, this increase was clinically insignificant. The IOP reverted towards baseline values on subsequent visits at 2 weeks and 6 weeks post-injection. The number of injections did not have any effect on the IOP change.

**Clinical significance:** Our study evaluated the effect of intravitreal injection of bevacizumab on intraocular pressure in an Indian population and found no clinically significant rise in the same.

**Keywords:** Bevacizumab, Intraocular pressure, VEGF-A.

### Introduction

Bevacizumab is a recombinant humanized monoclonal antibody against vascular derived endothelial growth factor (VEGF)- A, used in treatment of metastatic colorectal carcinoma, non-squamous non-small cell lung carcinoma, glioblastoma and renal cell carcinoma. Due to its anti-VEGF properties, it is used off label intravitreally, for the treatment of ocular neovascular diseases including diabetic retinopathy, retinal vein occlusions and choroidal neovascular membranes (CNVM).<sup>1-3</sup> During the treatment of these conditions, repeated injections may be needed in some cases. There are reports of raised intraocular pressure (IOP) after single or repeated intravitreal injections of anti-VEGF agents. However other studies have disputed this claim. The studies analyzing such a result have been largely specific regarding the disease for which the injection was given, as well as the type of anti-VEGF administered.<sup>4</sup> There were very few studies analyzing IOP changes after intravitreal bevacizumab in patients from the Indian subcontinent.

We aimed to study the effect of bevacizumab on IOP for various retinal neovascular diseases in a South Indian population.

### Materials and Methods

**Study Design:** This was a single center, prospective observational study conducted at the Department of Ophthalmology of a tertiary care University hospital in

South India, from October 2014 to June 2016. It was conducted in accordance with the tenets of the Declaration of Helsinki. The Institutional Ethical Committee approval was obtained prior to the onset of recruitment of patients. A written informed consent was obtained from all patients who participated in the study. Consecutive consenting patients who were scheduled for receiving their first intravitreal injection of bevacizumab, for various indications including diabetic retinopathy, macular degeneration, and sequelae of vascular occlusions, were included. Only one eye per patient was included. Patients on treatment for ocular hypertension or open angle glaucoma with IOP less than or equal to 21mmHg were also included.

The patients diagnosed to have neovascular glaucoma were excluded. The patients with shallow anterior chamber as determined by a van Herrick grading of 1 or less were excluded.

**Technique of Intravitreal Injection:** After pupillary dilatation with tropicamide 1% eye drops, the posterior segment examination was performed using +90 D lens on a slit lamp biomicroscope, and with an indirect ophthalmoscope. All the injections were administered under sterile environment in an operating room after instillation of topical anesthetic proparacaine hydrochloride 0.5 % and 5% povidone iodine. Intravitreal bevacizumab [Avastin®- Genentech Inc., Roche] in the dose of 1.25 mg/0.05 ml was administered through a 1cc syringe with a 30-gauge

needle, 3.5 mm to 4 mm from the limbus in the inferior temporal region. A cotton tip applicator was used to occlude the insertion site after the injection.

All intraocular pressure measurements were taken under sterile precautions by a single trained observer (AR), using a single calibrated Goldmann Applanation Tonometer (GAT), to minimize observer and instrument bias. In the patients receiving the first injection, the IOP was recorded at 4 hours, at 2 weeks and at 6 weeks following the procedure. If the patient was receiving a repeat injection, the IOP measurement taken after 6 weeks of the last injection was considered.

The sample size was calculated using the nMaster2.0 software. Statistical analysis was done using statistical package for social sciences (SPSS) version 20 for windows. The repeated measure ANOVA test was used to analyze the intraocular pressure differences in the single injection group. The independent t test was used to compare the final intraocular pressure outcome at 6 weeks between the single injection group and the multi injection group.

**Results**

A total of 95 patients were included in the study. The details concerning the patients, and the ocular indications for treatment are mentioned in Table 1.

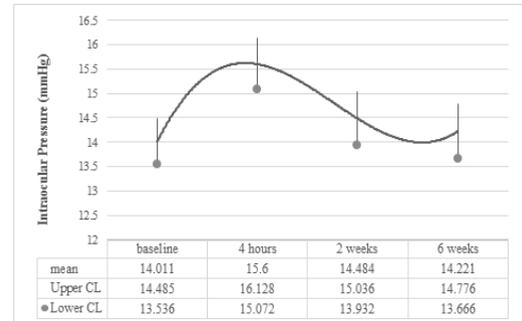
**Table 1:**

Table 1		Number of patients
Gender	Male	50
	Female	45
Lens status	Phakic	80
	Pseudophakic	15
Eye	Right	48
	Left	47
Pre-existing glaucoma	Present	8
	Absent	87
Number Of injections received	1	55
	More than 1	40
Diabetes mellitus	Present	63
	Absent	32
Hypertension	Present	49
	Absent	46
Ocular indication	Diabetic retinopathy	55
	Retinal venous occlusions	31
	CNVM	16
	Others	3
Age (years)	19-82 (mean-58.6)	

The repeated measure ANOVA test was used to analyse the change in IOP at different time intervals from the baseline, after a single injection. (Table 2; Fig. 1)

**Table 2: Mean IOP changes after intravitreal bevacizumab**

	Mean IOP (mmHg)	Std. Deviation
Baseline	14.01	2.327
After 4 hours	15.60	2.590
2 weeks	14.48	2.709
6 weeks	14.22	2.726



**Fig. 1: Intraocular pressure at different intervals following intravitreal bevacizumab**

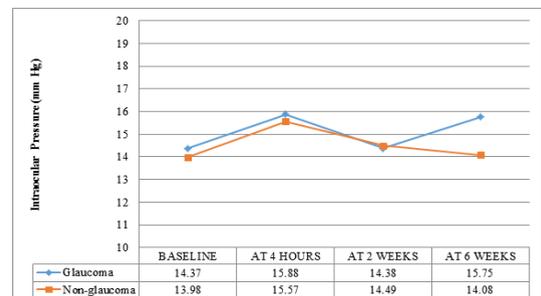
There was a statistically significant rise in IOP 4 hours after the injection compared to the baseline IOP; p value= .000 and 95% confidence limits of -2.07 to -1.11 and mean difference of -1.59.

There was no statistically significant rise in IOP at 2 weeks (p= 0.32; 95 % confidence limits of -1.13 and 0.18; mean difference of -0.47) or at 6 weeks (p= 1.00; 95% confidence limits of -0.86 and 0.44; mean difference of -0.21).

Though there was a statistically significant rise in IOP at 4 hours after the injection, the rise in mean in IOP was 1.59 mm of Hg which is a clinically insignificant rise.

The maximum rise in IOP in a single patient at 4 hours after the injection observed was 9 mm of Hg (baseline of 14 mm Hg, at 4 hours 23 mm Hg, at 2 weeks 18 mm of Hg, at 6 weeks 18 mm of Hg).

Eight patients had pre-existing glaucoma. As the sample size was small statistical significance of the difference was not calculated. (Fig. 2)



**Fig. 2: Intraocular pressure changes after intravitreal bevacizumab in pre-existing glaucoma**

The comparison of presence of change in IOP in 55 patients who had received a single injection versus 40 who had multiple injections, was done considering the mean value at six weeks following the last injection. The mean endpoint IOP of single injection group was 14.13 mm of Hg and that of multiple injection group was 14.33 mm of Hg. The analysis was done using the Independent sample t- test, and showed no statistically significant difference between the two groups. ( $t=-0.32$ ,  $df=92$ , significance value= $0.749$ , 95% confidence interval  $-1.48$  to  $1.07$ ).

## Discussion

The anti-VEGF agent, bevacizumab, administered as an intravitreal injection, has become an important therapeutic option in many retinal diseases. It is being routinely used in the treatment of either neovascularization or certain forms of maculopathy in retinal disorders including diabetic retinopathy, age related macular degeneration and retinal venous occlusions.<sup>1,2</sup>

Steroids such as dexamethasone and triamcinolone have been used for similar indications and are especially helpful in decreasing vascular permeability in macular oedema. However, their use is restricted due to adverse effects of secondary cataract and steroid induced glaucoma.<sup>5-8</sup>

The changes in intraocular pressure after intravitreal anti-VEGF agents are also reported. The various hypotheses include blockade of the trabecular meshwork by either the high molecular weight drug bevacizumab itself,<sup>9</sup> or the silicone and protein microdroplets of the packaging material which get mixed during the repackaging of the aliquots,<sup>10,11</sup> inflammation of the trabecular meshwork and recurrent transient IOP elevations eventually leading to sustained rise in IOP.<sup>4,12,13</sup> The increased volume of the vitreous following the injection was thought to induce transient rise in IOP.<sup>14</sup>

In our study, we did a prospective analysis of IOP changes after the intravitreal injection of bevacizumab.

There was a statistically significant rise ( $p$  value= $.000$ ) in the intraocular pressure at 4 hours after the injection when compared with the baseline IOP. There was no statistical significance in IOP rise at 2 weeks ( $p=0.32$ ) or at 6 weeks ( $p=1.00$ ) after the injection.

Although a rise of 9 mmHg was seen in an individual patient at the end of 4 hours of injection, the mean rise in IOP amongst the group was only 1.59mmHg, which can be considered as clinically insignificant.

Hence our observations are in confirmation with study by Falkenstein et al and other studies<sup>14-18</sup> which showed that there is only short-term rise in IOP after the injection of intravitreal bevacizumab. As the raised IOP would revert towards baseline values over 6 weeks, the risk of glaucomatous optic nerve damage is less

likely. This suggests that the intravitreal injection of bevacizumab is safe with respect to its effect on IOP.

Our study contradicts the results of other studies<sup>19-21</sup> which reported a sustained rise of IOP after intravitreal injection of anti-VEGF agents.

We also compared the effect of multiple injections versus single injections.

The endpoint IOP, when compared between the single injection group to multiple injection group, revealed no statistical significance ( $p=0.75$ ). This is in confirmation with the studies by Menke et al<sup>22</sup> and Kim et al<sup>18</sup> which showed that the number of injections had no role in the change in IOP after the injection. Contrary to our study, the study by Adelman<sup>8</sup> and other studies<sup>21-23</sup> had shown that the number of injections had a role in the change in IOP, with patients receiving higher number of injections having a significantly raised IOP than those receiving lesser number of injections. The study by the Diabetic Retinopathy Clinical Research Network Investigators on the use of repeated injections of Ranibizumab for Diabetic macular edema, concluded that there was a 3-fold higher risk of increase in IOP, but were unsure whether it was a result of the drug itself, the volume of fluid injected repeatedly, or intrinsic factors in the susceptible patients.<sup>24</sup>

The role of pre-existing glaucoma or ocular hypertension has been considered important in the post injection rise in IOP in studies by Good et al<sup>19</sup> and others. However, Kim D et al<sup>18</sup> have had differing results. Although we initially aimed at studying the role of pre-existing glaucoma or ocular hypertension, the same could not be statistically analysed due to small sample size. But the difference of IOP between both the groups at each time point was not clinically significant.

The results from our study add to the existing literature on the effects of intravitreal bevacizumab injection on the IOP. Our study was prospective in design and inclusion was not restricted to a single retinal disease.

Data from this study reflects that the IOP elevation after intravitreal injection of bevacizumab is transient. The number of injections and the presence of pre-existing glaucoma do not have any effect on the long-term change in post-injection IOP. To the best of our knowledge our study is the first to analyse the change of IOP after intravitreal bevacizumab in an Indian population.

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