Intraocular Pressure Changes after Intravitreal Bevacizumab or Ranibizumab Injection: A Retrospective Study

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Abstract

Purpose: To determine intraocular pressure (IOP) changes after intravitreal bevacizumab or ranibizumab injection administered for various retinal disorders.

Methods: A retrospective chart review of 796 eyes of 574 patients receiving intravitreal ranibizumab (0.5 mg) and/or bevacizumab (1.25 mg) injection for different retinal diseases from March 2009 to December 2016 was performed. Ocular hypertension (OHT) was defined as IOP >21 mmHg or an increase in IOP of >5 mmHg from the baseline. IOP at the baseline and at various time periods after the injection was evaluated in the injected eyes and fellow control eyes.

Results: One hundred and thirty-one eyes received either a single dose of bevacizumab or ranibizumab intravitreal injection unilaterally, 222 patients received single injection in both the eyes ($n = 444$ eyes), and 221 eyes received multiple doses of the injection. OHT was noted in 11 eyes (1.38%), of which 3 eyes (0.38%) had transient OHT and 8 eyes (1%) had delayed and sustained OHT and among them, 3 eyes (0.4%) progressed to glaucoma. Preinjection IOP was significantly higher in the treated eyes when compared to the control untreated eyes ($P = 0.006$).

Conclusions: Incidence of delayed and sustained OHT is low after a single or multiple intravitreal bevacizumab and ranibizumab injections. Clinicians should be aware of possibility of OHT or glaucoma after the procedure.

Keywords: Bevacizumab, Intraocular pressure, Intravitreal injection, Multiple injections, Ocular hypertension, Ranibizumab

INTRODUCTION

Intravitreal injection of anti-vascular endothelial growth factor (VEGF) agents is the mainstay for the treatment of choroidal neovascularization, secondary to the neovascular age-related macular degeneration (ARMD) or pathological myopia, macular edema secondary to the retinal vein occlusion (RVO) and diabetic retinopathy (DR).[1-4] Commonly used intravitreal VEGF-antagonists are ranibizumab (Lucentis; Genentech/Novartis, Inc., San Francisco, CA, USA) and bevacizumab (Avastin; Genentech/Hoffmann-La Roche Inc., CA, USA).

Serious adverse events after anti-VEGF injections are uncommon and include inflammation, endophthalmitis, cataract progression, vitreous or subretinal hemorrhage, retinal detachment, ocular hypertension (OHT), and glaucoma.[5,6] Intraocular pressure (IOP) elevation after an anti-VEGF injection can be acute and transient because of an increase in the ocular volume or a sustained rise in IOP, which may be related to the pharmacologic drug properties.[7-17] Mechanism for the delayed OHT after an intravitreal anti-VEGF is not well understood. It is hypothesized that it could be due to the direct trabecular meshwork damage, secondary to the mechanical

effect of anti-VEGF agent, or particles obstructing aqueous outflow,[18,19] drug toxicity,[20] drug-induced trabeculitis or uveitis, and preexisting glaucoma.[12] Number of injections[15] and interval between the injections[10] can also be attributed to increase in the IOP due to accumulation of immune complexes or small anti-VEGF particles. Another theory of sustained the IOP, increase is that the anti-VEGF agent may develop silicone oil micro droplets from the syringe barrel, rubber stopper, and/ or protein aggregates in the repackaged bevacizumab during storage and transportation in the plastic syringes, which can obstruct the aqueous outflow.[18-20] Most of the previous studies looked at an IOP rise or OHT/glaucoma after the intravitreal injection in the eyes with ARMD.[9-16] The purpose of this study was to evaluate the IOP changes in the injected eye as well as the untreated, contralateral eye after a single or multiple, repeated intravitreal bevacizumab and/or ranibizumab injections for the various retinal disorders.

METHODS

A retrospective review of medical records of 609 consecutive patients receiving intravitreal ranibizumab or bevacizumab at our institute was performed after obtaining approval of the Anand Eye Institute Review Board. Patients were included if they had received at least one intravitreal ranibizumab or bevacizumab injection and had a minimum follow-up of 1 month after the injection. Exclusion criteria were: Age <18 years, iris or angle neovascularization, preexisting glaucoma or OHT, patients on anti-glaucoma medications (AGMs), active uveitis, history of intraocular steroid injection, and vitreoretinal surgery.

Data were collected on the diagnosis, indication, number and interval between the injections, follow-up duration, ocular surgeries prior to or postinjection, and IOP measurement with Goldmann applanation tonometry at each visit.

For patients receiving injection on the their first visit, IOP from that visit was used as the baseline. Those receiving multiple injections, baseline IOP was calculated as the most recent IOP recorded before the last received anti-VEGF injection. IOP at the baseline, 1 day, 1 week, 1 month, 3 months, 6 months, and yearly till the last follow-up visit after the injection were analyzed in the injected eye and non-injected fellow eyes. After written informed consent, under topical anesthesia, 1.25 mg of bevacizumab (Avastin; Genentech/Hoffmann-La Roche Inc., CA, USA) or 0.5 mg of ranibizumab (Lucentis; Genentech/Novartis, Inc., San Francisco, CA, USA) was injected with a 30G needle through the inferotemporal pars plana region at 3.5 mm from the limbus in pseudophakic and 4 mm from the limbus, in phakic patient. Paracentesis was not performed for any of the patients.

OHT was defined as >21 mmHg[10,12] or an increase of >5 mmHg from the baseline.[15,17] Glaucoma was defined as IOP >21 mmHg and glaucomatous optic atrophy. As preexisting glaucoma or OHT was one of the exclusion criteria of the study, none of the study or fellow eyes were on AGM or had undergone prior glaucoma filtering surgery.

Descriptive analysis was calculated as the mean and standard deviation. The test of homogeneity of variances was tested with Levene's statistics. IOP difference between the injected and control eyes was measured using *t*-test. IOP difference between the baseline preinjection IOP and at various time interval during the follow-up was calculated using repeated measures analysis of variance/paired *t*-test with *post hoc* of least significant difference. The prevalence or frequency of IOP difference between the eyes receiving bevacizumab and ranibizumab was analyzed using Chi-square/Fisher's exact test. General estimating equations were used to account for correlation between the eyes of individual patients. The statistical analysis was performed using commercial SPSS software (version 19, IBM, Chicago, IL, USA). A $P < 0.05$ was considered statistically significant.

RESULTS

A total of 796 eyes of 574 patients met the inclusion criteria, and 35 patients were excluded. Seven hundred and ninety-six eyes had received a total of 1588 intravitreal bevacizumab ($n = 1333$) or ranibizumab ($n = 255$). Forty eyes had a history of receiving intravitreal anti-VEGF, prior to coming to our institute. Demographics and baseline characteristics of the patients are presented in Table 1.

Mean age at treatment was 58.1 ± 11.5 years (range, 21–95), and 35.3% were female. The mean follow-up duration was 13 ± 17.2 months (range, 1–96 months). Macular edema secondary to DR was the most frequent indication for the injection (62.2%) [Table 1]. There was no significant difference between the eyes receiving bevacizumab or ranibizumab with regards to the age, gender ratio, lens status, and baseline IOP [Table 1].

One hundred and thirty-one eyes received single injection, 221 eyes multiple injections ($n = 1013$), and 222 patients received an injection in both the eyes ($n = 444$ eyes). In the eyes receiving multiple injections, 25 eyes were treated with ranibizumab, 181 received bevacizumab, and 15 received both. The mean number of total injections/patient was 3.1 ± 1.5 (range, 2–11). Time interval between the multiple injections was 8.3 ± 13.1 months (range, 1–96).

In the non-injected, fellow eyes ($n = 352$) of patients receiving anti-VEGF, 28 eyes had scarred choroidal neovascular membrane (CNVM), 78 eyes had proliferative DR, 28 eyes had dry ARMD, 6 eyes had best disease, 7 eyes had Eales disease, 26 eyes had old branch RVO, 41 eyes had non-proliferative diabetic retinopathy (non-PDR), 5 eyes had absolute glaucoma, and 133 eyes did not have any ocular pathology.

To know the influence of anti-VEGF on IOP change, baseline IOP measured before each injection was compared to the IOP at subsequent visits. Mean baseline IOP was 13.6 ± 2.5 mmHg and 13.2 ± 2.4 mmHg in the injected and non-injected eyes, respectively ($P = 0.06$). IOP difference between the treated and non-treated fellow eyes was significant at day

Table 1: Baseline and clinical characteristic of the study population receiving intravitreal bevacizumab and ranibizumab injections

Anti-VEGF injection	Bevacizumab (n=1333)	Ranibizumab (n=255)	P	Overall injections
Mean age±SD at first injection (years)	57.6±11.5	56.6±10.5	0.41	58.08±11.5
Gender (male:female)	874:459	155:100	0.14	1029:559
Laterality of eye (right/left)	654/678	138/117	0.15	792/795
Co-morbidities				
DM	926	168	0.14	1094
HTN	799	139	0.11	938
CAD	122	32	0.09	154
Number of injections in eyes	1333	255	1.0	1588
Indications for injection				
Diabetic macular edema	495	69	0.002	564
CRVO	60	6	0.12	66
Branch retinal vein occlusion	142	11	0.002	153
Neovascular age-related macular degeneration	196	50	0.05	246
Idiopathic polypoidal choroidal vasculopathy	10	22	<0.0001	32
Central serous chorio retinopathy	1	7	<0.0001	8
PDR–VH	340	79	0.07	419
Myopic choroidal neovascularization	33	3	0.2	36
Eales disease	11	2	0.95	13
Best disease	2	4	0.001	6
Idiopathic CNVM	7	0	0.61	7
Parafoveal telangiectasia	36	2	0.07	38
Lens status				
Phakic/cataract	1016	203	0.24	1219
PS	307	52	0.33	359
Aphakia	3	7		10
Number of multiple injections in eyes				
2-3	46	25	<0.0001	71
4-5	23	9	0.06	32
6-7	12	1	0.41	13
8-9	5	0	0.33	5
10-11	1	0	1.00	1
Mean baseline intraocular pressure±SD (mmHg)	13.54±2.48	13.56±2.59	0.71	13.6±2.51

VEGF: Vascular endothelial growth factor, CNVM: Choroidal neovascular membrane, SD: Standard deviation, DM: Diabetes mellitus, CAD: Coronary artery disease, HTN: Hypertension, CRVO: Central retinal vein occlusion, PDR-VH: Proliferative diabetic retinopathy vitreous hemorrhage, PS: Pseudophakia

1 ($P = 0.004$) and 1 year ($P = 0.004$). Mean paired difference increase in the IOP from baseline to after the injection was statistically significant at 1 day, 1 month, and 3 months of follow-up [Table 2].

Comparison of baseline IOP to the IOP measurements at subsequent visits during follow-up did not show any significant difference in the fellow control eyes. There was no difference of IOP between bevacizumab and ranibizumab injected eyes at the baseline or during the subsequent follow-up visits, postinjection (all $P > 0.05$). In the treated eyes, 11 eyes (1.38%) had OHT after anti-VEGF [Table 3], 2 eyes of which had OHT in both eyes following bilateral injection. In 3 eyes (0.4%), IOP elevation was transient and returned to the baseline levels without AGM after a week. Eight eyes (1%) had sustained IOP elevation, and IOP was controlled with AGM. Three out of 11 eyes experienced IOP elevation of >5 mmHg from baseline during the follow-up, and 8/11 experienced IOP of >21 mmHg postinjection. The mean age of patients in this subgroup was

58.4 ± 9.4 years, 54.5% were male, and macular edema secondary to DR (45.4%) was the most common indication for injection.

Mean time to develop OHT after the last injection was 9.9 ± 14.9 months (range, 1 day to 4 years), after a mean 1.8 ± 0.6 number of injections, mean baseline IOP was 14.9 ± 3.6 mmHg, and the average peak IOP in sustained IOP elevation eyes was 24.9 ± 4.1 mmHg. Average time interval between the injections in patients receiving multiple injections was 14.6 ± 15.7 months (range, 1–96 months), and in those with OHT, it was 8.7 ± 13.1 months (range, 1–39). In 3/8 patients with sustained IOP rise, 5 had PDR, 1 had ARMD with CNVM, 1 had myopic CNVM, and 1 had central RVO with CNVM [Table 3]. Three eyes progressed to glaucoma and 1 eye (case 1) underwent combined cataract and trabeculectomy surgery, 2 years after the injection [Table 2].

IOP elevation after multiple injections was seen in 8 eyes (3.6%). The prevalence of OHT between patients who received

Table 2: Mean paired intraocular pressure difference when compared to the baseline at each visit in the eyes receiving intravitreal ranibizumab or bevacizumab injections and non-injected fellow eyes

Time interval from baseline IOP measurement to the follow-up period after the injection (number of eyes at follow-up period)	Treated eyes			Fellow control eyes		
	Mean paired IOP difference	SD	*P*	Mean paired IOP difference	SD	*P*
1 day (*n*=796)	0.2917	2.3551	<0.0001	0.1811	2.0828	0.086
1 week (*n*=796)	0.2196	2.8504	0.186	0.3333	2.5590	0.305
1 month (*n*=796)	0.2787	2.5491	<0.0001	0.1494	2.3450	0.235
3 months (*n*=783)	0.3814	2.4777	<0.0001	0.1784	2.2148	0.212
6 months (*n*=625)	0.1283	2.5935	0.211	0.1105	2.1776	0.507
1 year (*n*=513)	0.0093	2.4748	0.931	0.1064	2.1034	0.549
2 year (*n*=226)	0.0760	2.1088	0.638	0.3793	2.7310	0.461
3 years (*n*=157)	0.0115	1.8646	0.954	0.8235	3.3955	0.332
4 years (*n*=52)	−0.0923	1.7829	0.678	1.2000	4.1312	0.382
5 years (*n*=52)	−0.3529	1.5152	0.184	0.0000	2.8284	1.000
6 years (*n*=25)	−0.1538	1.7246	0.753	−3.0000	1.4142	0.205
7 years (*n*=8)	0.3333	0.8165	0.363			

IOP: Intraocular pressure, SD: Standard deviation

Table 3: Clinical summary of 11 eyes of 9 patients with ocular hypertension or glaucoma following anti-vascular endothelial growth factor intravitreal injection

Case	Eye laterality	Gender/age (years)	Indication for injection	Anti-VEGF intravitreal injection	Total number of injections prior to IOP rise	Baseline IOP (mmHg)	Time of rise in IOP	Postinjection maximum IOP rise (mmHg)	Number of AGM	Systemic comorbidity	Lens status
Sustained IOP rise											
1	RE	Male/62	PDR CSME	Bevacizumab	2	12	6 months	24	2	DM/HTN/CAD	NS
2	LE	Male/62	PDR CSME	Bevacizumab	2	12	6 months	27	2	DM/HTN/CAD	NS
3	RE	Male/49	CRVO CME	Bevacizumab	2	16	2 years	28	1	-	Clear
4	LE	Female/63	ARMD CNVM	Bevacizumab	2	14	3 months	26	1	DM/HTN/CAD	NS
5	LE	Female/39	Myopic CNVM	Bevacizumab	1	12	4 years	24	1	-	Clear
6	RE	Male/53	PDR VH	Bevacizumab	2	16	1.5 years	34	2	DM	Clear
7	RE	Male/71	PDR CSME	Ranibizumab	2	18	1 day	23*	2	DM	PS
8	LE	Female/65	PDR CSME	Bevacizumab	1	14	3 months	26	2	DM/HTN/CAD	Clear
Transient IOP rise											
9	RE	Female/68	Myopic CNVM	Ranibizumab	2	18	1 day	24*	None	-	Clear
10	LE	Male/64	PDR VH	Bevacizumab	3	12	1 day	22*	None	DM/HTN	NS
11	RE	Female/57	PDR CSME	Bevacizumab	1	14	1 day	22*	None	DM	NS

*>5 mmHg from baseline. VEGF: Vascular endothelial growth factor, IOP: Intraocular pressure, AGM: Anti-glaucoma medication, RE/LE: Right eye, left eye, PDR CSME: Proliferative diabetic retinopathy, clinical significant macular edema, CRVO CME: Central retinal vein occlusion, cystoid macular edema, ARMD CNVM: Age-related macular degeneration, choroidal neovascular membrane, PDR VH: Proliferative diabetic retinopathy, vitreous hemorrhage, Myopic CNVM: Myopic choroidal neovascular membrane, DM: Diabetes mellitus, HTN: Hypertension, CAD: Coronary artery disease, NS: Nuclear sclerosis, PS: Pseudophakia

multiple injections and those with single injection was not significant ($P = 0.7$). The prevalence of OHT between bevacizumab (9 eyes) and ranibizumab subgroup (2 eyes) was not significant ($P = 0.98$).

Discussion

In our study, we found transient OHT in three eyes postinjection, which after a week returned to the baseline, without any treatment. Previous studies[7,8,14] have reported transient IOP spikes immediately after the intravitreal

ranibizumab or bevacizumab due to an increase in the vitreous volume, altering aqueous outflow.

A study[12] reported that the patients receiving intravitreal bevacizumab are more prone to IOP elevation, whereas another study[13] noted more cases of OHT in the patients receiving ranibizumab, and others[9] did not find any difference between bevacizumab and ranibizumab attributing to the IOP elevation. As bevacizumab is a full-length antibody, the crystallizable fragment is involved in the binding of the immune molecules, such as complement factors, and has the potential to trigger

an immune response, leading to the complement mediated cytotoxicity. However, Kernt *et al.*[21] found no *in vivo* trabecular meshwork toxicity with the standard bevacizumab concentration. We did not find any difference in IOP changes between bevacizumab and ranibizumab at the baseline or during subsequent follow-up visits.

The prevalence of sustained IOP rise after ranibizumab and/or bevacizumab has been reported to vary from 1.6–11%.[9-13,15,16] The definition of sustained IOP rise varies between the studies, but most of them have a criterion of IOP >21 mmHg on 2 consecutive visits or an increase of 5 mmHg or more from the baseline, preinjection measurements. Compared to these studies, the prevalence of sustained OHT in our study was low (1%), which could be because of the stringent criteria used to define OHT, exclusion of patients receiving intravitreal steroids, preexisting glaucoma, or OHT (to remove the bias in finding prevalence of OHT postinjection). Preexisting glaucoma or OHT has been implicated as a causative factor for the postinjection OHT as these eyes have a compromised outflow system and are more prone to develop OHT.[12,17] However, other studies failed to find such an association.[10,16] Another possibility is that the delayed OHT may be due to the cumulative effect of anti-VEGF agent seen after the multiple injections, and in our study, the maximum number of injections given was 11, for a patient. A direct comparison with previous studies cannot be made as they all have reported OHT in eyes receiving injections for only neovascular ARMD, whereas our study has included all the eyes receiving injections for various vitreoretinal disorders, and the most common indication for the intravitreal injection was macular edema secondary to the DR [Table 4].[10,12,13,15,16]

Multiple number of injections has been implicated as a causative factor for OHT after anti-VEGF, as there is a possibility of small particles (immune complexes) accumulating, occluding trabecular meshwork, and reducing aqueous outflow.[11] Hoang *et al.*[15] reported that 11.6% of treated and 5.3% of control eyes experienced long-term OHT, and the total number of injections showed a statistically significant association with IOP elevation ($P = 0.05$) in eyes receiving ≥29 injections compared with eyes receiving ≤ 12 injections in 449 eyes receiving anti-VEGF bilaterally. Good *et al.*[12] reported sustained IOP elevations in 13/215 eyes (6%) after a median of

9 injections of ranibizumab and/or bevacizumab in exudative ARMD. Higher OHT prevalence was found in the eyes receiving bevacizumab (9.9%) compared with those receiving ranibizumab (3.1%) ($P = 0.049$). This was significantly higher in patients with preexisting glaucoma than in those without glaucoma (33% vs. 3.1%; $P < 0.001$). No association between the development of delayed OHT and number of injections was found. In our study, untreated, contralateral control eyes did not show significant IOP elevation during the follow-up. Two hundred and twenty-one eyes (27.8%) received >2 injections (range, 2–11) with a mean follow-up of 13 months after the initial injection. Eight out of 221 (3.6%) eyes receiving multiple injections developed a long-term IOP increase when compared to 3/575 (0.52%) eyes receiving a single injection ($P = 0.74$), with a mean time period of 10 months for the measured peak IOP after the last injection. No significant association between mean IOP and the mean number of injections was observed. This is in agreement with other studies, which did not find the number of injections to be a risk factor for IOP elevation.[12,14]

Delayed and sustained OHT could be due to inhibition of VEGF in the trabecular meshwork, causing reduced aqueous outflow facility. Mathalone *et al.*[10] reported that if the interval between injections was <8 weeks (17.6%), the risk of OHT was higher, compared to those with an interval of >8 weeks (6%, $P = 0.009$) in 22/201 eyes (11%) receiving bevacizumab for neovascular ARMD. Another study did not observe such correlation.[12] In our study, for the eyes with OHT, the average time interval between multiple injections was 8 months (range, 1–39 months), and in eyes without OHT receiving multiple injections, it was 15 months (range, 1–96 months). This could be another possible explanation for the low rate of delayed OHT, as many patients received multiple, repeat injections with an increased time interval between injections, allowing the anti-VEGF agent to clear from the eye.

We found that the mean baseline IOP was higher in patients receiving anti-VEGF when compared to the fellow untreated eyes. This difference in IOP was significant on day 1 and at 1 year of follow-up between the two groups. This could be another predisposing factor for OHT in the eyes treated with anti-VEGF and needs to be explored in future prospective studies. We cannot directly compare our results with previous studies because of many variables studied, a lack

Table 4: Review of previous studies with sustained intraocular pressure rise after ranibizumab or bevacizumab intravitreal injection

Study	Controls	Overall prevalence of OHT (%)	Inclusion of eyes with preexisting history of OHT or glaucoma	Mean number of injections at the time of IOP rise	Postinjection IOP range
Good *et al.*[12]	-	13/215 (6)	Yes	Median - 5	23-36
Mathalone *et al.*[10]	-	22/201 (11)	Yes	5	22-36
Adelman *et al.*[13]	-	4/116 (3.45)	No	13.3	28-36
Hoang *et al.*[15]	Fellow eyes	32/449 (7.1)	Yes	25.8	
Wehrli *et al.*[16]	Fellow eyes	5/302 (1.6)	Yes	8	25-29
Our study	Fellow eyes	8/796 (1)	No	1.8	23-34

OHT: Ocular hypertension, IOP: Intraocular pressure

of controls in most studies, the inclusion of patients with preexisting glaucoma, different anti-VEGF or a combination of the ≥2 anti-VEGF agents used, indication of treatment (most studies-neovascular ARMD),[9,10,12,13,15,16] differences in intervals between injections and total number of injections. In addition, there are differences in the syringes used for injection, preparation, handling, freezing, and storage of bevacizumab.

A limitation of this study is its retrospective nature and variable postinjection follow-up visits. In eyes with IOP ≤21 mmHg, IOP was not re-checked. Strengths of this study include its large sample size, long follow-up duration, inclusion of the fellow eye as control, standardized treatment protocol of injection procedure, and inclusion of all the eyes receiving intravitreal anti-VEGF for the various retinal conditions.

In conclusion, after a single or multiple intravitreal bevacizumab or ranibizumab, IOP should be monitored at every visit, even though the incidence of OHT is low.

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Conflicts of interest
There are no conflicts of interest.

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