ORIGINAL ARTICLE

Predictors of elevated intraocular pressure after intravitreal injection of anti-vascular endothelial growth factor: a prospective observational study

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Abstract

Purpose: To investigate the patterns and predictors of intraocular pressure (IOP) changes after intravitreal injection (IVI) of anti-vascular endothelial growth factor (anti-VEGF).

Methods: This study enrolled 32 men and 16 women (mean age, 65.3±12.3 years) who underwent IVI of anti-VEGF between January and March 2020 in our department. IOPs were measured using Goldmann applanation tonometry. Potential predictors included age, sex, lens status, axial length, history of glaucoma, number of previous IVIs, diagnosis, and post-injection vitreous reflux.

Results: The respective mean IOP was 16.2 mmHg, 32.7 mmHg, 21.7 mmHg, and 18.3 mmHg at baseline and at 5, 15, and 30 minutes after IVI. IOP elevation of ≥15 mmHg was observed in 48% of eyes at 5 minutes after IVI; all spikes resolved and the IOP reduced to <21 mmHg within 60 minutes. Previous IVI number (r=0.346, p=0.016) and baseline IOP (r=0.304, p=0.04) were associated with IOP at 5 minutes after IVI. Baseline IOP was associated with IOPs at 15 and 30 minutes after IVI (r=0.488-0.573, p<0.001). In multivariate regression analysis, the previous IVI number (b=0.55, p=0.04) was an independent predictor of IOP at 5 minutes after IVI.

Conclusion: Transient but substantial IOP elevation shortly after IVI of anti-VEGF was positively correlated with the number of previous IVIs; this could be used to stratify patients for IOP spike prophylaxis, especially those with advanced glaucoma at risk of further optic nerve damage secondary to acute ocular hypertension. Ophthalmologists should assess patient susceptibility to glaucomatous damage, along with the risks and complications of prophylaxis for IOP spike prevention.

Key words: Bevacizumab; Glaucoma; Intraocular pressure; Intravitreal injections; Retina

Introduction

Intravitreal injection (IVI) of anti-vascular endothelial growth factor (anti-VEGF) is widely used for the treatment of various retinal pathologies such as neovascular age-related macular degeneration,[1,2] diabetic macular edema,[3] and retinal venous occlusion.[4] Although IVI is a safe procedure, complications have been reported, including acute angle closure[5] and

substantial short-term elevated intraocular pressure (IOP) leading to retinal arterial occlusion.[6] Sudden expansions of vitreous volume are presumably responsible for these short-term increases in IOP immediately after IVI of anti-VEGF. Nonetheless, the application and protocol of IOP monitoring after IVI varies among institutions. Although the effects of elevated IOP might be transient, visual damage might occur, especially in patients with preexisting glaucoma. Research in animal models has shown that acutely elevated IOP can lead to axonal transport blockade to the optic nerve head,[7] as well as reduced juxtapapillary retinal and optic nerve head blood flow; if the IOP remains uncontrolled, these changes can result in ocular ischemia and functional damage.[8] Because the central vision is usually already impaired in patients with retinal disorders that require anti-VEGF treatment, it is important to preserve their peripheral vision and optic nerve function, both of which are important for night vision and activities of daily living. Any substantial increase in IOP (ie, an IOP spike) should be avoided and timely treatment should be offered to patients with sustained IOP elevation. To the best of our knowledge, there is no guideline for monitoring short-term IOP changes after IVI of anti-VEGF; furthermore, there have been limited studies concerning predictors of severe IOP spikes.[9] Thus, this study aimed to examine the frequency and severity of IOP elevation at 5, 15, and 30 minutes after IVI of anti-VEGF and to determine predictors of elevated IOP that can be used for risk stratification.

Materials and methods

This prospective study was approved by the Joint Chinese University of Hong Kong-New Territories East Cluster Clinical Research Ethics Committee (Ref: CRE-2019.162). Informed consent for enrollment in the study was obtained from each patient. All procedures were conducted in accordance with the principles of the Declaration of Helsinki. Patients were enrolled if they underwent IVI of anti-VEGF between January 2020 and March 2020 in the Department of Ophthalmology and Visual Sciences, Prince of Wales Hospital. Exclusion criteria were known diagnosis of secondary glaucoma (including uveitic glaucoma, neovascular glaucoma, pigmentary glaucoma, pseudoexfoliation, and iridocorneal endothelial syndrome); a history of glaucoma surgery or laser procedures; and/or the use of systemic, regional, and topical steroids within 1 month of IVI.

One eye from each patient was included; the lens status, baseline IOP, and axial length were measured before IVI. IVIs were performed by two qualified retinal surgeons using standardized techniques and instruments. Each procedure was performed under topical anesthesia with 0.5% proxymetacaine, without the application of IOP-lowering eye drops. Povidone iodine (5%) was used to irrigate the conjunctival fornices, while povidone iodine (10%) was used to disinfect the lid margin and periorbital skin. A skin drape and lid speculum were applied; 0.05 mL of ranibizumab or aflibercept was then injected through displaced conjunctiva over the infero- or supero-temporal quadrant using 30-gauge needles; injections were performed at 3.5 mm and 4 mm behind the limbus in pseudophakic and phakic eyes, respectively. Firm pressure was applied to the injection site with a cotton-tip applicator for at least 5 s immediately on retrieval of the injection needle to minimize vitreous reflux. Light perception vision was checked after each injection; anterior chamber paracentesis was performed in patients who exhibited loss of visual function. Finally, the ocular surface was irrigated with 0.5% levofloxacin eye drops.

IOP at 5, 15, and 30 minutes after IVI was measured in an upright position using Goldmann applanation tonometry. For eyes with IOP of >21 mmHg at 30 minutes after IVI, additional measurements were performed at 45 and/or 60 minutes (until the IOP was <21 mmHg). Eyes with persistent IOP of >21 mmHg at 60 minutes after IVI were administered topical IOP-lowering medications and re-examined the next day. All IOPs were measured twice and the mean value was recorded when the difference was <2 mmHg. A third measurement was performed when the difference was >2 mmHg; the median of the three measurements was then recorded. The presence of vitreous reflux from the injection site and the requirement for anterior chamber paracentesis after IVI were documented.

Statistical analysis was performed using SPSS Advanced Statistical Software, version 11.0 (Chicago, IL, USA). Two-tailed Pearson correlations and Student's *t* tests were used to determine the correlations of IOPs at 5, 15, and 30 minutes after IVI with potential predictors of IOP changes (eg, age, sex, diagnosis, lens status, axial length, history of glaucoma [defined as the use of IOP-lowering medications with clinical evidence of glaucomatous optic neuropathy], presence of

Table 1. Demographics and clinical characteristics of patients who underwent intravitreal injection (IVI) of anti-vascular endothelial growth factor for the treatment of retinal pathologies*

Characteristic	
Age, y	65.3±12.3
Sex	
Female	16 (33.3)
Male	32 (66.7)
Diagnosis	
Age-related macular degeneration	22 (45.8)
Diabetic macular edema	19 (39.6)
Retinal venous occlusion	4 (8.3)
Others (punctate inner choroidopathy, juxtafoveal telangiectasia, and myopic choroidal neovascularization)	1 (6.3)
No. of previous IVIs of anti-vascular endothelial growth factor	4.6±5.6
Lens status	
Phakic	32 (66.7)
Pseudophakic	16 (33.3)
Known history of glaucoma	4 (8.3)
Axial length, mm	24.0±1.8
Vitreous reflux after IVI	6 (12.5)

* *Data are presented as mean±standard deviation or No. (%) of patients*

vitreous reflux, and type of anti-VEGF injected). A p value of <0.05 was considered statistically significant. Multivariate regression analysis of statistically significant potential predictors was performed to identify independent predictors of IOP changes.

Results

In total, 32 men and 16 women (mean age, 65.3±12.3 years) were included (**Table 1**). The most common diagnoses were age-related macular degeneration (45.8%) and diabetic macular edema (39.6%); other diagnoses comprised retinal venous occlusion (8.3%) and others (6.3%; ie, punctate inner choroidopathy, juxtafoveal telangiectasia, and myopic choroidal neovascularization). Overall, 66.7% of patients were phakic and 8.3% had a known history of glaucoma. The mean axial length was 24.0±1.8 mm.

The mean IOP was 16.2±3.2 mmHg at baseline; it increased to 32.7±10.5 mmHg at 5 minutes after IVI, then decreased to 21.7±5.3 mmHg at 15 minutes and to 18.3±3.8 mmHg at 30 minutes. The mean differences from baseline were 16.4±10.0 mmHg, 5.5±4.7 mmHg, and 2.1±3.3 mmHg, respectively.

At 5 minutes after IVI, IOP had increased to ≥25 mmHg in 70.8% of patients (**Table 2**); moreover, IOP had increased by ≥10 mmHg in 68.8% of patients. Notably, IOP had increased to >50 mmHg in three patients (2.1%), with the maximum value of 57.9 mmHg (an increase of 40.6 mmHg). At 15 minutes after IVI, IOP remained ≥25 mmHg in 22.9% of patients. At 30 minutes after IVI, IOP remained ≥25 mmHg in only 4.2% of patients; 20.8% of patients exhibited an increase of ≥5 mmHg from baseline. At 45 minutes after IVI, IOP in eight (16.7%) patients remained ≥21 (range, 21.1-22.2) mmHg but reduced to <21 mmHg within 60 minutes. No IOP-lowering medications were required, nor was anterior chamber paracentesis necessary to prevent loss of visual function. Vitreous reflux after IVI was noted in 12.5% of patients.

The number of previous IVIs (r=0.346, p=0.016) and baseline IOP (r=0.304, p=0.04) were associated with IOP at 5 minutes after IVI. Baseline IOP was also associated with IOPs at 15 and 30 minutes after IVI (r=0.488-0.573, p<0.001) (**Table 3**). Patient diagnosis was not associated with IOPs at 5, 15, or 30 minutes after IVI (**Table 4**). Multivariate regression analysis showed that the number of previous IVIs (b=0.55, standard error=0.26, p=0.04) was an independent predictor of IOP at 5 minutes after IVI, after controlling for baseline IOP (**Table 5**).

Discussion

Consistent with the findings in previous studies,[10-14] the present study showed substantial IOP spikes at 5 minutes after IVI. However, these spikes were transient and the IOP reduced to <21 mmHg at 30 minutes in 83.3% of patients. In the remaining patients, the IOP continued to gradually decrease to <21 mmHg at 60 minutes. At 30 minutes after IVI, an IOP increase of 2.1±3.3 mmHg from baseline is not clinically significant. This indicates that short-term IOP elevation after IVI has a good safety profile. However, at 5 minutes after IVI, 77% of patients had an IOP of ≥40 mmHg; notably, three patients had an IOP of ≥50 mmHg. Such IOP spikes secondary to sudden volume expansion in the vitreous cavity can potentially deform the contour of the lamina cribrosa at the optic nerve head,[15] induce a reduction in ocular perfusion pressure that exceeds the auto-regulatory range of the optic nerve head blood flow,[16] and disturb axonal transport.[7] In an animal study, low perfusion pressure was associated with variable outer retinal layer damage and

Table 2. Intraocular pressure (IOP) at baseline and at 5, 15, and 30 minutes after intravitreal injection (IVI) of anti-vascular endothelial growth factor*

IOP, mmHg	Baseline	5 minutes after IVI	Difference from baseline	15 minutes after IVI	Difference from baseline	30 minutes after IVI	Difference from baseline
Mean	16.2±3.2	32.7±10.5	16.4±10.0	21.7±5.3	5.5±4.7	18.3±3.8	2.1±3.3
<0	0	0	0	0	5	0	15
0-<5	0	0	7	0	20	0	23
5-<10	2	0	8	0	16	0	9
10-<15	16	1	10	3	6	6	1
15-<20	24	5	5	14	0	31	0
20-<25	6	8	8	20	1	9	0
25-<30	0	6	6	8	0	2	0
30-<35	0	7	2	2	0	0	0
35-<40	0	10	1	1	0	0	0
40-<45	0	4	1	0	0	0	0
45-<50	0	4	0	0	0	0	0
50-<55	0	2	0	0	0	0	0
≥55	0	1	0	0	0	0	0

* *Data are presented as mean ± standard deviation IOP or No. of eyes*

severe atrophy of the ganglion cells, nerve fiber layer, and optic nerve.[17] Substantially elevated IOP during laser-assisted in situ keratomileusis has been shown to reduce retinal nerve fiber layer thickness; this reduction can be induced by sustained IOP of >65 mmHg for >20 s.[18] Furthermore, losses of fixation[19] and visual fields[20] secondary to IOP spikes after cataract extraction in patients with advanced glaucoma also imply that transiently elevated IOP can cause optic nerve damage. Although a short-term IOP spike after IVI is likely to be trivial in healthy eyes, it can have detrimental effects on the remaining nerve fiber layers in patients with pre-existing advanced glaucoma.[21] Thus, the cumulative long-term structural and physiological sequelae should be considered, especially when repeated IVIs are required. Each patient's IOP should be measured within 5 to 15 minutes of IVI because IOP tends to be greatest immediately after injection.

Table 3. Correlations of intraocular pressures at 5, 15, and 30 minutes after intravitreal injection (IVI) with potential predictors.

Potential predictor	Correlation coefficient / mean difference (standard error)	p Value
Age		
5 minutes after IVI	0.013	0.93
15 minutes after IVI	-0.010	0.95
30 minutes after IVI	-0.114	0.44
No. of previous IVIs		
5 minutes after IVI	0.346	0.02
15 minutes after IVI	0.242	0.10
30 minutes after IVI	0.187	0.20
Baseline intraocular pressure		
5 minutes after IVI	0.304	0.04
15 minutes after IVI	0.488	<0.001
30 minutes after IVI	0.573	<0.001
Axial length		
5 minutes after IVI	-0.061	0.68
15 minutes after IVI	0.076	0.61
30 minutes after IVI	0.137	0.35
Sex		
5 minutes after IVI	3.36 (3.22)	0.30
15 minutes after IVI	1.88 (1.63)	0.25
30 minutes after IVI	1.13 (1.15)	0.33
Lens status		
5 minutes after IVI	4.05 (3.20)	0.21
15 minutes after IVI	0.61 (1.65)	0.71
30 minutes after IVI	0.36 (1.16)	0.76
History of glaucoma		
5 minutes after IVI	4.06 (5.52)	0.47
15 minutes after IVI	2.06 (2.81)	0.47
30 minutes after IVI	1.63 (1.97)	0.41
Vitreous reflux		
5 minutes after IVI	1.31 (4.64)	0.78
15 minutes after IVI	1.25 (2.35)	0.60
30 minutes after IVI	0.13 (1.66)	0.94

In the present study, the number of previous IVIs was an independent predictor of IOP at 5 minutes after IVI. Each previous IVI was associated with an IOP increase of 0.55 mmHg at 5 minutes after the current injection. The number of previous IVIs has been identified as a risk factor for ocular hypertension.[22-26] Delayed elevated IOP was reported after repeated IVIs of bevacizumab/ranibizumab over a mean of 15 months, typically after 10 injections.[27] The odds ratio of sustained IOP elevation is 16.1-fold greater in eyes with ≥29 injections than in those with ≤12 injections.[28] In some instances, surgical intervention (eg, filtration surgery) is required for severe ocular hypertension.[29] Possible mechanisms for the development of severe ocular hypertension after IVIs include toxic or inflammatory effects of repeated IVIs on the trabecular meshwork, as well as mechanical alternation and blockage of outflow facilities by protein aggregates or contaminant particles (eg, silicone microdroplets in the packaging and injection vehicles).[30] Cumulative injury to the trabecular meshwork also contributes to acute exaggeration of elevated IOP shortly after IVI, in addition to the impact of a sudden increase in vitreous volume. Recurring substantial IOP spikes from previous injections alone can also perpetuate trabecular meshwork damage and result in further outflow obstruction and IOP elevation.[24]

The long-term effect of glaucoma development/progression secondary to repeated transient IOP spikes after IVI has not yet been elucidated. Withholding IVIs of anti-VEGF is not a desirable option given the potential comorbidities and visual loss that can arise from uncontrolled pre-existing retinal conditions. Therefore, prophylactic IOP-lowering

Table 4. Correlations of diagnosis with intraocular pressure (IOP) at 5, 15, and 30 minutes after intravitreal injection (IVI)

Diagnosis	Mean±SD IOP, mmHg		
	5 minutes after IVI	15 minutes after IVI	30 minutes after IVI
Age-related macular degeneration	32.6±10.5	21.6±5.3	18.2±4.3
Diabetic macular edema	33.3±12.0	21.6±6.3	18.3±3.8
Retinal venous occlusion	29.1±1.3	21.7±1.6	18.5±0.8
Others (punctate inner choroidopathy, juxtafoveal telangiectasia and myopic choroidal neovascularization)	32.5±10.6	21.6±5.4	18.3±3.8
p Value	0.92	1.00	0.99

Table 5. Multivariate regression analysis of potential predictors for intraocular pressure at 5 minutes after intravitreal injection

Potential predictor	b (standard error)	p Value
No. of previous intravitreal injections	0.55 (0.26)	0.04
Baseline intraocular pressure	0.79 (0.46)	0.09

measures are suggested to avoid IOP spikes and minimize trabecular damage, which may result in ocular hypertension or glaucomatous changes in the optic nerve. In a review that summarized the evidence concerning pharmacological and non-pharmacological methods for blunting acute IOP elevation, the topical application of IOP-lowering medications (eg, apraclonidine, timolol, dorzolamide-timolol, brimonidine-timolol, and brinzolamide-timolol) was considered mildly effective for reducing short-term IOP spikes.[31] However, IOP cut-offs and observation intervals vary among studies, making comparisons difficult, and the clinical benefits of these topical IOP-lowering eye drops remain uncertain. Although prophylactic oral acetazolamide can reduce IOP at 15-30 minutes after IVI, it is ineffective for minimizing IOP spikes immediately after injection (ie, when IOP elevation is greatest).[32,33] Non-pharmacological methods such as anterior chamber paracentesis and ocular decompression have beneficial effects in terms of preventing IOP spikes but carry important risks.[34] Complications such as endophthalmitis,[35] infective keratitis,[36] and anterior lens capsule laceration with localized cataract formation[37] have been reported after anterior chamber paracentesis. The benefits of these prophylactic measures in dampening the transient IOP spike after IVI remain unclear. Nonetheless, in patients susceptible to glaucomatous progression from substantial IOP spikes—especially those with advanced glaucoma and known transient visual loss related to severe acute IOP spikes and a history of repeated IVIs—these measures may be appropriate for minimizing the potential damage,[38] but they should only be implemented after a full explanation of the risks and benefits to each patient. In addition to the assessment of post-IVI visual acuity, some have suggested routine fundus examinations for signs of central retinal arterial occlusion immediately after IVI.[39] This may help to detect substantial IOP spikes in susceptible patients and allow timely administration of IOP-lowering treatment.

The limitations of this study included its small sample size and the involvement of few patients who had pre-existing glaucoma, which led to underpowered subgroup analyses and correlation studies. Furthermore, the diversity of patient diagnoses did not allow clear identification of correlations between individual diagnoses and IOP spike patterns. Nevertheless, this heterogeneous group of patients is representative of real-world patient populations and thus the results are applicable to clinical practice. Notably, a history of steroid response could be a predictor of substantial IOP spikes because of the potentially reduced trabecular outflow reserve. However, patients with steroid use within 1 month of IVI were excluded from the analysis; therefore, the potential effects of steroids on IOP spikes could not be assessed.

Conclusion

Transient but substantial IOP elevation shortly after IVI of anti-VEGF was positively correlated with the number of previous IVIs. This finding can aid in patient stratification concerning pharmacological and non-pharmacological prophylaxis for IOP spikes, especially among patients with pre-existing advanced glaucoma who are at risk of further optic nerve damage secondary to acute ocular hypertension. Ophthalmologists are advised to assess patient susceptibility to glaucomatous damage, as well as the risks and complications of various prophylactic measures for the prevention of IOP spikes.

Authors contributions

Concept or design: JT, AY
Acquisition of data: JT, IL
Analysis or interpretation of data: JT, SL
Drafting of the article: JT, NC
Critical revision for important intellectual content: all authors

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflict of interest

As an editor of the Journal, A Young was not involved in the peer review process for this article. Other authors have disclosed no conflicts of interest.

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Ethics approval

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