Original Article

Intraocular Pressure Elevation Following Intra-Vitreal Injection of Bevacizumab, Ranibizumab and Triamcinolone Acetonide

Rishabh Rathi[1], Smita Patel[2], Amisha Jain[3], Komal Jaiswal[4], Nitin Nema[5]
[1,3,4,5]*Sri Aurobindo Medical College & Postgraduate institute, Indro, Madhya Pradesh, India.* [2]*People's College of Medical Sciences & Research Center, Bhopal, Madhya Pradesh, India*

ABSTRACT

Purpose: To record intraocular pressure (IOP) at different time intervals after intravitreal injection (IVI) and to correlate the rise in IOP with refractive error and post-injection reflux.

Study Design: Retrospective review of records.

Place and Duration of Study: Sri Aurobindo Medical College & Postgraduate institute, Indore, Madhya Pradesh, India. September 2022 and December 2022.

Method: We included 126 untreated eyes of 120 patients. The indications of IVI were macular edema and age-related macular degeneration. IOP and refractive status were determined. Bevacizumab, Ranibizumab or Triamcinolone Acetonide was injected. Presence of vitreous reflux was noted at the injection site immediately after injection. IOP was measured at 10, 20, 30, and 45-minutes after injection. Descriptive statistics were calculated as mean and standard deviation for quantitative variables and frequency and percentage for qualitative variables. Repeated measure ANOVA was applied and p-value of <0.05 was considered significant.

Results: Transient IOP rise was observed in 95.24% cases whereas 4.76% patients showed sustained rise beyond 30 minutes, which returned to normal after use of topical beta-blocker. Hypermetropic eyes injected with Triamcinolone injection showed significant sustained rise of IOP ($p < 0.05$). Vitreous reflux was seen in 47 (37.3%) eyes that showed significantly lower mean IOP of 20.89 $\pm$ 5.159 mm Hg ($p < 0.05$) when compared to eyes with no vitreous reflux (IOP = 30.75 $\pm$ 7.384 mm Hg).

Conclusion: IVI results in transient rise of IOP which is lesser with vitreous reflux. Triamcinolone has a propensity to cause sustained rise of IOP especially in hypermetropic eyes that require intervention.

Key Words: Intraocular pressure, Bevacizumab, Ranibizumab, Triamcinolone.

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Correspondence: Nitin Nema
Sri Aurobindo Medical College & Postgraduate institute, Indro, Madhya Pradesh, India
Email: nemanitin@yahoo.com

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INTRODUCTION

Vascular endothelial growth factor (VEGF) is a glycoprotein required in many physiological processes and also in some pathogenic processes.[1] Physiologically VEGF is helpful in healing as well as it plays a key role in pathogenesis of ocular diseases like diabetic retinopathy, age-related macular degeneration, retinal vein occlusion, retinopathy of prematurity, leading to irreversible vision loss. It is, therefore, 'truly a double-edged sword'.

Angiogenesis is a biologic phenomenon of a series of cascades promoting growth factors to stimulate proliferation and vascular endothelial cell migration.[2] VEGF induces vasodilation and increases vascular

permeability. Moreover, it changes the blood flow dynamics and homeostasis. It is produced in retina by hypoxic stimulation of different retinal cells – vascular endothelium, retinal pigment epithelial cells, Müller cells, etc.[3]

Anti-VEGF agents have been in use for more than 18 years after being first introduced in 2004. Since their introduction, there is a lot of research around this area and today they are widely used in the management of various posterior segment pathologies. Currently, these drugs are the mainstay treatment option for neovascular and inflammatory retinal pathologies. The process of angiogenesis is heavily mediated by VEGF. Blocking the actions of VEGF has shown to be an effective way of suppressing neovascularization thereby substantially limiting the vision loss associated with proliferative retinopathies.[4] To make drug reach in the desired concentration at the site of pathology, anti-VEGF agents have to be injected intravitreally.

Raised IOP after anti-VEGF IVI has been reported as an ocular adverse event in MARINA and ANCHOR clinical trials as well as HAWK and HARRIER trials.[5,6] IOP rise after anti-VEGF injections may cause deleterious effect on retinal ganglion cells and retinal nerve fiber layer (RNFL). It is hypothesized that raised IOP occur due to direct pharmacologic effect of the drug leading to trabecular meshwork damage, particle obstruction, drug toxicity and drug induced trabeculitis.[7,8] The proposed mechanism for steroid-induced elevation of IOP has been linked to myocilin gene.[9]

Early detection of cases with raised IOP can help prevent or minimize ocular damage by timely intervention. This study aims to assess IOP rise at different time intervals post IVI to identify eyes that require intervention and evaluate correlation of IOP rise with refractive errors and vitreous reflux.

METHODS

This retrospective review of records included 126 treatment-naïve eyes of 120 patients who had received IVI of anti-VEGF drug or Triamcinolone Acetonide between September 2022 and December 2022. A written informed consent was taken from all the patients after explaining them about the treatment options and procedure. The study was approved by the Institutional Ethical Committee (IEC No. SAIMS/IEC/2021/16) and conducted in adherence to the tenets of Declaration of Helsinki. Sample was collected through convenience sampling method and data of 126 untreated eyes of 120 patients was included on the basis of inclusion and exclusion criteria set for the study.

The indications of IVI were macular edema either due to retinal vein occlusion (branch or central) or diabetic retinopathy and age-related macular degeneration. Baseline IOP was recorded using Goldmann applanation tonometer and a complete ocular examination was done including slit lamp biomicroscopy and dilated fundus evaluation. Refractive status of the study eye was determined and converted to spherical equivalent. Eyes with spherical equivalent values between ± 0.5D were labelled as emmetrope, those > + 0.5D as hypermetrope and those < -0.5D as myope.

The patients with irregular and scarred corneas, where recording of pressure by applanation tonometer was not possible, patients with history of glaucoma or previous intraocular surgery and those who had already received IVI were excluded from the study.

The patients were divided into three groups depending on the intravitreal drug that was injected – Bevacizumab, Ranibizumab and Triamcinolone Acetonide. Patients were further sub-grouped on the basis of refractive status of their eye. Presence of vitreous reflux was noted at the injection site immediately after withdrawal of needle.

Prior to injection topical proparacaine 0.5% was instilled and the eye was prepared and draped. Eyelids were retracted using a guarded eye speculum. The injection site was marked. Cornea was covered with 2% Hydroxypropyl Methyl Cellulose (HPMC) to prevent dryness. A Q-tip soaked in 0.5% proparacaine and 5% povidone-iodine solution was moderately pressed on the marked site for 30 seconds. After displacing the conjunctiva, the drug was injected in inferotemporal quadrant using a 30-gauge needle. 0.05 ml of the drug was injected in the vitreous cavity. Post-injection a cotton tip applicator was applied at the site of injection, the eye was thoroughly washed to remove all HPMC from the corneal surface and a drop of 5% povidone-iodine was instilled in the conjunctival cul-de-sac.

IOP was measured at 10, 20, 30, and 45-minutes interval after the injection. The difference between the baseline and post-injection IOP was recorded. IOP of > 21 mm Hg after 30 minutes of IVI was considered as

sustained rise of IOP. Patients with increased IOP beyond 30 minutes were started on topical beta blocker (0.5% Timolol Maleate).

Data was analysed by SPSS software trial version and was presented in frequency table. Descriptive statistics were calculated as mean and standard deviation (SD) for quantitative variables and frequency and percentage for qualitative variables. Repeated measure ANOVA was applied for more than one time follow-up comparison and post hoc test was used for multiple paired wise comparison in given tables. P-value of < 0.05 was considered as significant.

RESULTS

Total 126 treatment-naïve eyes of 120 patients were recruited. There were 82 (65.1%) males and 44 (34.9%) females. Age varied from 41 to 75 years with mean age of 59.2 ± 8.63 years. Distribution of refractive errors in the sample eyes is shown in Table 1.

Mean baseline IOP was 13.55 ± 2.61, 14.56 ± 2.17 and 13.61 ± 1.95 mm Hg in the eyes that received Bevacizumab, Triamcinolone and Ranibizumab respectively. Transient IOP rise was observed in 95.24% cases whereas 4.76% patients showed sustained rise beyond 30 minutes, which returned to normal after use of topical beta-blocker (Tables 2, 3 and 4).

Vitreous reflux was compared with IOP at 10 minutes post-injection and it was seen in 47 eyes (37.3%). Eyes with vitreous reflux showed significantly (p value < 0.05) lower IOP with mean IOP of 20.89 ± 5.159 mm Hg at 10 minutes post-injection as compared to the eyes with no vitreous reflux (62.7%) which had mean IOP of 30.75 ± 7.384 mm Hg.

DISCUSSION

Intraocular pressure rise after IVI occurs when the injected drug causes sudden increase in volume of closed vitreous cavity.[10] This volume effect alters the aqueous outflow resulting in immediate transient increase in IOP. However, the mechanism of chronic IOP elevation is more controversial.[11] Prolonged increase in IOP may lead to decreased juxta-papillary retinal and optic nerve head blood flow causing irreversible damage to RNFL.[12]

Table 1: *Distribution of refractive errors in eyes receiving IVI*

Refractive Errors	Bevacizumab	Ranibizumab	Triamcinolone	Total (%)
Emmetropes	9 (7.1%)	12 (9.5%)	28 (22.32%)	38.9%
Hypermetropes	28 (22.32%)	16 (12.6%)	10 (7.9%)	42.9%
Myopes	8 (6.3%)	12 (9.5%)	3 (2.3%)	18.2%
Total (%)	35.7%	31.7%	32.6%	100%

Table 2: *Intraocular pressure changes after injection of Bevacizumab at different time intervals.*

Refractive Status Post-Injection IOP	Emmetropes Mean ± SD (mmHg)	Hypermetropes Mean ± SD (mmHg)	Myopes Mean ± SD (mmHg)
At 10 minutes	24.67 ± 6.08	25.39 ± 9.22	25.5 ± 9.07
At 20 minutes	16.89 ± 2.80	19.25 ± 6.36	17.88 ± 7.95
At 30 minutes	13.67 ± 2.29	15.46 ± 5.15	15.0 ± 5.80
At 45 minutes	14.11 ± 2.14	13.93 ± 3.31	14.0 ± 2.56
P value*	< 0.05	< 0.05	< 0.05

*Repeated measure ANOVA test used for follow-up comparison

Table 3: *Intraocular pressure changes after injection of Ranibizumab at different time intervals.*

Refractive Status Post-Injection IOP	Emmetropes Mean ± SD (mmHg)	Hypermetropes Mean ± SD (mmHg)	Myopes Mean ± SD (mmHg)
At 10 minutes	27.25 ± 4.92	28.63 ± 6.05	26.17 ± 6.39
At 20 minutes	23.67 ± 5.71	23.50 ± 4.69	20.08 ± 5.56
At 30 minutes	20.25 ± 4.63	19.56 ± 3.59	19.56 ± 3.59
At 45 minutes	14.25 ± 2.70	14.88 ± 3.48	13.31 ± 1.82
P value*	< 0.05	< 0.05	< 0.05

*Repeated measure ANOVA test used for follow-up comparison

Table 4: *Intraocular pressure changes after injection of Triamcinolone at different time intervals.*

Refractive status Post-injection IOP	Emmetropes Mean ± SD (mmHg)	Hypermetropes Mean ± SD (mmHg)	Myopes Mean ± SD (mmHg)
At 10 minutes	27.64 ± 8.2	31.7 ± 12.87	28 ± 9.16
At 20 minutes	24.11 ± 4.66	22.8 ± 6.3	21 ± 4.35
At 30 minutes	20.29 ± 3.44	18.8 ± 5.84	17.6 ± 5.1
At 45 minutes	15.21 ± 3.13	17.8 ± 5	17.3 ± 3
P value*	< 0.05	< 0.05	> 0.05

*Repeated measure ANOVA test used for follow-up comparison

The aim of this study was to find the relationship between IOP elevation post IVI and refractive status of eye and vitreous reflux. On injecting equal volumes of drugs in eyes, the resulting IOP change depends upon the dimension of the eyeball. Short hypermetropic eyes experience a greater IOP rise than long myopic eyes.[10] It was seen in our study as well. Kotliar et al, recommended that one must remain watchful in treating hypermetropic eyes to reduce the likelihood of a significant acute elevation in IOP immediately following IVI.[13] However, other studies did not find association between axial length and immediate post-injection IOP rise.[14]

The quantitative estimation of reflux is difficult to assess because of clear nature of fluid and obscuration of injection site by the conjunctiva.[15] In our study we observed vitreous reflux in 47 out of 126 (37.3%) eyes that had a significantly lower post-injection mean IOP at 10 minutes than the eyes with no vitreous reflux. Small diameter needles that are used for IVI may disrupt the scleral integrity at the site of injection.[16] Fluid leakage from injection site takes some time to stop following the retraction of needle. More vitreous reflux has been reported with large bore needles resulting in a lower immediate mean IOP after injection. We used 30-gauge needle in all cases to inject drug. Muto et al, compared the effect of 30-gauge and 32-gauge needles on vitreous reflux and IOP following first time IVI of anti-VEGF drug.[17] The authors reported a higher immediate IOP in patients receiving IVI with 30-gauge needle. Further, they suggested that vitreous reflux could not be correlated with factors such as needle size, axial length or lens status.

We observed acute sharp rise of IOP after IVI irrespective of the drug used that returned to normal range (< 21 mm Hg) in 30 minutes in 95.24% (120 out of 126) eyes without intervention. A meta-analysis by de Vries et al, reported immediate spike of IOP after IVI which returned back to baseline at 1 week.[18] Others have also described transient IOP rise following IVI.[19]

A study reported that patients who received intravitreal Bevacizumab were prone to IOP elevation,[12] whereas Tseng et al, did not find association between Bevacizumab and IOP elevation.[19] In our study we found an early rise of IOP in eyes injected with Bevacizumab that rapidly returned below 21 mm Hg within 30 minutes post-injection in 44 out of 45 (97.77%) eyes without intervention.

The mechanism described for raised IOP after IVI of anti-VEGF agents has been attributed to the decreased activity of nitric oxide synthase enzyme that leads to reversal in ionic gradient causing retention of potassium and calcium into trabecular meshwork cells. It impairs trabecular meshwork contractility ultimately resulting in decreased outflow of aqueous.[7,8] Moreover, a systemic mechanism for raised IOP, as well as high blood pressure, following IVI of anti-VEGF agents is proposed which has been assigned to reduced levels of nitric oxide synthetase in blood. It was noticed that 39 out of 40 (97.5%) Ranibizumab injected eyes had IOP below 21 mm Hg within 30 minutes after the injection in our study. Goktas et al, reported transient increase in IOP after IVI of Ranibizumab and found no association between raised IOP and axial length of the eyeball.[20]

Triamcinolone Acetonide is available in suspension form that exits through the outflow channels after IVI.[17] Previous studies showed that water soluble component of Triamcinolone gets rapidly eliminated from the eye within first 2 months post IVI followed by prolonged slow exit of crystalline form of the drug.[21] One of the major side effects of IVI of Triamcinolone Acetonide is elevation of IOP.[23,24] The proposed mechanism for IOP elevation post Triamcinolone injection is related to myocilin gene.[10] In our study, 37 out of 41 (90.24%) eyes that received intravitreal Triamcinolone Acetonide had IOP

< 21 mm Hg 30 minutes post-injection. Sustained rise of IOP was seen in four eyes out of which three were hypermetropic and one emmetropic.

Various studies have found long-term elevated IOP following IVI of Bevacizumab and Ranibizumab.[18,24] Chronic elevation of IOP can be related to altering levels of modulators like nitric oxide. It has been proposed that the toxic effect of drug induces inflammatory damage to the angle of anterior chamber leading to rise of IOP.[25] In spite of excluding patients with raised baseline IOP and those who had received prior IVI,6 out of 126 (4.76%) eyes developed sustained rise of IOP (> 21 mm Hg) beyond 30 minutes of injection in our study. Moreover, we found that hypermetropic eyes injected with Triamcinolone injection had a high susceptibility for prolonged elevation of IOP.

There are some limitations of this study. First, it is a retrospective observational study wherein data was retrieved from the case records. Second, the small sample size with unequal distribution in groups, particularly in myopic eyes in Triamcinolone group, might have caused bias in results. We recommend a prospective randomized study with large sample size to validate the results.

CONCLUSION

IVIs of anti-VEGF drugs are safe but may be associated with raised IOP. Immediate and transient rise of IOP post IVI is common that shows a rapid fall in majority of patients within 30 minutes post-injection.

Conflict of Interest: Authors declared no conflict of interest.

Ethical Approval

The study was approved by the Institutional review board/Ethical review board **(SAIMS/IEC/2021/16).**

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Author's Designation and Contribution

Rishabh Rathi; Senior Resident: *Concepts, Design, Literature Search, Statistical Analysis, Manuscript Editing, Manuscript Review.*

Smita Patel; Senior Resident: *Concepts, Design, Literature Search, Data Acquisition, Data Analysis, Manuscript Preparation, Manuscript Review.*

Amisha Jain; Associate Professor: *Literature Search, Data Analysis, Statistical Analysis, Manuscript Review.*

Komal Jaiswal; Resident: *Design, Data Acquisition, Manuscript Preparation, Manuscript Editing, Manuscript Review.*

Nitin Nema; Professor: *Concepts, Design, Literature Search, Data Acquisition, Data Analysis, Statistical Analysis, Manuscript Preparation, Manuscript Editing, Manuscript Review.*