Mean Changes in Intraocular Pressure after Intravitreal Injection of Bevacizumab in Exudative Age Related Deneration and Proliferative Diabetic Retinopathy.

Rebecca, Shafi Muhammad Jatoi, Fahad Feroz Shaikh, Muhammad Shahid*

Isra University Hospital, Hyderabad Pakistan, *Armed Forces Institute of Ophthalmology/National University of Medical Sciences (NUMS) Rawalpindi Pakistan

ABSTRACT

Objective: To monitor the effect of intravit real injection of Bevacizumab on intraocular pressure to know whether intraocular pressure-lowering medication or paracentesis is required prophylactically or after that.
Study Design: Case series.
Place and Duration of Study: Department of Ophthalmology, Isra University Hospital, Hyderabad, from May to Oct 2019.
Methodology: A total 90 eyes of patients with proliferative diabetic retinopathy and exudative age-related macular degeneration, received intravitreal injection of Bevacizumab. Intraocular pressure was recorded with a Goldman applantaion tonometer at baseline, and then after a procedure at 5 minutes, 30 minutes, 1 hour and 1 week. The patients' age, gender, disease, intraocular pressure, history of glaucoma, previous surgery, phakic status, topical and systemic medications were recorded.
Results: The mean baseline intraocular pressure was 13.54 ± 2.1mmHg in proliferative diabetic retinopathy and 12.76 ± 1.8mmHg in exudative age-related macular degeneration (*p*-value 0.091). The mean intraocular pressure elevation following intravitreal Bevacizumab at 5 minutes was 32.89 ± 6.3mmHg and 32.18 ± 5.7mmHg (*p*-value 0.592), at 30 minutes was 16.71 ± 2.6mmHg and 15.53 ± 2.4mmHg (*p*-value 0.036), at one hour was 14.20 ± 2.0mmHg and 13.47 ± 1.9mmHg (*p*-value 0.098) and at one week 13.82 ± 1.7mmHg and 13.06 ± 1.7mmHg (*p*-value 0.051) in proliferative diabetic retinopathy and exudative age-related macular degeneration respectively. There was no significant difference between the two diseases.
Conclusion: There is an abrupt and transient rise in the intraocular pressure following intravitreal injection of Bevacizumab, but it did not remain elevated for longer duration; hence there was no need for intraocular pressure lowering medication and paracentesis.

Keywords: Age-related macular degeneration, Bevacizumab, Intraocular pressure, Intravitreal injection, Proliferative diabetic retinopathy.

How to Cite This Article: *Rebecca, Jatoi SM, Shaikh FF, Shahid M. MEAN Changes in Intraocular Pressure After Intravitreal Injection of Bevacizumab in Exudative Age Related Deneration and Proliferative Diabetic Retinopathy. Pak Armed Forces Med J 2022; 72(2): 564-567.*
DOI: https://doi.org/10.51253/pafmj.v72i2.5727

INTRODUCTION

The standard gold treatment for patients with retinal ischemic and vascular diseases like patients with diabetic retinopathy, patients with exudative age-related macular degeneration, hypertensive retinopathy, and central retinal vein and artery occlusions are various forms of thermal lasers like argon laser, diode laser and photodynamic therapy.[1] The photocoagulation laser causes retinal damage, pain, and loss of peripheral or central vision.[2] So, intravitreal anti-Vascular endothelial growth factor (anti-VEGF) is used as an alternative or as an adjunct in managing retinal ischemic diseases in which vascular endothelial growth factor(VEGF) is released to cause neovascularization and increased vascular permeability.[3] There are many types of anti-VEGFs available like Aflibercept, Ranibizumab and Bevacizumab; the former two are expensive while Bevacizumab is cost effective.[4,5] Bevacizumab is a recombinant humanised monoclonal immuno-globulin G1 antibody that inhibits vascular endothelial growth factor (VEGF).[6] The delivery of intravitreal injection of Bevacizumab in the vitreous cavity causes intraocular pressure and decreases the retinal and optic nerve blood supply.

It is reported in many studies that the reason for sustained elevation in intraocular pressure (IOP) after intravitreal injection of bevacizumab (IVB) is due to the quick delivery of the intravitreal drug, injury to the uveoscleral, trabecular meshwork, and schlemm canal.[6-8] Eyes having intravitreal anti-VEGF are at greater risk of damage to the ganglion cell fibres, which have already optic nerve disease and glaucoma, and it has been found in many studies that phakic eyes have more post-injection elevation in IOP than pseudo-phakic eyes.[9,10]

Correspondence: Dr Rebecca, House No. 100, Muslim Co-Operative Housing Society Hyderabad, Pakistan
Received: 23 Nov 2020; revision received: 26 Jan 2021; accepted: 27 Jan 2021

The short-term or long-term elevation in IOP can affect perfusion pressure of the optic nerve, which can cause unreparable visual loss.[10] Hence, it is essential to evaluate the IOP following intravitreal Bevacizumab to know the duration of IOP elevation and whether paracentesis is needed.

METHODOLOGY

A case series of 90 eyes was carried out at the Department of Ophthalmology, Isra University Hospital, Hyderabad, after approval from Ethical Review Committee (IUH/DEAN(CS)/206/17) from May 2019 to Oct 2019.

Inclusion criteria: Patients with proliferative diabetic retinopathy and age-related macular degeneration were included.

Exclusion Criteria*:* Patients with recent prior history of intravitreal injection, ocular surgery, glaucoma, and anti-glaucoma medications were excluded.

Written informed consent was taken from the patients. The procedure, administration route, and possible complications like endophthalmitis, raised IOP, retinal detachment, and ocular inflammation were addressed to the patient. A written proforma was filled, including the bio-data, visual acuity, disease and IOP.

A detailed slit lamp examination was done, including IOP by Goldman applanation tonometer (GAT), Fundoscopy with 90D volk lens. IOP was recorded before the procedure and post-procedure at 5 min, 30 min 1hour, and after one week.

The standard protocol was followed by the surgeon, prior to injection eye was washed with providing iodine, 0.5% proparacaine eye drops were instilled, intravitreal Bevacizumab injection (1.25mg in 0.05ml) was given at 3.5 to 4 mm from the limbus according to the pseudophakic and phakic status of the patient.

Statistical Package for Social Sciences (SPSS) version 20.0 was used for the data analysis. Quantitative variables were summarized as mean ± SD and qualitative variables were summarized as frequency and percentages. The baseline values and individual values of PDR and ARMD at each point of time were analysed using the ANOVA test, and the *p*-value of ≤0.05 was considered significant. The main outcome measure was the proportion of patient post-injection of IOP taken at 5 min, 30 min, 1 hour, and 1 week.

RESULTS

We included 90 eyes (n= 90) of the patients, out of which 47 were males and 43 were females. Eyes with PDR (n=56) and exudative ARMD (n=34) were compared. Mean age in PDR was found to be 56.71 ± 4.83 years and in exudative ARMD was 66.71 ± 5.99 years (*p*-value <0.001), as shown in Table-I.

Table-I: Statistical Analysis of demographic characteristics of the study sample (n=90).

Variables	Proliferative Diabetic Retinopathy (n=56) %	Age Related Macular Degeneration (n=34) %
Gender		
Male	27 (48.2%)	20 (58.8%)
Female	29 (51.8%)	14 (41.2%)
Age in Groups (Years)		
45 to 55	22 (39.3%)d	1 (2.9%)
56 to 65	32 (57.1%)	11 (32.4%)
66 to 70	2 (3.6%)	22 (64.7%)
Age in Years		
Mean ± SD	56.71 ± 4.83	66.71 ± 5.99
(Range)	(48 to 67 Years)	(48 to 75 Years)

The mean baseline IOP before IVB was found to be 13.54 ± 2.1 mmHg in the PDR group and 12.76 ± 1.8mmHg in exudative ARMD (*p*-value 0.091). The mean IOP elevation following IVB at 5 min was 32.89 ± 6.3 mmHg in the PDR group, and exudative ARMD

Table-II: Statistical analysis of retinal disease with different slots of times including baseline using intravitreal injection of bevacizumab (n=90).

Retinal Disease	Anova Results				
	Baseline	Intraocular Pressure at 5 Min	Intraocular Pressure at 30 Min	Intraocular Pressure at 1 Hour	Intraocular Pressure at 1 Week
Proliferative Diabetic Retinopathy (n=56)	13.54 ± 2.1	32.89 ± 6.3	16.71 ± 2.6	14.20 ± 2.0	13.82 ± 1.7
Age Related Macular Degeneration (n=34)	12.76 ± 1.8	32.18 ± 5.7	15.53 ± 2.4	13.47 ± 1.9	13.06 ± 1.7
Mean Intraocular Pressure	13.24	32.62	16.26	13.92	13.53
p-value	0.091	0.592	0.036*	0.098	0.051*

was 32.18 ± 5.7mmHg (*p*-value 0.592) (Figure).

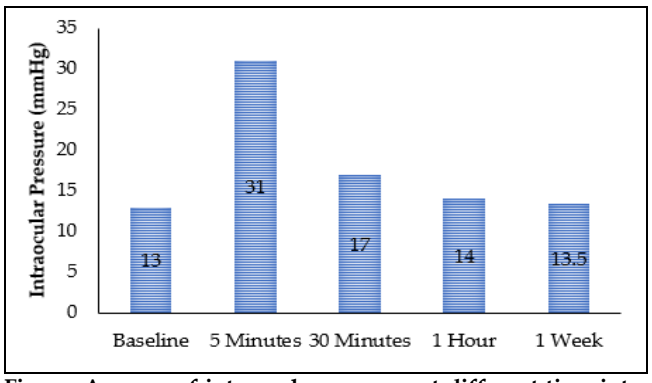

Figure: Average of intraocular pressure at different time intervals following Intravitreal Bevacizumab.

No significant difference was seen between the two diseases. The mean IOP at 30 min in PDR and exudative ARMD was 16.71 ± 2.6 mmHg and 15.53 ± 2.4 mmHg (*p*-value 0.036) respectively, while at one hour in PDR and exudative ARMD 14.20 ± 2.0 mmHg and 13.47 ± 1.9 mmHg *(p*-value 0.098) respectively and at one week 13.82 ± 1.7 mmHg and 13.06 ± 1.7 mmHg (*p*-value 0.051) in PDR and exudative ARMD. Table-II indicated there was no significant difference between the two diseases.

DISCUSSION

Bevacizumab has been used for the treatment of many retinal vascular diseases. One of the complications is raised intraocular pressure, but its duration of elevation is important.[11,12]

Our study found that the dose of intravitreal injection of Bevacizumab has a shorter-term elevation of IOP. There is a rise in IOP at 5min after the procedure, which returns to <21mmhg at 30 min to 1 hour. Hence, the intravitreal bevacizumab (0.05ml) dose is safe enough to use.

Moraru *et al*, determined that one of the risks factors for sustained ocular hypertension is the smaller interval between injections that is <8 weeks and greater than 6 number of injections.[13] Hoang *et al*, reported that eyes receiving >29 injections are at higher risk of a rise in IOP of 5 mmHg on two consecutive visits than eyes receiving,[12] or fewer injections.[14] But this study did not compare the IOP on eyes with multiple injections. A previous study, reported that eyes recei-ving volume >0.05ml in <01 sec 5.56 times are at more risk of sustained elevation of IOP 14 while it was not found in our study.

In this study, for 90 studied patients, the mean IOP values at baseline, 5 mins, 30 mins, 1 hour and one week after injection were 13.2 mmHg (95% CI 12.78–13.67), 30.70 mmHg (95% CI 29.27-32.14), 16.26 mmHg (95% CI 15.72–16.81), 13.92 mmHg (95% CI 13.50–14.34) and 23.53 mmHg (95% CI 13.16–13.91), respectively.

Many researchers, showed a transient rise of 30mmhg IOP change from baseline following IVB. In several studies, IOP decreased to <25 mmhg at 30 to 60min without anti-glaucoma medication.[15,16] We also found in our study that IOP normalises by 30min after IVB. Posture has its role in IOP fluctuation. It rises in the supine position and decreases in the sitting position.[17,18] In this study the authors did not evaluate the posture effect on IOP. Trehan *et al*, and Karakurt et al, found short term rise in the IOP, which did not show any influence on retinal blood flow and returned to baseline within 30 min to 1 hour following Intravitreal Anti-VEGF.[19,20]

We enrolled 90 eyes of the patients in our study with baseline IOP 13.54 ± 2.1, which elevated to 32.89 ± 6.3 at 5 minutes following IVB and returned to baseline between 30 min to 1 hour. The significant determinants of IOP alterations following IVB are the method of application, amount of reflux, volume of fluid injected, axial length of the eyeball, posterior vitreous detachment, size of the needle, vitreous liquefaction and scleral thickness.[21]

Some authors like Lorenz *et al*, reported the direct relationship between the thickness of the needle and sub-conjunctival reflux grade in their study. Hence the more sub-conjunctival reflux limits chances of paracentesis needed for IOP reduction. Another signi-ficant influence on sub-conjunctival reflux is the incision technique, higher with the non-beveled approach and lesser with the bevelled approach seen in their study.[22-24] This study did not monitor the subcon-junctival reflux and influence of needle thickness. Some authors also studied the relation between the frequency of anti-VEGF injection with thinning of retinal nerve fibre layer but found no significant difference.[25] This study did not determine the Retinal nerve fibre layer changes.

LIMITATIONS OF STUDY

In this study, we could not evaluate the scleral thickness and axial length of the eyeball. We obtained our results after the first injection of Bevacizumab, repeated injections should also be evaluated.

CONCLUSION

There is an abrupt and transient rise in the intraocular pressure following intravitreal injection of Bevacizumab, but

it did not remain elevated for longer duration; hence there was no need for intraocular pressure lowering medication and paracentesis.

Conflict Of Interst: None.

Authors' Contribution

R: Conceived, designed and statistical analysis & editing of manuscript, is responsible for integrity of research, FFS: Data collection and manuscript writing, SMJ: Review and final approval of manuscript. MS: Statisical analysis.

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