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Association Of Conjunctival Vitreous Reflux With Intraocular Pressure Spikes After Intravitreal Bevacizumab Injection

Kanwal Zareen Abbasi[1], Ameera Jamil[2], Muhammad Rizwan Khan[3], Bilal Humayun Mirza[4], Salman Tariq[5], Muhammad Sajid Rafiq Abbasi[6]

Abstract

Objective: To evaluate the effect of conjunctival vitreous reflux on intraocular pressure immediately after intravitreal bevacizumab injection.

Methods: A prospective interventional study was done at Benazir Bhutto Hospital, for 6 months from 13-01-2021 to 12-07-2021.Patients were selected through a non-probability consecutive sampling technique. A total of 88 eyes undergoing intravitreal bevacizumab were included in the study. IOP was checked before injection, immediately after injection, at 30 minutes and 60 minutes. The presence or absence of conjunctival reflux was noted. Data was analyzed to see the association of post-injection IOP and conjunctival reflux.

Results: Those having conjunctival reflux positive had mean Intraocular pressure before intravitreal injection 13.14+2.569, the p-value was 0.0001. Immediately after injection at 0 minutes it was 27.95+3.988, and the p value was 0.0001. At 30 minutes, it was reduced to 21.58+2.814, the p-value was 0.0001, and at 60 minutes, the mean intraocular pressure was 17.26+1.853, and the p-value was 0.001. Those having conjunctival reflux negative had mean Intraocular pressure before intravitreal injection 13.44+2.981, p-value 0.0001. Immediately after injection at 0 minutes it was 33.69+5.608, and the p-value was 0.0001. At 30 minutes, it was reduced to 24.51+5.337, the p-value was 0.0001, and at 60 minutes, the mean intraocular pressure was 18.98+2.973, and the p-value was 0.001.

Conclusion: Patients with vitreous reflux positive had less IOP elevation as compared to those with vitreous reflux negative.

Keywords: Intravitreal bevacizumab injection, Intraocular pressure, conjunctival reflux.

[1] Associate Professor Ophthalmology, HBS Medical & Dental College, Islamabad; [2] Post Graduate Trainee Ophthalmology, Rawalpindi Medical University; [3] Assistant Professor Ophthalmology, Shifa Tameer-E-Milat University, Islamabad; [4] Assistant Professor Ophthalmology, Shifa Tameer-e-Milat, University, Islamabad; [5] Senior Registrar, Ophthalmology, Rawalpindi Medical University; [6] Associate Professor, Nephrology, PIMS, Islamabad.

Correspondence: Dr. Kanwal Zareen Abbasi, Associate Professor Ophthalmology, HBS Medical & Dental College, Islamabad. **Email:** dr_maninoor_abbasi@yahoo.com

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1. Introduction

Bevacizumab (Avastin, Genentech) is an antivascular endothelial growth factor. It is a humanized monoclonal antibody which was approved for colorectal cancer and is used off-labeled as it is cost-effective and has comparative usefulness to other anti-VEGFs. [1,2] As this agent is used widely, it also has multiple side effects like subconjunctival haemorrhage, crystalline lens injury, an acute rise in intraocular pressure and endophthalmitis.[3]

Intraocular pressure rise after intravitreal injection can have a damaging effect on the optic nerve, mainly in diagnosed cases of glaucoma.[4]

After intravitreal injection, an immediate rise in intraocular pressure occurs which is usually more than 10 mmHg at 10 minutes and typically returns to baseline within an hour.[5]

Patients who receive repeated intravitreal antiVEGF injections can develop a sustained rise in IOP.[6] Multiple studies have been conducted reporting about IOP rise after intravitreal anti-VEGF agents.[7,8,9] Various researchers have worked on knowing the different risk factors which are responsible for the potential rise in IOP. These risk factors are multiple injections, absence of vitreous reflux, tunnelled injection technique, smaller needles and already diagnosed cases of glaucoma.[10] The idea is that a transient rise in IOP occurs because the vitreous volume is increased after bevacizumab is injected intravitreally and it is usually when 50 microliters are injected into the vitreous cavity.[11]

Reflux of a small amount of fluid is a common event observed after intravitreal injections. It is an important factor affecting post-injection transient IOP rise. This vitreous reflux significantly decreases the IOP spikes and the same does not happen in eyes with no reflux.[12] We aimed this study to see the rise in IOP after intravitreal injections and the association of conjunctival vitreous reflux with this IOP change.

2. Materials & Methods

A prospective interventional study was done at Benazir Bhutto Hospital, for 6 months from 13-01-2021 to 12-07-2021.

Non-probability consecutive sampling was used on 80 eyes of 80 patients (calculated through the WHO formula). Both females and males of the age group 10 to 80 years were included in the study. Patients having any indication for intravitreal bevacizumab were included in the study. We excluded patients who were pseudophakic for less than three months, patients who received intravitreal steroids during the last 3 months, those who were injected with intravitreal antibiotics during the last month, patients who were already diagnosed as having glaucoma and patients who didn't give informed consent.

The study was started after getting approval from the ethical committee of Rawalpindi Medical University. After informed written consent from the patients, a detailed history and ophthalmological examination were done for intravitreal injection and those fulfilling the criteria were included in the study.

Before the procedure, intraocular pressure was measured through a hand-held Perkins tonometer under topical anaesthesia. After instilling topical anaesthesia, 5% povidone-iodine was instilled in the conjunctival sac and around the eyelid. After scrubbing and draping and under proper aseptic measures, an eye speculum was applied. The eye was marked with the calliper 3.5mm from the limbus in pseudophakic and 4mm from the limbus in the phakic eye in the inferotemporal region. Injection bevacizumab with a dose of 1.25mg in 0.05ml was injected through pars-plana into the vitreous cavity, Any conjunctival reflux (vitreous reflex) was noted whether it was present or not. In the end, 0.5% moxifloxacin was instilled in the conjunctival sac. Immediately after the procedure, intraocular pressure was measured by a hand-held tonometer. It was repeated at 30 min and 60 min.

Statistical analysis was performed with SPSS version 17. Categorical variables such as gender and conjunctival reflux were expressed as frequency and percentage of patients and continuous variables such as age and intra-ocular pressure were expressed as mean +SD. One sample t-test was used to make a comparison between mean intraocular pressure, a 'p' value less than 0.05 was considered as significant. Effect modifiers like age, gender, and vitreous reflux were controlled by stratification. Post-stratification independent sample t-test was applied. P value <0.05 was significant.

3. Results

88 eyes of 88 patients were included in the study. These were the patients who were candidates for intravitreal bevacizumab injections according to inclusion criteria. The mean age was 58.30±8620.

Gender distribution shows that 56.8%(n=50) were females while 43.2%(n=38) were males. Figure 1

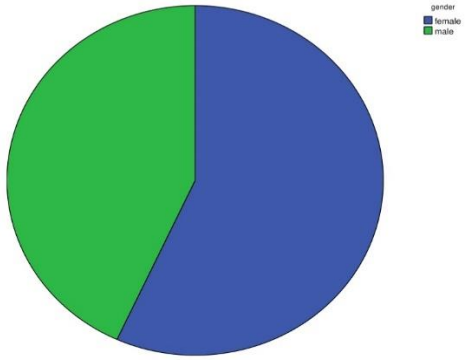


Figure 1: Gender Distribution

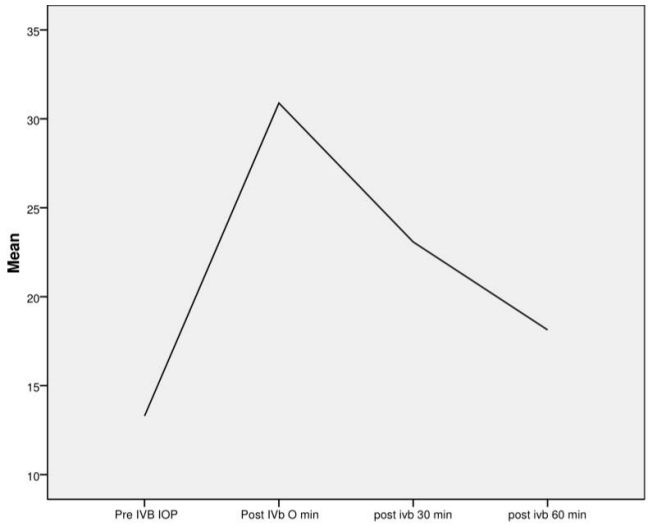
Conjunctival reflux was positive in 48.9%(n=43) and negative in 51.1%(n=45). Table 1

Table 1: Frequency of conjunctival reflux

Conjunctival reflux	Frequency	Percent	Valid percent	Cumulative percent
Yes	43	48.9	48.9	48.9
No	45	51.1	51.1	100.0

The mean Intraocular pressure before intravitreal injection was 13.30±2.776 with p p-value of 0.0001. Immediately after injection at 0 minutes it was 30.89±5.648, and the p-value was 0.0001. At 30 minutes, it was reduced to 23.08±4.516, the p-value was 0.0001, and at 60 minutes, the mean intraocular pressure was 18.14±2.623, and the p-value was 0.001. (figure 2)

Mean change in IOP after intravitreal Injection, Figure 2. Effect modifier, the conjunctival vitreous reflux effect was controlled by stratification. Post-stratification independent sample t-test was applied. P value <0.05 was significant.



Our results showed that those having conjunctival reflux positive had mean Intraocular pressure before intravitreal injection 13.14+2.569, the p-value was 0.0001. Immediately after injection at 0 minutes it was 27.95+3.988, and the p value was 0.0001. At 30 minutes, it was reduced to 21.58+2.814, the p-value was 0.0001, and at 60 minutes, the mean intraocular pressure was 17.26+1.853, and the p-value was 0.001. Our results showed that those having conjunctival reflux negative had mean Intraocular pressure before intravitreal injection 13.44+2.981, p-value 0.0001. Immediately after injection at 0 minutes it was 33.69+5.608, and the p-value was 0.0001. At 30 minutes, it was reduced to 24.51+5.337, the p-value was 0.0001, and at 60 minutes, the mean intraocular pressure was 18.98+2.973, and the p-value was 0.001. Table 2.

Table 2: Effect of conjunctival reflux on post-injection IOP

Conjunctival reflux	Pre IVB IOP	Post IVB 0 MIN	Post IVB 30 min	Post IVB 60 min
Yes mean	13.14	27.95	21.58	17.26
N	43	43	43	43
Std deviation	2.589	3.988	2.814	1.853
No mean	13.44	33.69	24.51	18.96
N	45	45	45	45
Std deviation	2.981	5.608	5.337	2.973
Total mean	13.30	30.89	23.08	18.14
N	88	88	88	88
Std devation	2.776	5.648	4.516	2.623

4. Discussion

Transient IOP elevation after intravitreal bevacizumab is a serious issue as immediate transient elevation in IOP can be a threat to the optic nerve. There are multiple factors which affect this IOP rise and one of these is an important factor, the vitreous reflux. The relation between IOP rise and vitreous reflux is vice versa. It was noted that there were increased intraocular pressure levels when vitreous reflux was positive as compared to those eyes where reflux was negative secondly in reflux-positive eyes, IOP rise was less where the amount of reflux was more. Another point in these studies was that the amount of reflux decreases as the total number of injections increases.[10,12,13]

Pang CE, et al noted in their study that as there was more vitreous reflux (53%) in eyes who received injections through 30 gauge as compared to 32 gauge needle (13%), so eyes with vitreous reflux positive and comparatively more vitreous reflux had less post-injection IOP rise. In this study, 34 eyes were injected with a 30-gauge needle and among these 34 eyes, 16 eyes had no vitreous reflux and a mean IOP rise of 29.6± 2.10 mmHg which was significantly higher than the rest of the 18 eyes who had vitreous reflux and mean IOP rise of 4.5± 1.74mmHg, P<0.0001. Similarly, among 31 eyes injected with 32-gauge, 27 eyes had no vitreous reflux and a mean IOP rise of 29.5 ± 1.99 mmHg, which was significantly higher than the 4 eyes who had vitreous reflux and mean IOP rise of 9.5 ± 4.05 mmHg, P < 0.001.[14]

Lemos-Reis, et al. observed in their study that 21.3% had subconjunctival reflux and had low IOP elevation (P<0.001) as compared to those who had no vitreous reflux. They said that intravitreal bevacizumab injection causes IOP elevation and more IOP rise occurs if there is no subconjunctival reflux.[15]

Shoeibi N, et al. conducted a study and also noted that there was a statistically significant negative correlation between conjunctival vitreous reflux and IOP elevation. Secondly, they checked the effect of IOP-decreasing drugs on after-injection IOP rise and found no pressure-lowering effect of these prophylactic medications.[16]

Knecht PB, et al used two techniques for intravitreal injection. One, with the straight entry of the needle and the second with the tunnelled entry of the needle. In this study, it was noted that the amount of vitreous reflux was greater with the straight injection technique so IOP elevation after injection was less in these patients and it was vice versa in the tunnelled injection technique. IOP elevation was 35.97 ± 8.13 in the tunnelled technique and 30.19 ± 12.14 in the straight technique. The difference in IOP is significant after 1 minute post-injection, otherwise till the end of 5 minutes it becomes insignificant.[17]

Rathi R, et al, showed the same results as ours as far as vitreous reflux is concerned with IOP change, that after intravitreal injection, there is acute transient elevation of IOP which is comparatively less in eyes with

conjunctival vitreous reflux. According to this study, 47 (37.3%) eyes had conjunctival reflux and showed less mean IOP of 20.89 ± 5.159 mm Hg ($p < 0.05$) in comparison with eyes who had no vitreous reflux with mean post-injection IOP of 30.75 ± 7.384 mm Hg.[18]

Contrary to most of the studies which were favouring our results, the study of Alshahrani ST Showed that change in IOP is not that different in eyes with reflux and eyes without reflux.[19] In this study, 56 eyes had vitreous reflux positive, and IOPs before and after injection were 13.6±2.7 mmHg and 16.4±5.0 mmHg, respectively. 67 eyes had vitreous reflux negative with IOPs before and after injection 13.6±2.9 mmHg and 17.0±5.2 mmHg, respectively. So, the IOP change after injection in both groups was almost the same.[19] Dogatovic N, et al noted that a significant rise in IOP occurs after intravitreal injection. After 20 minutes, the IOP values return to below 25 mmHg spontaneously. This showed that vitreous reflux is an important factor as far as short-term elevation occurs but not that important from a long-term perspective.[20]

Another study against our observation is the study of Ansari EA, et al. In this study, it was observed that the impact of conjunctival reflux bleb formation on immediate post-injection intraocular pressure was statistically insignificant ($p=0.3$).[21] Zhou NL, et al.preferred tunnelled incision saying that although it is not effective for preventing the immediate post-injection rise as there is less or no vitreous reflux, favouring our results, this technique is very much helpful to decrease the incidence of post-injection endophthalmitis.[22] Similar observation was shared by Irsan I et al and Muto T, et al that with a small gauge needle, high IOP elevation occurs and the reason is again the same that with a small gauge needle, less or no vitreous reflux occurs.[23,24]

If seven or more injections of intravitreal bevacizumab injection are given in a year, there will be a sustained rise in intraocular pressure and in that case, it will not be significantly associated with the presence or absence of conjunctival vitreous reflux.[25] Another important information associated with repeated intravitreal injections has been observed by Uyer E, et al. They said that these repeated intravitreal injections gradually decrease the amount of conjunctival reflux and so increase the frequency of immediate short-term IOP spikes after injections.[26]

Till now, it is evident that intravitreal injections cause an instant rise in intraocular pressure which is associated with or without vitreous reflux and ultimately IOP returns to baseline within an hour but in those cases where pre-injection IOP is >15 mmHg, IOP spikes are usually high and should be managed with prophylactic IOP lowering agents.[27]

Although we did a comparison of our study with different studies we can say that it is not the exact comparison because of the different anti-VEGF agents used the different injecting techniques like straight or tunnelled the different types of tonometers used and most importantly, the different periods when IOPs were measured after injection.

5. Conclusion

After doing the above-mentioned analysis of all the studies including ours, it is quite evident that conjunctival reflux, after intravitreal injection, if present, would be an indicator of less rise in immediate post-injection IOP and in that case, we can hope that optic nerve would not be at that much risk as in patients with no reflux. To make sure the occurrence of reflux, we can use large gauge needles and we can inject the drug straight instead of tunnelled technique under full aseptic measures. Studies, using different needle sizes and different techniques of injecting intravitreally, can be conducted in our setup too.

CONFLICTS OF INTEREST- None

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Contributions:

K.Z.A, A.J, M.R.K, B.H.M, S.T, M.S.R.A - Conception of study
K.Z.A, A.J, M.R.K, B.H.M, S.T, M.S.R.A - Experimentation/Study Conduction
K.Z.A, A.J, M.R.K, B.H.M, S.T, M.S.R.A - Analysis/Interpretation/Discussion
K.Z.A, A.J, M.R.K, B.H.M, S.T, M.S.R.A - Manuscript Writing
K.Z.A, A.J, M.R.K, B.H.M, S.T, M.S.R.A - Critical Review
K.Z.A, A.J, M.R.K, B.H.M, S.T, M.S.R.A - Facilitation and Material analysis

All authors approved the final version to be published & agreed to be accountable for all aspects of the work.

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