RESEARCH ARTICLE

# Intra-ocular pressure changes after intravitreal injection of bevacizumab

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## Abstract

**Objectives:** To evaluate the short-term and sustained intraocular pressure changes after intravitreal bevacizumab in patients with diabetic retinopathy.

**Method:** The quasi-experimental study was conducted at the District Headquarter Teaching Hospital, Gujranwala, Pakistan, from January to December 2020, and comprised diabetic patients of either gender aged 18-60 years with indication for intravitreal bevacizumab. Intraocular pressure was measured at 5, 10 and 30 minutes for short-term elevation, and the patients were followed up weekly for one month to record any sustained elevation in intraocular pressure. Data was analysed using SPSS 25.

**Results:** Of the 42 patients, 20(47.61%) were male and 22(52.38%) were female. The overall mean age was 52.4±5.7 years. Intraocular pressure increased significantly in the short term post-injection ($p<0.001$), while the difference was not significant in the weekly check-ups ($p=0.264$).

**Conclusion:** There was short-term rise in intraocular pressure after intravitreal bevacizumab, but no sustained elevation was noted over the following month.

**Keywords:** Vascular endothelial growth factor, Bevacizumab, Intraocular pressure, Diabetic retinopathy.

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## Introduction

Retinal hypoxia caused by any clinical condition results in the formation and release of vascular endothelial growth factor (VEGF) which is the cause of abnormal neo-vessels at aberrant ocular sites. These neo-vessels can in turn lead to a range of ophthalmic complications. Intravitreal injections of anti-VEGFs are used to prevent the formation of these neo-vessels. Three major classes of anti-VEGFs are used routinely; aflibercept (Eylea®), ranibizumab (Patizra®/Lucentis®) and bevacizumab (Avastin®). Intravitreal bevacizumab injection is more popular than others mainly because of its cost-effectiveness.[1]

Uncommon ocular adverse events reported with the use of intravitreal injection of bevacizumab include lens damage, intraocular inflammation, retinal tears, vitreous haemorrhage, endophthalmitis,[1] fluctuation in intraocular pressure (IOP) and ocular perfusion pressure.[2] IOP fluctuation can be of two types. The first is an acute or short-term elevation of IOP[2] (after a few minutes), and the second is sustained IOP elevation (after few months), first reported in a case series of four patients.[3]

Regarding short-term elevation of IOP, the chief reason described is the addition of volume into the small vitreous cavity.[2] The major factor that can influence the short-term IOP is the presence of vitreous reflux[4] from the injection site. Other less significant factors include age, gender, lens status, number of previous injections, and posterior vitreous detachment.[4] Regarding the sustained elevation of IOP, various mechanisms can be associated, like reduced aqueous outflow in patients receiving longer courses of intravitreal injections,[5] released silicon droplets from the syringes carrying the drug,[6] acute onset sterile inflammation in response to protein aggregation and silicon oil,[7] delayed onset vasculitis,[7] inhibition of nitric oxide-mediated relaxation of smooth muscles and size of trabecular meshwork cells by anti-VEGF.[8]

As the intravitreal use of bevacizumab is growing exponentially, ocular side effects related to it are of fundamental importance. There is a need to investigate changes in IOP post-procedure. The current study was planned to evaluate the short-term and sustained IOP changes after intravitreal bevacizumab in patients with diabetic retinopathy (DR).

## Patients and Methods

The quasi-experimental study was conducted at the Ophthalmology Department of the District Headquarter (DHQ) Teaching Hospital, Gujranwala, Pakistan, from January to December 2020. After approval from the ethics review board of Gujranwala Medical College (GMC) and the Advanced Studies and Research Board of the University of Health Sciences (UHS), Lahore, the sample

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size was estimated using 95% confidence level and 80% power of test[9] using WHO sample size calculator.[10] Non-probability purposive sampling technique was followed. The sample was raised from the ophthalmology outpatient department (OPD). Those included were diabetic patients of either gender aged 18-60 years, with indication for intravitreal bevacizumab. Patients diagnosed with glaucoma or ocular hypertension pre-injection, patients with active uveitis, previous history of use of intravitreal steroids, systemic steroids or beta-blocker were excluded.

After taking written informed consent from the patients, detailed history was taken and thorough clinical examination was carried out by a consultant ophthalmologist. Basic demographic information along with a brief ocular and medical history of each patient was recorded on a predesigned proforma.

IOP was measured with Goldmann applanation tonometer (GAT) (Haag-Streit® AT 900 C/M). Tonometer applanation prism was disinfected by using 70% isopropyl alcohol swabs.[11] Fundoscopic evaluation was performed to record the stage of DR. Patients with clear fundal view had an ocular coherence tomographic (OCT) scan of the macula (Optovue®, model iVue 500) to note the central macular thickness (CMT). Patients with no fundal view had B-Scan ultra-sonogram to note any traction on the retina. Intravitreal injection of bevacizumab was advised after discussion with a consultant vitreoretinal surgeon.

The injection was given intravitreally in the operation theatre (OT) on the scheduled days. The protocol for intravitreal injection was as per the Lahore General Hospital (LGH) protocol.[1] Patients were positioned supine on OT table. A solution of 5% povidone-iodine was used for periorbital skin and eyelash disinfection. After 5 minutes of application of povidone-iodine, the eyelashes and lids were cleaned with an alcohol swabs. A sterile drape was used to cover the face and Sterile Opsite® was applied to cover the eyelashes. Wire lid speculum was applied for lid control.

Topical anaesthetic (0.5% proparacaine) eye drops were instilled in the conjunctival fornix. Before injection, 5% povidone-iodine solution was instilled into the conjunctival fornix. The intravitreal bevacizumab injection (0.05ml-1.25mg) supplied in a 1cc insulin syringe (30-gauge x 5/16 inch) was used in all patients. The needle was inserted through pars plana at a distance of 3.5-4mm from the limbus, depending on the phakic status of the eye. After injection into the vitreous, the injection needle was brought out after holding the conjunctiva at the injection site with plain forceps (Figure). Any vitreous reflux from the injection site was noted. Topical antibiotic drops (0.5% moxifloxacin hydrochloride) were instilled into the conjunctival fornix post-injection. Eye pad was applied and secured by sticking.

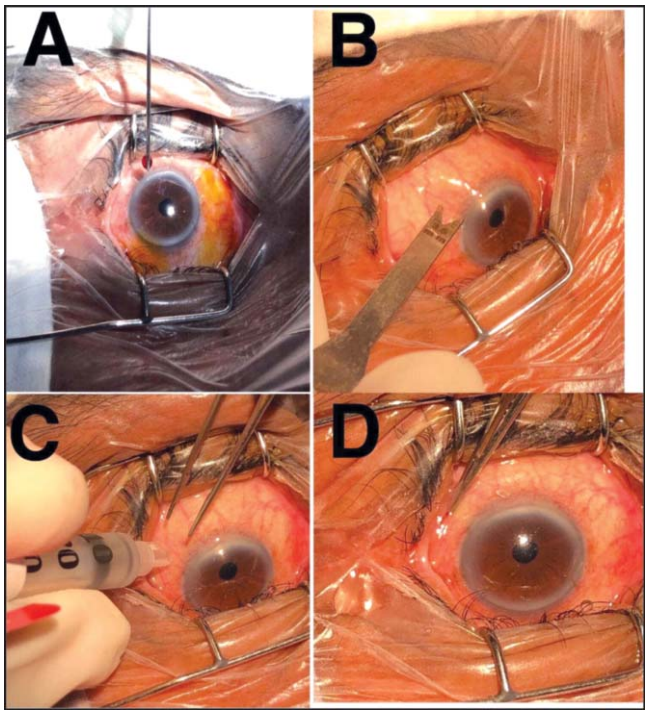


**Figure:** Figure: (A) 5% Povidone-iodine installed in conjunctival fornix and washed after 5 minutes, (B) Measurement of Pars Plana from Limbus, (C) Injection of Bevacizumab (0.05ml) (D) Injection site conjunctiva being held with forceps to prevent any drug reflux.

All the patients were examined by slit-lamp bio-microscope after injection and an IOP measurement was performed at 5, 10 and 30 minutes. Tonometer applanation prisms which were used for applanation tonometry just after the injection were sterilised by dipping in a solution of EndoStar® and left in the tray to get air-dried. Recommended guidelines by the Centre for Disease Control (CDC) and tonometer manufacturers were observed during tonometer prism disinfection.[11]

Patients were followed up on an outdoor basis for IOP check at 1 week interval for 4 weeks. Patients who missed the appointment were contacted on phone. On each visit, IOP was noted. Further treatment strategy was advised after repeating OCT scan of the macula and fundoscopy.

Data was analysed using SPSS 25. Mean ± standard deviation (SD) values were computed for normally distributed numeric data. Median and interquartile

ranges (IQRs) were calculated for non-normally distributed numeric data. Frequency and percentage were calculated for categorical variables Normality of the data was checked using Shapiro-Wilk test. Mean pre-injection IOP was compared with mean short-term and sustained IOP elevation measurements using Friedman test. Since the data was not normally distributed, therefore non-parametric test Wilcoxon was applied for pair-wise comparison. P<0.05 was taken to be statistically significant.

## Results

Of the 42 patients, 20(47.61%) were male and 22(52.38%) were female. The overall mean age was 52.4±5.7 years. There were 33(78.6%) patients with non-proliferative diabetic retinopathy (NPDR) and all of them had clinically significant macular oedema (Table-1). Clear fluid reflux post-injection was noted in 23(54.76%) patients from the injection site.

IOP increased significantly in the short term post-injection (p<0.001) (Table-2)., while the difference was not significant in the weekly check-ups (p=0.264) (Table-3).

**Table-1:** Demographic data.

| Demographic Details Of Patients | |
|---|---|
| Mean Age | 52.4 ± 5.7 |
| **Gender Distribution** | **Frequency (%)** |
| Male | 20 (47.61%) |
| Female | 22 (52.38%) |
| **Stage of Diabetic Retinopathy** | |
| Non-proliferative Diabetic Retinopathy (NPDR) | 33 (78.6%) |
| Proliferative Diabetic Retinopathy (PDR) | 4 (21.4%) |
| **Treatment Regime for Diabetes:** | |
| On Insulin | 25 (59.5%) |
| Oral hypoglycaemic. | 17 (40.5%) |
| **Number of Injection** | |
| first dose of injection, | 26 (61.9%) |
| 2nd dose | 8 (19%) |
| 3rd dose | 3 (7.1%) |
| 4th dose | 2 (4.8%) |
| 5th dose | 2 (4.8%) |
| 6th dose | 1 (2.4%) |

**Table-3:** Sustained intraocular pressure (IOP) fluctuation after Intravitreal Bevacizumab.

| Intraocular Pressure (IOP) | Mean ± SD | Median ( Q1 - Q3) | p-value[a] |
|---|---|---|---|
| Pre Injection | 11.5 ± 2.3 | 11.0 (10.0 - 14.0) | 0.264 |
| One week | 12.0 ± 2.1 | 12.0 (10.0 - 13.0) | |
| Two week | 11.8 ± 2.1 | 11.0 (10.0 - 13.0) | |
| Three week | 11.9 ± 2.1 | 12.0 (10.0 - 13.3) | |
| Four week | 11.7 ± 1.9 | 11.5 (10.0 - 13.0) | |

[a] comparison was made by Friedman test.
SD: Standard deviation.

## Discussion

The study showed statistically significant short-term IOP fluctuation after intravitreal bevacizumab. Although this short-term rise of IOP was not high enough to cross the normal upper limit of IOP, i.e., 21mmHg. Regarding sustained IOP elevation, the study did not find any effect in the population with normal pre-injection IOP up to 1 month of follow-up.

Mean baseline IOP of the patients in our study was 11.5±2.3mmHg measured with GAT. Range of IOP on GAT in Pakistani individuals is reported to be 7-21mmHg.[12] Mean baseline IOP in the study population was in the lower limit of the reported IOP range.

The short-term IOP elevation was statistically significant in the study, but not as high as reported earlier.[13-15] Biatas-Niedziela et al. reported short-term IOP elevation of only 1.54mmHg from baseline.[16] The current study showed short-term mean IOP elevation of 3.5mmHg from the baseline. The frequency of reflux from the injection site was 54.76%. This can be one of the reasons that high spikes of IOP were not observed in the current patients. Frequency of reflux is reported to be one in three eyes (33%) for the 30G needle used for injection.[17] Uyar et al. have reported the frequency of reflux from the injection site to be as high as 78.5% including the patients of two groups showing <3mm and >3mm conjunctival bleb.[4]

**Table-2:** Short-term intraocular pressure (IOP) fluctuation after Intravitreal Bevacizumab with pair-wise comparison.

| Intraocular Pressure | Mean ± SD | Median (Q1 - Q3) | p-value[a] | Intraocular Pressure | | p-value[b] |
|---|---|---|---|---|---|---|
| Other Eye | 11.8 ±2.4 | 12.0 (8.0 - 18.0) | < 0.001* | Pre Injection | Five Minutes | < 0.001* |
| Pre Injection | 11.5 ± 2.3 | 11.0 (10.0 - 14.0) | | Pre Injection | Ten Minutes | < 0.001* |
| Five Minutes | 15.0 ± 2.7 | 14.5 (13.0 - 17.3) | | Pre Injection | Thirty Minutes | < 0.001* |
| Ten Minutes | 14.2 ± 2.4 | 14.0 (12.0 - 16.0) | | Five Minutes | Ten Minutes | 0.135 |
| Thirty Minutes | 13.8 ± 2.4 | 13.0 (12.0 - 16.0) | | Five Minutes | Thirty Minutes | 0.001* |
| | | | | Ten Minutes | Thirty Minutes | 0.835 |

[a] comparison by Friedman test, *significant, [b] comparison made by Wilcoxon signed-rank test.
SD: Standard deviation.

Reflux from the injection site depends on the size of the needle used and the site of intravitreal injection. Vitreous reflux with the use of a 30G 1cc syringe is documented to be more common than with the use of 32G needle.[18,19] Reflux is less common when injection is given in infero-temporal quadrant.[20] In the current study, only a 30G needle was used and the injections were given mostly in the supero-temporal quadrant. Sub-conjunctival haemorrhage, which is one of the common minor complications of intravitreal injection,[21] supero-temporal quadrant injections were given so that if any sub-conjunctival haemorrhage occurred it would be covered by the upper lid and would not affect cosmesis of the patient. Presence of vitreous reflux prevents higher IOP rise after intravitreal injection.[14,18,22] Similar results were observed in the current study.

Reflux from the injection site is not always the injected drug. Boon et al. added 1% fluorescein to bevacizumab, which was to be injected intravitreally in patients who had clear fluid reflux from the injection site noted on previous injections. Only 3 out of 13 patients had reflux of fluorescein labelled fluid from the injection site. Out of these 3, only 1 patient had largely fluorescein labelled fluid, the remaining 2 had only trace of it.[23] Refluxes from injection site do not affect the therapeutic effect of the drug injected intravitreally. Uyar et al. evaluated the effect of reflux from the injection site on the therapeutics of intravitreal ranibizumab, and concluded that reflux from the injection site did not affect the decrease in macular thickness in diabetic and Age-related macular degeneration (AMD) patients.[24] Similar results were reported by Tanwar et al., showing that reflux did not cause a therapeutic compromise in terms of best-corrected visual acuity (BVCA) and macular thickness following intravitreal injection.[25]

The current study did not show any significant IOP rise till one month of follow-up. The proportion of patients showing sustained IOP elevation was overall low. Mansoori et al. reported that the incidence of delayed or sustained ocular hypertension following repeated intravitreal injection was only 1%.[26] They reported that the prevalence of sustained IOP rise between patients who received single injection and those who received multiple injections was not significant.[26] Kähkönen et al in their retrospective cohort study concluded that intravitreal anti-VEGFs were not associated with any sustained elevation of IOP.[27] They also negated the claim that repeated intravitreal injections can be a risk factor for sustained elevation of IOP.[27] The reason for not observing any sustained IOP elevation in the current study can be the reason that the majority (61.9%) of the patients had their first dose of intravitreal bevacizumab. The included patients in the current study had no history of glaucoma or ocular hypertension. Additionally, the mean baseline IOP in the study population was in the lower limit of the reported range of IOP.

The strength of the current study is its prospective design, while limitations included a small sample size, inclusion of patients with no history of glaucoma or ocular hypertension, and only a subset of the population with DR.

Multicentre studies with larger sample sizes and inclusion of subjects other than DR are recommended. Comparison of IOP elevation with the use of syringes of different gauges, injection site, technique and long follow-up time should also be compared.

## Conclusion

Intravitreal bevacizumab was found to be a safe treatment regime in terms of IOP for patients with retinal ischaemia due to DR. There is short-term fluctuation of IOP after intravitreal injection of bevacizumab, but this spike is not high if there is clear fluid reflux from the injection site. This study shows no sustained elevation of IOP up to 1 month of follow-up after intravitreal bevacizumab.

**Disclaimer:** The text is based on an academic thesis.

**Conflict of Interest:** One of the co-authors was also part of the ethics review board which approved the study proposal.

**Source of Funding:** None.

**Ethical Approval and Consent to Participate:** Ethical approval was taken from institutional review board Gujranwala Medical College, Punjab, Pakistan (Admin/131/GMC). This study was approved by Advanced Studies & Research Board, University of Health Sciences, Lahore (UHS/Education/126-20/210) dated 20 January 2020. Written consent was taken from all the patients after explaining about the study.

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