Effect of Intravitreal Anti-Vascular Endothelial Growth Factor Injection on Intraocular Pressure and Systemic Blood Pressure

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ABSTRACT

Objective: To determine the effect of intravitreal anti-vascular endothelial growth factor injections on intraocular pressure and systemic blood pressure in the immediate post-injection period.

Study Design: Quasi-experimental study.

Place and Duration of Study: Armed Forces Institute of Ophthalmology, Rawalpindi Pakistan, from Aug 2020 to Jan 2021

Patients and Methods: Patients over the age of 21 years receiving the first anti-vascular endothelial growth factor injection for various retinal vascular disorders were included in the study. Intraocular pressure (measured with Tono-pen) and systemic blood pressure were recorded 5 minutes before (baseline) and after, as well as 30 minutes after intravitreal injection.

Results: One hundred and thirty-two patients were included in the study. The median intraocular pressure value in the study population was 14.00 (5) mmHg, while median systolic and diastolic blood pressure values were 147.00 (27) mmHg and 86.00 (19) mmHg, respectively. There was a significant rise in median intraocular pressure up to 29.00 (10) mmHg after 5 minutes and up to 29.00 (9) mmHg after 30 minutes ($p \leq 0.001$). Similarly, systolic blood pressure was elevated up to 160.00 (25) mmHg at 5 minutes and 151.00 (32) mmHg after 30 minutes ($p \leq 0.001$). No statistically significant correlation between intraocular pressure and blood pressure was seen ($p=0.156$).

Conclusion: Intravitreal anti-vascular endothelial growth factor injections are associated with a significant rise in intraocular pressure and blood pressure in the immediate post-injection period, so the patients need to be monitored during this period to avoid any ocular or cardiovascular complications.

Keywords: Anti-vascular growth factor, Intraocular pressure, Intravitreal injection, Systemic blood pressure.

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INTRODUCTION

Vascular endothelial growth factor (VEGF) is a regulator of angiogenesis and has been implicated in the pathogenesis of various retinal vascular disorders.[1] Blocking the action of VEGF has been shown to effectively reduce the pathological angiogenesis and vascular permeability; thereby, anti-VEGF agents are effective in reducing the visual loss associated with these retinopathies.[2] VEGF inhibitors are used in many disorders, including diabetic macular oedema, proliferative diabetic retinopathy, retinal vein occlusion, exudative age-related macular degeneration, etc.[3,4] Intravitreal injections have become one of the most commonly performed intra-ocular procedures world-wide, with an estimated 5.9 million injections administered in the USA in 2016.[5] The number of patients requiring intravitreal anti-VEGF injections is likely to increase further due to new indications and an ageing population.[5] Bevacizumab, Ranibizumab and Aflibercept are the most widely used anti-VEGF agents worldwide under different treatment regimens, with high efficacy.[6]

These intravitreal injections are generally considered safe, but long-term use and repeated injections can increase the risk of ocular and systemic side effects.[7] Several studies have recently reported that multiple intravitreal anti-VEGF injections are associated with an increased risk of sustained intraocular pressure (IOP) elevation along with thinning of the retinal nerve fibre layer.[8] Some studies have also shown that some patients' intravitreal anti-VEGF injections induce or exacerbate systemic hypertension.[9] This rise in systemic blood pressure (BP) has been hypothesized to occur through nitric oxide or secondary to endothelial dysfunction.[10]

The objective of this study was to determine the short-term effect of intravitreal anti–VEGF agents on our patients' intraocular pressure and systemic blood pressure to establish a safety profile of this widely used intraocular intervention.

METHODOLOGY

This quasi-experimental study included 132 eyes treated with an intravitreal anti-VEGF injection of 0.05ml per dose in an operating room at the Armed

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Forces Institute of Ophthalmology, Rawalpindi Pakistan, from August 2020 to January 2021. A sample size of 44 was calculated using Open Epi Software (Online), keeping a reference prevalence of 2.9%,[11] (Confidence interval 95%, Confidence limit as 5 %) for the rise in IOP after intravitreal anti-VEGF injection. However, we included all 132 eyes meeting the inclusion criteria by non-probability consecutive sampling technique.

Inclusion Criteria: We included patients over 21 years of age undergoing their first anti-VEGF injection in either eye for diabetic macular oedema (DME), choroidal neovascularization, retinal vein occlusion, proliferative diabetic retinopathy (PDR), and DME combined with PDR.

Exclusion Criteria: Patients who had undergone previous ocular surgery (exception of phacoemulsification), were on anti-glaucoma medication, had a previous vitrectomy in the concerned eye, or using steroids (topical or systemic) were excluded from the study.

All patients included in the study were provided with a detailed description of the procedure, and informed consent was obtained. The Institutional Ethical Review Committee approved the study (ERC No. 218A/ERC/AFIO) and the procedure followed the Declaration of Helsinki for research involving humans.

All the patients were prepped uniformly while maintaining strict sterile protocols and included the application of topical 5% povidoneiodine, a drape sheet, and topical 0.5% Proparacaine hydrochloride (Alcaine®, Alcon Pty Ltd, Fort Worth, TX, USA). Anti-VEGF agents included in the study were Bevacizumab 1.25 mg/0.05 ml (Avastin®, Genentech Inc., CA USA), Ranibizumab 0.5 mg/0.05ml (Lucentis®, Genentech Inc., CA the USA), and Aflibercept 2mg/0.05 ml (Eylea®, Regeneron Pharmaceuticals Inc., NY USA). Intravitreal injection of 0.05ml anti-VEGF agent was given in the inferotemporal quadrant at a 3.5-4.0mm distance from the corneal limbus via a 30-gauge needle, followed by installation of a topical fourth-generation fluoroquinolone. The patients were advised to use the same topical Fluoroquinolone four times a day for the next three days.

Intraocular pressure (IOP) and blood pressure (B.P.) were both recorded 5 minutes before (baseline) and after, as well as 30 minutes after the injection with the patient sitting comfortably in a chair. IOP was recorded using an advanced handheld tonometer (Tono-Pen AVIA®, Reichert Inc., NY USA) using a new sterile tip cover for each patient. In contrast, B.P. was recorded by an automated patient monitor (Vizor 12®, HEYER Medical AG, Germany). All the procedures were performed between 12:00 pm to 2:00 pm to minimise any diurnal variation effect in IOP and B.P. Each step was performed by the same operator in all the patients to maintain consistency.

Statistical analysis was performed in Statistical Package for the Social Sciences (SPSS) version 26 for Windows. Demographics and baseline characteristics were measured using descriptive analysis.

Intraocular pressure (IOP) and Blood pressure (B.P.) data were considered interval data, and the mean measurements were analyzed for changes from baseline by using the Friedman rank-sum test. The correlation between IOP and B.P. was analyzed using the Spearman correlation analysis. The *p*-value of ≤0.05 was considered statistically significant in the study.

RESULTS

During the 6-month study period, a total of 132 eyes receiving an intravitreal anti-VEGF injection were included. Demographics and baseline characteristics for all patients were presented in Table-I.

Table-I: Demographics and basic characteristics.

Study Parameters	n (%)
Eyes	132
Age (Mean ± SD)	61.88 ± 10.61 years
Gender	
Male	82 (62.12%)
Female	50 (37.88)
Co-Morbids	
With Diabetes	95 (72%)
With Hypertension	91 (68.9%)
With Ischemic Heart Disease	21 (15.9%)
With Asthma	10 (7.6%)

Patients' mean age in the study was 61.88 ± 10.61 years (median 61.50). There was a gender predilection, with 82 (62.12%) subjects being male. Diabetes Mellites was the most frequent systemic disease observed in the sample population, present in 95 (72%), followed by hypertension in 91 (68.9%). Of the 132 participants, 72 (56.06%) had both diabetes mellites and hypertension.

Diabetic Macular Edema (DME) in 62 (46.97%) of the patients was the most frequent common indication for intervention in our study, followed by Retinal Vein Occlusion (RVO) in 27 (20.45%) (Figure-1).

Among the three different intravitreal types of AntiVEGF injections used in the study, Bevacizumab (Avastin®) was the most commonly administered to 107 (81.06%) participants (Table-II).

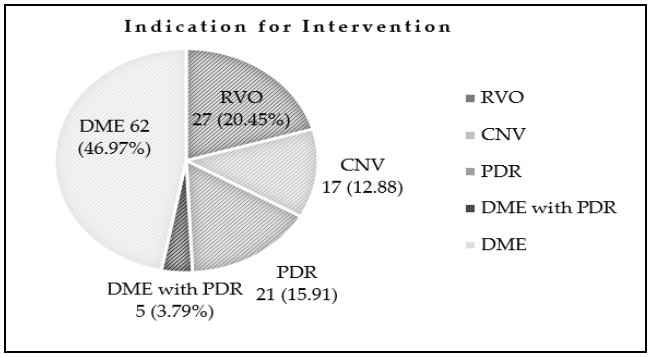

Figure-2. DME = Diabetic Macular Edema, RVO = Retinal Vein Occlusion, CNV = Choroidal neovascularization, PDR = Proliferative Diabetic Retinopathy with no active retinal traction.

Table-II: Anti-vascular endothelial growth factor (AntiVEGF) injection used.

AntiVEGF used	n (%)
Bevacizumab (Avastin®)	107 (81.06)
Ranibizumab (Lucentis®/Patizra®)	14 (10.61)
Aflibercept (Eylea®)	11 (8.33)

All types consistent with 0.05ml per dose.

The median IOP value in the study population was 14.77(5) mmHg, while systolic and diastolic B.P. values were 147(27) mmHg and 86(19) mmHg, respectively. There was a significant rise in IOP and B.P. post-injection at both 5 minutes and 30 minutes as compared to the baseline ($p < 0.05$) (Table-III).

Table-III: Pre-injection and post-injection IOP and B.P at 5 minutes and 30 minutes (Friedman rank-sum test).

Parameters	Baseline (Median [IQR])	5 Minutes Post-Injection (Median [IQR])	30 Minutes Post-Injection (Median [IQR])	*p*-value
Intraocular Pressure (mmHg)	14.00 (5)	29.00 (10)	29.00 (9)	<0.001
Systolic Blood Pressure (mmHg)	147.00 (27)	160.00 (25)	151.00 (32)	<0.001
Diastolic Blood Pressure (mmHg)	86.00 (19)	95.00 (19)	89.00 (21)	<0.001

Of the participants, a significant IOP rise to above 21mmHg was noted in 109 (82.6%) and 107 (81.1%) at 5 minutes and 30 minutes post-injection, respectively. In addition, systolic B.P. rise to a significant level of above 180mmHg was noted in 22 (16.7%) and 6 (4.5%) at 5 minutes and 30 minutes post-injection, respectively, while a diastolic B.P. rise to above 110mmHg was noted in 16 (12.1%) and 11 (8.3%) at 5 minutes and 30 minutes post-injection respectively.

The correlation between IOP and B.P. was examined from baseline values at 5 minutes post-injection when the IOP and B.P. had changed significantly. No statistically significant correlation between IOP and B.P. was seen (*p*-value=0.156, r-value=0.124) (Figure-2).

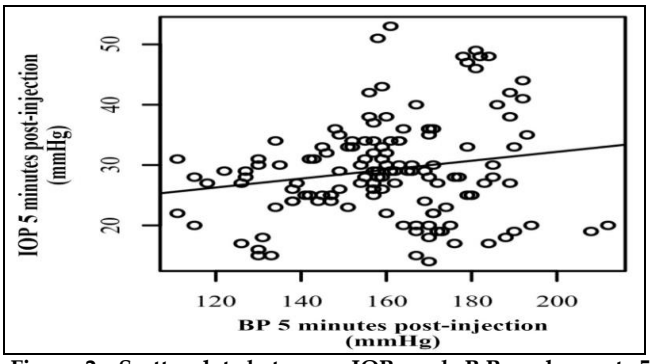

Figure-2: Scatterplot between IOP and B.P. values at 5 minutes post-injection with regression line (Spearman correlation analysis).

DISCUSSION

Anti-VEGF therapy has become the mainstay of treatment for various retinal vascular disorders and is one of the most widely practised intraocular procedures. This study was conducted to evaluate a few aspects of the safety of intravitreal anti-VEGF injections with regard to IOP and systemic B.P. in the immediate post-injection period.

IOP rise may occur acutely after intravitreal injection of any drug owing to an increase in intraocular volume. Although this rise is transient, it may obstruct the blood flow of the optic nerve head or central retinal artery.[8-10]

Our study discovered that IOP was significantly raised in all patients at immediate post-injection at 5min, and this rise was sustained at 30 minutes. These results were similar to other studies that have revealed IOP elevation after using intravitreal anti-VEGF injections. A recently conducted meta-analysis showed that IOP was significantly raised on the day of anti-VEGF injection at all measured time intervals but was slightly decreased on the day after injection and did not differ from baseline at later follow-up measure-ments.[8,11] They evaluated 27 studies investigating the effects of Bevacizumab on IOP, 14 studies of Ranibizumab and four studies for Aflibercept. They studied the relationship between intravitreal injection of anti-VEGF and post-injection IOP. The weighted mean difference

(WMD) with a corresponding 95% confidence interval (CI) in IOP was 25.95 immediately after injection and declined to 2.61, 30 minutes post-injection. The WMD (95% CI) the day after injection was significantly lower at–0.63. IOP normalized after one week.[8] Another recent study on the Pakistani population by Zafar *et al*, evaluated the effects of intravitreal Bevacizumab injections on IOP and had similar results to our research.[12] They concluded that significant IOP elevation occurred during the immediate post-op period.[12] However, the difference with our study was that the IOP returned to near normal at 30 minutes post-injection in most of their study population, while our patients had sustained rise in IOP even after 30 min. Our results were in coherence with the results of the de Vries *et al*, meta-analysis that showed that IOP remained significantly high on the day of injection, with multiple time interval readings and showed a downward trend from the next day onwards.[8] Hence large multicenter local trials with longer follow-up are required to evaluate the effects of intravitreal anti-VEGF injections on IOP in our population.

There have been concerns about the systemic side effects of intravitreal injections of Anti VEGF injections. We evaluated the transient impact of intravitreal Anti VEGF injections on systemic B.P. Our study revealed a statistically significant increase in systolic and diastolic B.P. patients after intravitreal anti-VEGF injections. Our findings were similar to a prospective observational study by Berger *et al,* that studied the association of intravitreal anti-VEGF injections with a rise in B.P.[13] They concluded that intravitreal injections are associated with a transient rise in B.P. Another study by Daroos *et al*. evaluated the effects of intravitreal Bevacizumab on systemic B.P. It revealed that elevation in systemic B.P. from baseline was noted in 90% of patients on first-day post-injection.[14] They also stated that no significant difference from baseline was observed in B.P. at later follow-ups (1 week, four weeks post-injection). A significant departure from this trend was published in a study by Risimic *et al,* and Ali *et al*, which conversely depicted a decrease in diastolic B.P. after administration of an intravitreal anti-VEGF injection.[10,15]

Based on the published data, few authors recommend topical medications to control the transient rise in IOP.[16,17] Recently, Ouadfel *et al,* have published a novel method to reduce anxiety while receiving an intravitreal injection.[18] They propose using a prerecorded relaxation breathing session before and during the intravitreal injection to decrease anxiety and its subsequent effect on B.P.[18]

Our study reveals a statistically significant rise in IOP and B.P. in the immediate post-injection period following intravitreal injections of anti-VEGF agents. However, in light of published research, it is assumed that this effect is only transient and not enough to cause severe systemic or ocular side effects. Nevertheless, it is still recommended that close monitoring and follow-up of patients be carried out in the immediate post-injection period to intervene and manage these complications timely.

LIMITATIONS OF STUDY

The limitation of our study is that it has been conducted on a relatively small group of patients with a short same-day follow-up only. Evaluation in a multicenter trial with longer follow-up is required to completely ascertain the effects of intravitreal anti-VEGF injection on IOP and systemic B.P. and recommend safety protocols and guidelines.

CONCLUSION

Intravitreal injections of anti-VEGFs are associated with immediate post-op elevation of intraocular pressure and systemic blood pressure that could increase the risk of other ocular and cardiovascular or cerebrovascular side effects. Further trials with longer follow-ups are required to establish safety protocols, especially for patients requiring frequent repeated injections.

Conflict of Interest: None.

Author's Contribution

BS:, MAK:, AK:, MHS:, SM:, DA: Substantial.

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