Scholars Journal of Applied Medical Sciences
Abbreviated Key Title: Sch J App Med Sci
ISSN 2347-954X (Print) | ISSN 2320-6691 (Online)
Journal homepage: https://saspublishers.com

OPEN ACCESS

Ophthalmology

Evaluation of Intraocular Pressure and Mean Ocular Perfusion Pressure Before and After Intravitreal Injection of Bevacizumab

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DOI: https://doi.org/10.36347/sjams.2025.v13i07.025 | **Received:** 04.06.2025 | **Accepted:** 26.07.2025 | **Published:** 30.07.2025

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Abstract **Original Research Article**

Background: Intravitreal injection of anti-vascular endothelial growth factor (anti-VEGF) agents has become increasingly important in managing vitreoretinal diseases such as age-related macular degeneration, central or branch retinal vein occlusion, and diabetic maculopathy, which are rising globally. This study aimed to assess the effect of intravitreal Bevacizumab injection on intraocular pressure (IOP) and mean ocular perfusion pressure (MOPP). ***Methods:*** This prospective observational study was conducted in the Department of Ophthalmology, BSMMU, Dhaka from March 2018 to August 2020. Within the period, total 85 cases of different vitreoretinal diseases those meet the inclusion criteria were included in study after receiving informed consent from the patient. ***Results:*** Mean IOP was 13.39±3.92 mmHg before injection, 16.65±4.48 mmHg at 30 minutes, 13.40±3.50 mmHg at 1 day, and 13.12±3.27 mmHg at 7 days. Mean MOPP was 50.94±6.87 mmHg before injection, 48.12±7.15 mmHg at 30 minutes, 50.47±6.64 mmHg at 1 day, and 50.66±4.98 mmHg at 7 days. A significant change was observed in IOP and MOPP within 30 minutes post-injection ($p < 0.05$), but not at 1 or 7 days ($p > 0.05$). ***Conclusion:*** After analyzing the results of present study it can be concluded that IOP is significantly increased within 30 minutes after injection and recover to their pre-injection value within 1 day after injection, this observation continued on 7th day follow up also. And MOPP is significantly decreased within 30 minutes after injection and recover to their pre-injection value within 1 days after injection and this observation continued on 7th day follow up also.

Keywords: Vitreoretinal disease, Bevacizumab, Intra ocular pressure, Mean ocular perfusion pressure.

INTRODUCTION

Intravitreal injection of antivascular endothelial growth factor (Anti-VEGF) has assumed a growing role in the treatment of vitreoretinal diseases like age related macular degeneration, central retinal vein or branch retinal vein occlusion, diabetic maculopathy in the last few years, which are increasing globally every year. Antivascular endothelial growth factor (anti-VEGF) antibodies in ophthalmologic therapies, there was a fundamental change in treatment option for various ocular disease. The volume of the intravitreal injection can directly increase the intra-ocular pressure (IOP) and thereby negatively affect the retinal and optic nerve blood supply. Animal studies have demonstrated that a sudden increase in intraocular pressure (IOP) can obstruct axonal transport to the optic nerve head, with the extent of optic nerve damage being directly related to the magnitude of the IOP elevation.[1] Additionally, an acute rise in IOP has been shown to reduce blood flow to the juxtapapillary retina and optic nerve head, in proportion to the degree of IOP increase.[2] Several mechanisms have been proposed to explain this rise in IOP, including the volume-related effect of the intravitreal injection.[3] Specific characteristics of Bevacizumab—being a full-length antibody with an Fc fragment—may trigger trabeculitis and/or contribute to IOP elevation through its presence, or by inhibiting VEGF within the trabecular meshwork, thereby impairing aqueous outflow.[4,5,6] Avastin (Bevacizumab, Novartis/Genentech Inc., South San Francisco, CA, USA) is commonly used off-label for the intravitreal treatment of various retinal conditions. The recommended dose is 1.25mg/.05 ml. It has become globally widespread because of its low cost and similar results like other anti VEGF.[7] Although previous studies focused on the rise in post-injection IOP, substantially the entire blood supply of the retina and

optic nerve head is affected by ocular perfusion pressure is more important than IOP. Mean ocular perfusion pressure (MOPP) is defined as the difference between the mean ophthalmic artery pressure and IOP.[8] The objective of this study was to analyze to change of IOP and MOPP before and after intravitreal anti VEGF injection and to evaluate the safety of the procedure.

METHODOLOGY & MATERIALS

This was a prospective observational study carried out in the Department of Ophthalmology at BSMMU from March 2018 to August 2020 (*2 Years and 5 Months)*. Depending on the inclusion and exclusion criteria, 85 patients were taken for the study who were diagnosed as a case of vitreoretinal disease undergoing intravitreal injection of bevacizumab of either sex were evaluated for intraocular pressure by Goldmann applanation tonometer and mean ocular perfusion pressure by using the formula *{MOPP = 2/3[diastolic pressure +1/3(systolic pressure – diastolic pressure)]—IOP}* just before the injection, within 30 min after injection, 1 day and 1 week after injection. Complete clinical evaluation including history, physical examination, relevant ocular examination, fundus examination was done in the department of ophthalmology, Bangabandhu sheikh Mujib Medical University. All the information's were recorded in a data collection sheet.

Demographic information such as age, sex, occupation were collected. The research protocol was approved by the ethical review committee of BSMMU before starting this study. Informed written consent was taken from each patient. Statistical analyses were done by using Statistical Package for Social Science (SPSS-26). Categorical measures were summarized as frequencies and percentage. One way ANOVA was performed to compare IOP and MOPP among time points (pre and post at 30 minutes, day 1 and day 7). For a single test, a p-value <0.05 was considered significant (difference). For multiple test (comparison among groups) Bonferroni adjustment was applied. That is, to keep our type I error at 5% level for all tests, we set significance level at lower level.

RESULTS

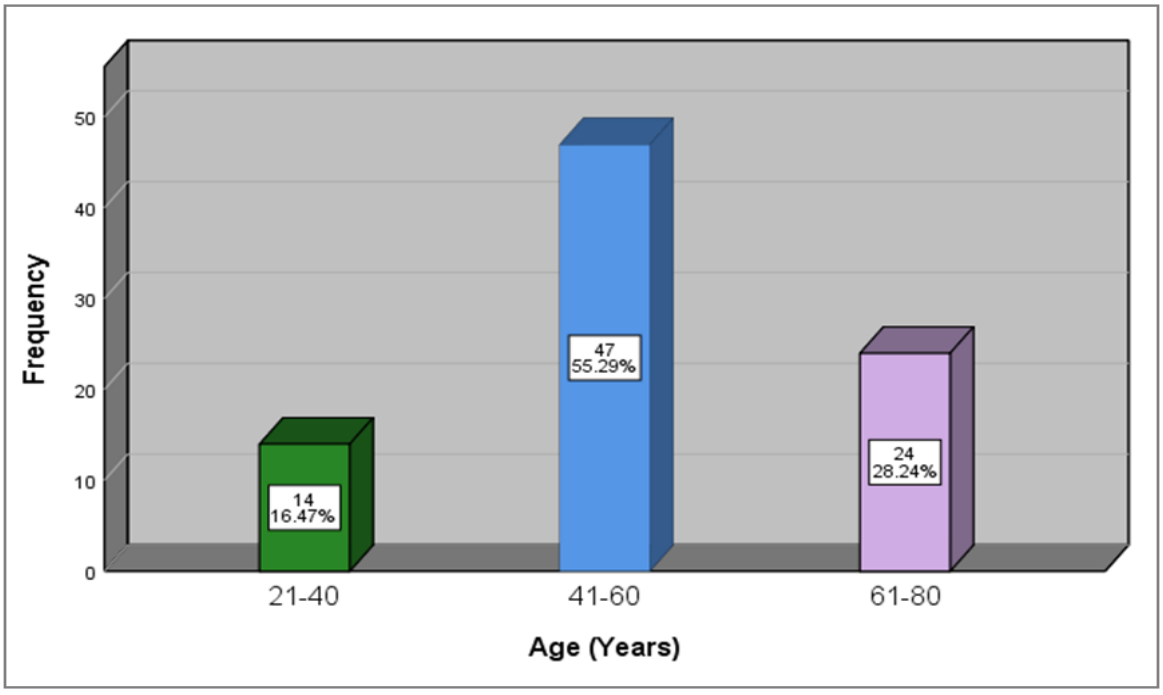

Figure-1: Bar diagram show distribution of the study subjects according to age (n=85)

In this study, 14(16.47%) were in age group of 21-40 years, 47(55.29%) were in age group of 41-60 years and 24(28.24%) were in age group of 61-80 years. The youngest and oldest population was 22 years and 80 years respectively. The mean± SD age was 54.00±11.78 years (figure 1).

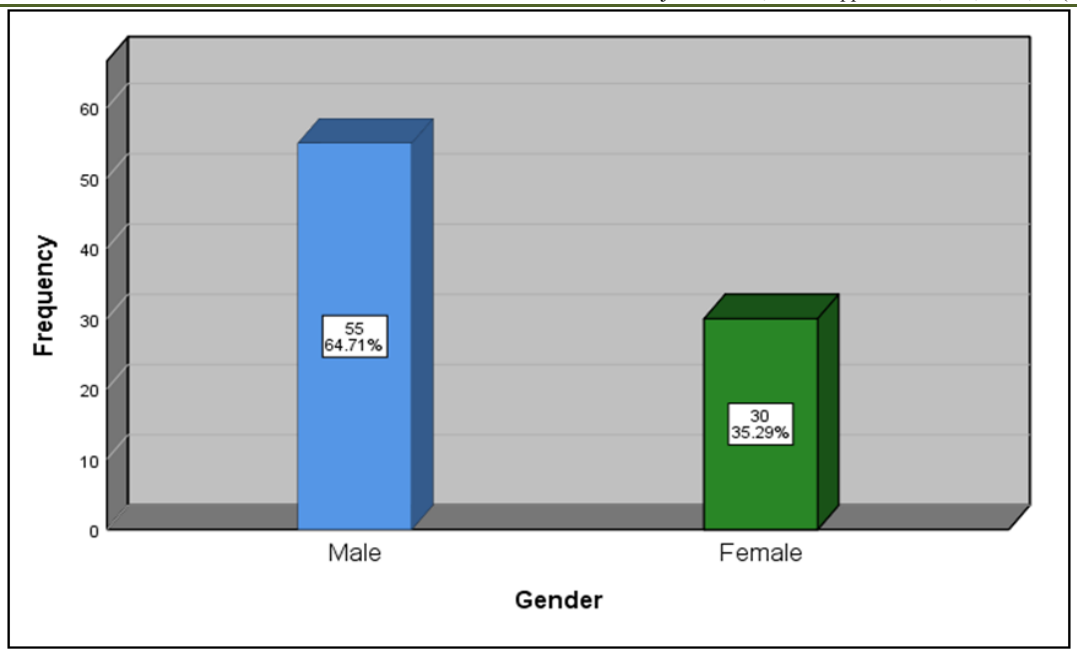

Figure-2: Bar diagram show distribution of the study subjects according to their Gender (n=85)

Among the study subjects, majority (64.71%) were male (55) and only 30(35.29%) female (figure 2).

Table-I: Intraocular Pressure (IOP) at baseline and at various times after intravitreal injection (n=85)

Before injection	30 min after injection	1 day after injection	7 days after injection
14(16.5%)	2(2.4%)	8(9.4%)	8(9.4%)
62(72.9%)	53(62.4%)	71(83.5%)	75(88.2%)
9(10.6%)	30(35.3%)	6(7.1%)	2(2.4%)

Data were expressed as frequency and percentage. n= study subjects. IOP= intraocular pressure

In this study, 30(35.3%) of the patient had an IOP greater than 20 mmHg and IOP values of 92.9% of the patients were recovered to less than 20 mmHg within 1 day (table I).

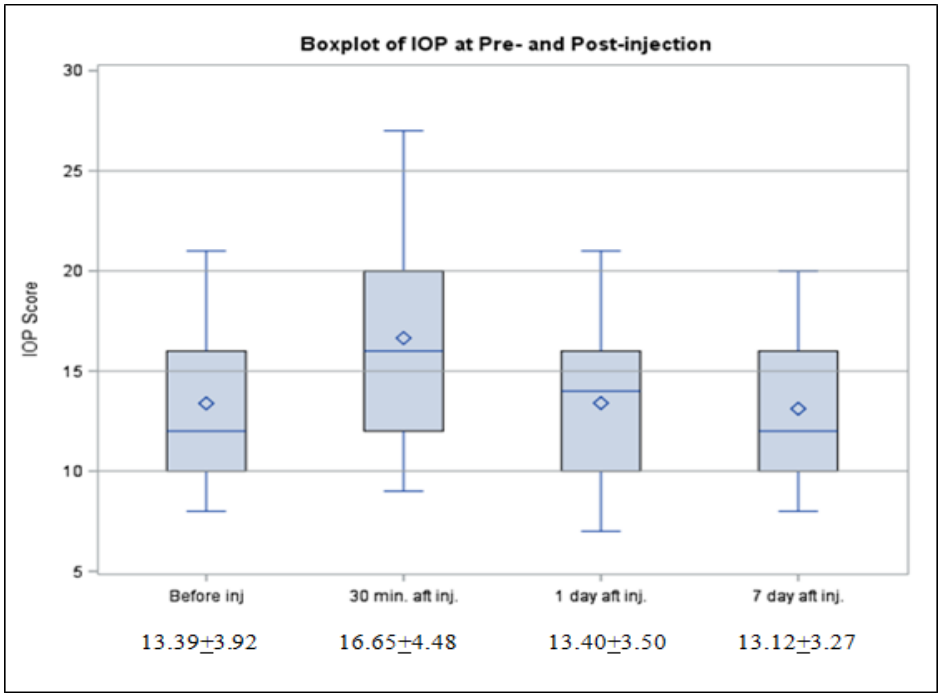

Figure-3: Changes in intraocular pressure (IOP) after intravitreal bevacizumab injection (n=85)

In this study, mean IOP was 13.39±3.92 mmHg before injection, 16.65±4.48 mmHg within 30 min after injection, 13.40±3.50 mmHg at 1 day after injection and 13.12±3.27 mmHg at 7 days after injection (figure 3).

Table-II: Comparison of Intraocular Pressure (IOP) at Different Time Points

Comparison	p-value	Significance
Overall (ANOVA)	<0.0001	***
Before vs. 3 min after injection	<0.0001	***
Before vs. 1 day after injection	1	ns
Before vs. 7 days after injection	1	ns
30 min after vs. 1 day after injection	<0.0001	***
30 min after vs. 7 days after injection	<0.0001	***
1 day after vs. 7 days after injection	1	ns

One way ANOVA followed by Bonferroni adjustment test was performed to compare between the different time point and within different time point ***/*=significant, ns=not significant (table II).

Table-III: Mean Ocular Perfusion Pressure (MOPP) at baseline and at various times after intravitreal injection (n=85)

Parameters	Before injection	Within 30 min after injection	1 day after injection	7 days after injection
MOPP (mmHg)				
20-29	-	1(1.2%)	-	-
30-39	7(8.2%)	10(11.8%)	4(4.7%)	-
40-49	27(31.8%)	40(47.1%)	37(43.5%)	36(42.4%)
50-59	43(50.6%)	29(34.1%)	38(44.7%)	45(52.9%)
60-69	8(9.4%)	5(5.9%)	6(7.1%)	4(4.7%)

Data were expressed as frequency and percentage. n= study subjects. MOPP= mean ocular perfusion pressure (table III)

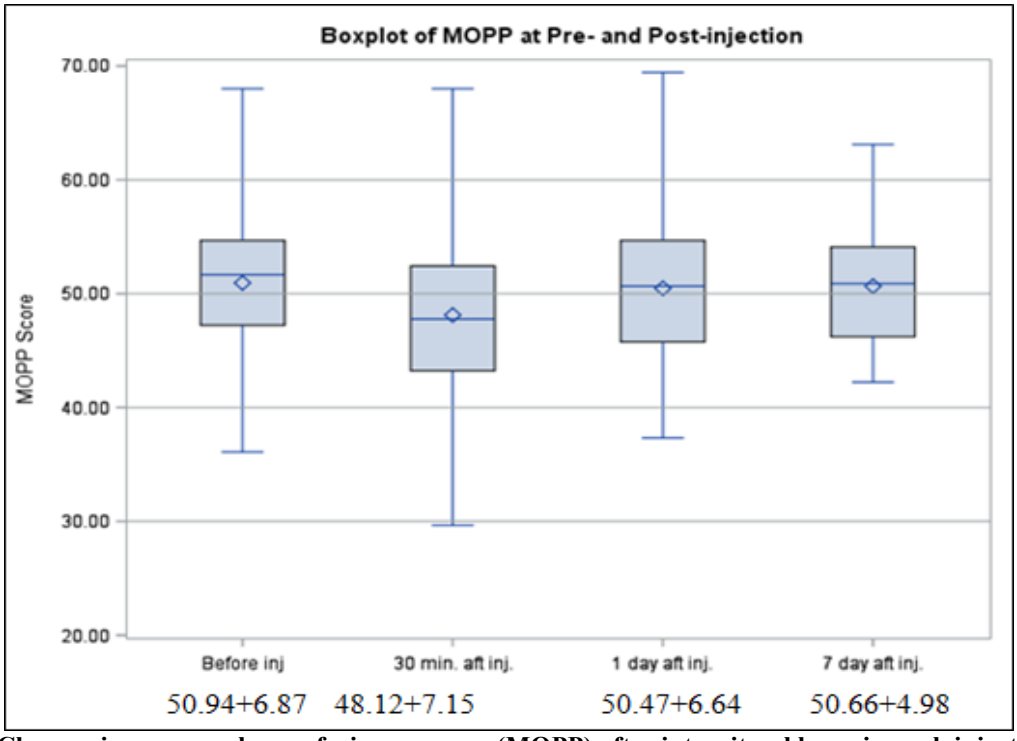

Figure-4: Changes in mean ocular perfusion pressure (MOPP) after intravitreal bevacizumab injection (n=85)

In this study, mean MOPP was 50.94±6.87mmHg before injection, 48.12±7.15mmHg within 30 min after injection, 50.47±6.64 mmHg 1 day after injection and 50.66±4.98mmHg 7 days after injection (figure 4).

Table-IV: Comparison of Mean Ocular Perfusion Pressure (MOPP) at Different Time Points

Comparison	p-value	Significance
Overall (ANOVA)	0.017	*
Before vs. 30 min after injection	0.028	*
Before vs. 1 day after injection	1	ns
Before vs. 7 days after injection	1	ns
30 min after vs. 1 day after injection	0.108	ns
30 min after vs. 7 days after injection	0.064	ns
1 day after vs. 7 days after injection	1	ns

***/*=significant, ns=not significant.

One way ANOVA followed by Bonferroni test was performed to compare between the different time point and within the different time point (table IV).

DISCUSSION

As intravitreal anti-VEGF injections are increasingly used for treating various vitreoretinal disorders, most existing studies have primarily concentrated on post-injection intraocular pressure (IOP) elevation, with only one study addressing mean ocular perfusion pressure (MOPP). However, changes in ocular perfusion pressure have a greater impact on retinal and optic nerve head blood flow than IOP alone. This current study emphasizes the reduction in MOPP following intravitreal injections, which is secondary to the rise in IOP, in addition to evaluating the IOP increase itself.

In this study, statistical analysis was performed using one-way ANOVA to compare IOP and MOPP across different time points (baseline, 30 minutes, 1 day, and 7 days post-injection). Bonferroni adjustments were applied for multiple comparisons. A statistically significant increase in IOP ($p < 0.0001$) and decrease in MOPP ($p < 0.05$) was observed within 30 minutes post-injection. However, values returned to baseline by day 1 and remained stable on day 7, consistent with earlier studies. [9,10] Lee *et al.,* reported that significant changes in IOP and MOPP were only observed immediately after injection. [10]

According to their findings, IOP and MOPP normalized within 30 minutes. Kim *et al.,* also noted that post-injection IOP spikes are common but transient [9]. Similarly, Hollands *et al.,* and Bakri *et al.,* reported that IOP increases following Bevacizumab injections return to below 25 mmHg within 30 to 60 minutes, without requiring treatment. [3,11] Frenkel *et al.,* concluded that post-injection IOP spikes are self-limiting and do not necessitate intervention such as anterior chamber paracentesis. [12]

In this study, 35.3% of patients had IOP greater than 20 mmHg and 13% had MOPP below 40 mmHg at 30 minutes post-injection. By 1day post-injection, 92.9% had IOP below 20 mmHg and 95.3% had MOPP above 40 mmHg. Lee *et al.,* found that 98.5% of IOP values normalized to <30 mmHg and 87.7% of MOPP values rose above 40 mmHg within 30 minutes. [10] Some studies suggest that frequent IOP monitoring immediately after injection may not be essential, as auto regulation preserves retinal and optic nerve head perfusion. [3,12] LaCour *et al.,* demonstrated that retinal microcirculation remains stable despite a 10–20 mmHg drops in MOPP. [13] However, Kyhn *et al.,* found that maintaining MOPP at 5 mmHg for 2 hours can lead to irreversible retinal damage. [14]

Lee *et al.,* hypothesized that changes in IOP and MOPP may be influenced by the injection volume (0.05 mL Avastin vs. 0.07 mL Lucentis) and presence of vitreous reflux after injection. [10] However, these factors were found to have minimal effect. In the present study, 0.05 mL of Avastin was administered using a 30-gauge needle, minimizing post-injection vitreous reflux.

The mean IOP increase from baseline to 30 minutes post-injection was 3.26 mmHg, and the mean MOPP decrease was 2.82 mmHg. One day after injection, changes from baseline were minimal—only 0.01 mmHg for IOP and 0.47 mmHg for MOPP—confirming full recovery within 24 hours.

Moreover, MOPP remained above 10 mmHg at all time points. Kyhn *et al.,* reported that MOPP maintained at 5 mmHg for 2 hours can cause irreversible retinal damage. [14] Our findings align with prior studies indicating that the transient drop in MOPP following anti-VEGF injection, driven by the temporary IOP spike, does not significantly impair retinal or optic nerve blood flow. Furthermore, the IOP elevation did not result in critically low perfusion levels (<10 mmHg).

Limitations of the Study

Study was conducted in a selected hospital. So, the study population might not represent the whole community. The sample was taken purposively. So, there may be chance of bias which can influence the results. Gonioscopy wa not done in every patient. We excluded patients with glaucoma and uveitis. If we could take those patients, we may have reported the real picture whether there is any change in IOP and MOPP after intravitreal injection of bevacizumab.

RECOMMENDATIONS

Further study can be done with long period of follow-up and multi-centre based with randomized sampling and by taking measurement of IOP and MOPP just immediately after injection to make more definitive results.

CONCLUSION

After analyzing the results of the present study, it can be concluded that IOP is significantly increased within 30 minutes and after that recovered to pre-injection value within 1 day after injection, this observation continued on 7th day follow up also. And MOPP is significantly decreased within 30 minutes and after that recovered to pre-injection value within 1 day after injection, this observation continued on the 7th day follow up aswell.

Financial support and sponsorship
No funding sources.

Conflicts of interest
There are no conflicts of interest.

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