

## CORRELATION OF INTRAOCULAR PRESSURE WITH OCULAR AXIAL LENGTH AFTER INTRAVITREAL INJECTION OF BEVACIZUMAB IN DIABETIC MACULAR EDEMA

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### ABSTRACT

**Objective:** To determine the effect of Intravitreal injection of Bevacizumab on IOP in eyes of different axial lengths.

**Study Design:** Cross sectional study.

**Place and Duration of Study:** This study was conducted at AFIO Rawalpindi, from Sep 2013 to Jan 2014.

**Material and Methods:** In this study 55 patients scheduled for intravitreal injection of bevacizumab for the treatment of diabetic macular edema were enrolled. An informed written consent was taken from all the patients. All patients underwent clinical ophthalmic examination including uncorrected distance visual acuity, corrected distance visual acuity, slit lamp bio-microscopy and fundus examination with 90 diopter lens. Axial length was measured before IVB using IOL master. Intra Ocular Pressure (IOP) was measured before and after 1 minute of administration of Intravitreal Bevacizumab (IVB) using Tono-Pen.

**Result:** The mean age of patients was  $54.51 \pm 7.53$  years with minimum age of 43 years and maximum age of 70 years. There were 26 (47.3%) male and 29 (52.7%) female patients. The mean axial length of the examined eyes was  $21.12 \pm 1.80$  with range of 6 mm. Mean IOP before IVB was  $13.09 \pm 1.62$  mmHg. After 1 minute of IVB, mean IOP was  $32.8 \pm 6.19$  mmHg. A good correlation was observed between the axial length and intraocular pressure rise after 1 min i.e. Pearson correlation ( $r$ ) = -0.914 ( $p$ -value <0.001) with  $R^2 = 0.835$ .

**Conclusion:** There is significant rise in IOP after intravitreal injection of bevacizumab in patients with short axial length as compared to long axial length.

**Keywords:** Axial length, Diabetic macular edema, Intraocular pressure, Intravitreal bevacizumab.

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### INTRODUCTION

Diabetic macular edema (DME) is the main cause of visual impairment in diabetic patients, particularly type 2<sup>1,2,24</sup>. Its prevalence has been reported to be around 10%<sup>1,24</sup>. Diabetic maculopathy refers to the presence of any retinopathy at macula, but commonly reserved for significant changes, particularly vision-threatening edema and ischemia.

Intravitreal injection of 1.25 mg/0.05 mL of Bevacizumab (Avastin) is being used successfully for the treatment of diabetic macular edema<sup>4,17,24</sup>. Bevacizumab is a humanized full length monoclonal antibody that inhibits the function of vascular endothelial growth factor

(VEGF), a natural protein that stimulate angiogenesis<sup>17,24</sup>. Intraocular pressure rise is one of the established side effect of intravitreal injection of Bevacizumab (IVB)<sup>7,26</sup>. IOP is an important aspect in the evaluation of patients at risk from glaucoma. Intraocular pressure is mainly determined by the coupling of the production of aqueous humor and the drainage of aqueous humor mainly through the trabecular meshwork located in the anterior chamber angle. An acute rise in IOP has also been shown to decrease juxtapapillary retinal and optic nerve head blood flow proportionally to the quantitative rise in IOP. Various studies<sup>3,9,12</sup> have reported that all intravitreal injections lead to short term IOP spike that may range from a few mmHg up to 80 mmHg. Various methods have been used to prevent the IOP rise after intravitreal injections such as paracentesis, IOP

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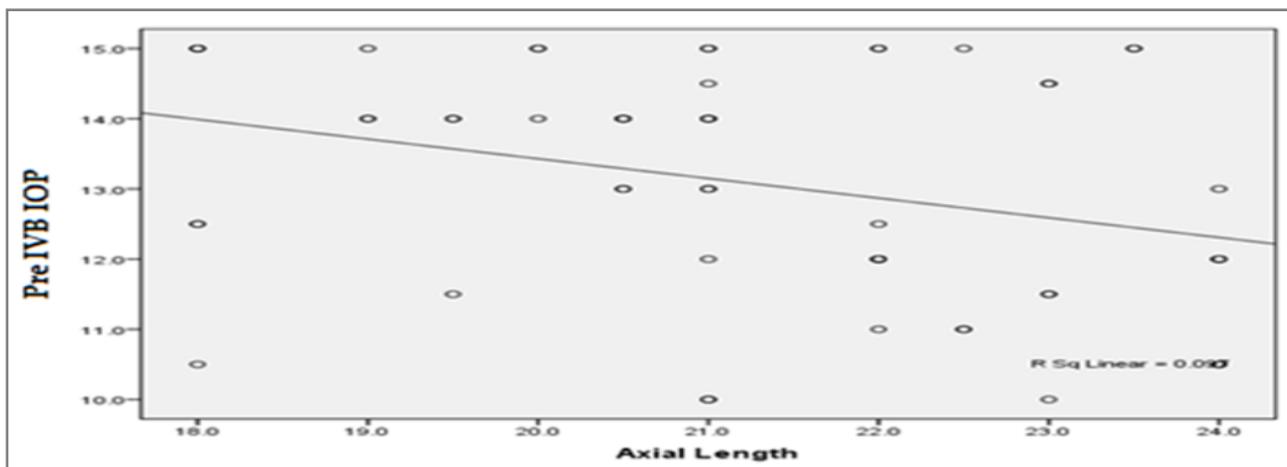
lowering medications and the use of medical devices, for example Honan IOP reducer. Some studies<sup>6,16,29</sup> recommend routine performance of paracentesis pre or post injection in all glaucoma patients in order to minimize the acute rise in IOP and to ensure that the full dose of bevacizumab remains in the vitreous cavity.

Studies<sup>27,28</sup> have shown that ocular anatomical features particularly eye size, as expressed by axial length measurement, presents a good indicator of expected intraocular pressure elevation after IVB. A study by A. Cacciamani et al revealed strong correlation between the axial length (AxL) and IOP elevation after both 1 (R2 = 0.752,  $p < 0.001$ ) and 15 min (R2 = 0.559,  $p < 0.001$ )<sup>5</sup>. The mean IOP change following IVB was  $21.92 \pm$

## PATIENTS AND METHODS

This cross-sectional study was conducted at Armed Forces Institute of Ophthalmology, Rawalpindi, from 20 September 2013 to 10 January 2014. Correlation calculator was used to calculate the sample size (Confidence Level: 95%,  $r$ : 0.752, Sample size= $n$ :55 patients)<sup>5</sup>. Newly diagnosed 55 eyes of diabetic macular edema patients, scheduled for IVB were included in the study. Sampling was done through consecutive non probability sampling. All patients had an open angle.

Patients having past history of intraocular surgery or trauma, laser photocoagulation or previous intravitreal injections, glaucoma, ocular hypertension, high myopes, corneal



**Figure-1: Correlation between Pre IVB IOP and axial length.**

Pearson correlation ( $r$ ) = -0.311 ( $p$ -value=0.021), R2 = 0.097

6.95 mmHg after 1 min and  $6.24 \pm 3.77$  mmHg. The mean axial length of the examined eyes was  $23.2 \pm 1.06$  mm.

No local data was available previously on the correlation of IOP changes and ocular axial length after administration of IVB<sup>8,19</sup>. The aim of our study was to investigate the relationship of IOP changes after IVB with different axial lengths in patients of diabetic macular edema among the Pakistani population. Our study was able to reveal that simple measurement of ocular axial lengths before the first IVB could provide useful information regarding the expected increase in IOP.

diseases or any other pre-existing ocular/retinal pathologies were excluded from the study. Following examinations were carried out; uncorrected distance visual acuity, corrected distant visual acuity, slit lamp bio-microscopy, fundus examination with 90 Diopter lens. DME was diagnosed by slit lamp bio-microscopy with 90D lens. Patients having any one of the following conditions were included in the study:

Retinal thickening within 500  $\mu$ m of the center of macula.

Exudates within 500 μm of the center of macula, if associated with retinal thickening which maybe outside 500 μm.

Retinal thickening one disc area (1500 μm) or larger, any part of which is within one disc diameter of the center of macula.

Axial length was measured preoperatively through IOL master (Carl-Ziess Meditec, AG 07740 Germany). IOL master uses the principle of partial coherence interferometry. Average of the three reliable readings was recorded for every patient.

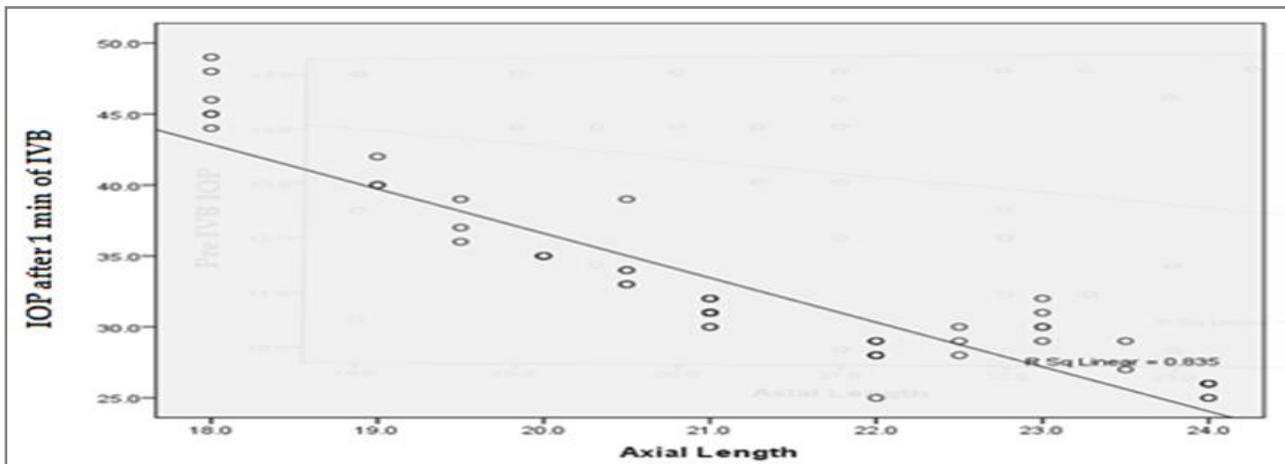
All IVBs were administered by the first author according to international guidelines. In brief, 10% povidone iodine was used as surface disinfectant. A sterile drape and a lid speculum

Same IOL master and Tono-Pen was used for measuring axial length and IOP and all measurements were taken by the first author.

Statistical analysis was performed using SPSS 14.0. Descriptive statistics was used to calculate mean and standard deviation for age, mean IOP after 1 min of injection and mean axial length. Frequency and percentages were evaluated for gender. Pearson correlation coefficient (r) in the range of (+1,-1) was calculated between mean axial length and mean IOP changes. A p-value ≤0.05 was considered statistically significant.

**RESULTS**

A total of 55 patients of diabetic macular edema received IVB during the study period.



**Figure-2: Correlation between “IOP after 1 minute of IVB” and Axial Length.**

Pearson correlation (r.) = -0.914 (p-value <0.001), R2 = 0.835

were applied. 1.25mg/0.05ml of bevacizumab (Avastin F.Hoffmann-La Roche Ltd Switzerland) was injected through Inferotemporal pars plana at 4mm away from limbus using 27 G needle. After removal of needle the injection site was temponaded with rigid sponge for 10-15 sec. Finally Moxifloxacin drops were instilled.

IOP was measured in the clino-static position before and immediately after the injection (within 1 min) using Tono-Pen AVIA Tonometer (Reichert USA). Tono-Pen was calibrated daily. Average of the three IOP readings was noted/recorded.

The mean age of patients was 54.51 ± 7.53 years with minimum age of 43 years and maximum age of 70 years. There were 26 (47.3%) male and 29 (52.7%) female patients. Statistics of Axial lengths, Pre-IVB IOP and Post-IVB IOP are given in table-I, II & III respectively.

Pearson correlation coefficient (Symbol r) is a measure of the linear dependence between two variables, ranging between +1 and -1; where 1 is total positive linear correlation, 0 is no linear correlation, and -1 is total negative linear correlation. In our study, a strong negative linear correlation was found between the axial length

and observed IOP changes after 1 min of IVB (fig-1 & 2).

**DISCUSSION**

Diabetic Macular Edema (DME) is the leading cause of severe vision impairment in patients with non-proliferative diabetic retinopathy in working age population worldwide<sup>10,23</sup>. The severity may range from mild and asymptomatic to profound loss of vision.

eyes. Levels of ocular VEGF are correlated with both the growth and permeability of new vessels. Intravitreal anti-VEGF agents such as bevacizumab is being used widely as a treatment for DME. Immediate short-term elevations of IOP after intravitreal bevacizumab are a known phenomenon. The main reason for IOP elevation is the sudden addition of fluid to the relatively small volume of vitreous cavity. Such elevations

**Table-I: Descriptive statistics of axial length (mm).**

	<b>Axial Length</b>
Mean	21.21
Std. Deviation	1.80
Range	6.0
Minimum	18.0
Maximum	24.0

**Table-II: Descriptive statistics of Pre IVB IOP.**

	<b>Pre IVB IOP</b>
Mean	13.09
Std. Deviation	1.62
Range	5.0
Minimum	10.0
Maximum	15.0

**Table-III: Descriptive statistics of IOP after I minute of IVB.**

	<b>IOP after 1 min of IVB</b>
Mean	32.8
Std. Deviation	6.19
Range	24.0
Minimum	25.0
Maximum	49.0

DME is a general term defined as retinal thickening within two disc diameters of the foveal center; it can be either focal or diffuse in distribution<sup>11,25</sup>. Diabetic macular edema is caused by excessive vascular permeability, resulting in the leakage of fluid and plasma constituents, such as lipoproteins into the surrounding retinal tissue which then accumulate within macula causing decrease in visual acuity<sup>13,14</sup>.

It has been well established<sup>15,21</sup> that vascular endothelial growth factor (VEGF) plays a vital role in promoting neovascularization and increased vascular permeability in diabetic

are usually transient. Many factors are likely to account for the variability of IOP spikes after intravitreal injection, including ocular anatomical features and surgical procedures including the volume of injected fluids, the amount of reflux after injection, the size of the injecting needle, the injection modalities and the subsequent scleral holetamponade<sup>5,23</sup>.

The observed changes in IOP in our study appeared to vary across the patients’ population and ranged from a minimum of 25mmHg to a maximum of 49mmHg.

In 2013, A Cacciamani et al reported that almost 75% of the variability of IOP changes after

injection is related to axial length. And according to their study an IOP change of about 5 mmHg might be expected for each mm of shorter axial length<sup>5</sup>. Our findings are consistent with the previously published data.

A study in 2013 by Kim et al reported that prophylactic administration of anti-glaucoma drugs prior to intravitreal anti- VEGF injection reduces the elevation in IOP<sup>20</sup>.

Hollands et al. evaluated the changes in IOP 2, 5 and 30 min after injection of 0.05 ml of bevacizumab and concluded that transient extreme IOP elevations may occur in majority of patients<sup>18</sup>.

A study in 2014 by Lemos-Ries et al showed that IOP increases after intravitreal injection of bevacizumab, reaching 50 mmHg or more in about one third of patients. A higher IOP is expected if subconjunctival reflux does not occur at all<sup>23</sup>.

Another study by Lee et al in 2016 revealed that the instant increase in IOP by intravitreal anti-VEGF injection led to a transient decrease in mean ocular perfusion pressure<sup>22</sup>.

It is difficult to quantify the volume of reflux after intravitreal injection. This volume of reflux definitely affects the short term IOP values assessed. The amount of reflux occurring after IVB depends on various factors, including baseline IOP, scleral rigidity, the degree of liquefaction of the vitreous and the presence of a posterior vitreous detachment. We should consider the fact that ocular anatomical features, such as high myopia associated with liquefaction of the vitreous, changes of scleral thickness and biomechanics, and the presence of a posterior vitreous detachment may cause lower IOP increases than expected after IVB. Higher scleral rigidity is a risk factor for IOP increases after IVB. In the same way, vitreous changes over age and as a consequence of multiple injections, which lead to liquefaction and posterior detachment of vitreous, may cause greater reflux after intravitreal injections.

Our study found higher correlation between IOP and axial length as compared to the other studies however, our study did not attempt to consider all the ocular parameters such as anterior chamber depth and lens thickness, which might affect the IOP spikes after IVB. In our study according to the inclusion criteria, all patients had an open angle and were phakic with no clinically significant cataract, but we did not measure anterior chamber depth prospectively. Thus, further studies are required to develop precise procedures to predict and prevent IOP rise and vitreous reflux after IVB.

## CONCLUSION

There is a significant relationship between IOP changes after IVB and difference in axial lengths in patients of diabetic macular edema. Thus prophylactic measures such as anterior chamber paracentesis or IOP lowering medications must be used before IVB injection to effectively reduce the IOP elevation in patients with shorter axial length.

## CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

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