

## ORIGINAL ARTICLE

## EFFECT OF INTRA VITREAL INJECTION OF BEVACIZUMAB ON INTRA-OCULAR PRESSURE

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**Background:** Bevacizumab has been in use as a therapeutic agent for macular oedema for several years. While its efficacy has been well documented, its use has been shown to cause a transient rise in the intra-ocular pressure. The aim of this study was to evaluate the long term effect of intra-vitreous injection of Bevacizumab on Intra-ocular pressure. **Methods:** One hundred eyes (n=100) of one hundred patients, requiring intra-vitreous injection of Bevacizumab for diabetic macular oedema were recruited from Shifa Foundation Community Health Centre (SFCHC) between January and December 2014. Patients of glaucoma, ocular hyper-tension, known allergy to Bevacizumab or had injections of Bevacizumab prior to the study were excluded. Intra-ocular pressure was measured using a Goldmann applanation tonometer, prior to, and at six and twelve months after the injection. The pre- and post- injection Intra-ocular pressure was entered into the database. Test of significance was applied to investigate whether there was a significant change in intra-ocular pressure after the injection. **Results:** The mean age of the patient was 56.97 years ( $\pm 14.97$ ). The mean intra-ocular pressure was 13.86 ( $\pm 3.16$ ) mmHg before injection, while post-injection mean Intra-Ocular pressure was 14.21 ( $\pm 3.12$ ) mmHg and 13.79 ( $\pm 3.07$ ) at six and twelve months respectively. Between baseline and six months there was a statistically significant difference in intra-ocular pressure ( $p=0.03$ ), while no significant difference existed in the intra-ocular pressure between baseline and twelve months ( $p=0.92$ ). **Conclusion:** Intra-vitreous injection of Bevacizumab is associated with a statically significant rise in intra-ocular pressure at six months, while no significant difference was seen at twelve months compared to baseline

**Keywords:** Bevacizumab, intra-ocular pressure, intra-vitreous, injection

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## INTRODUCTION

The primary treatment modality for managing complications of retinal vascular disorders, secondary to the release of the vascular endothelial growth factor, including diabetic retinopathy, hypertensive retinopathy, formation of choroidal neo-vascular membrane secondary to the effects of age, posterior segment inflammation and retinal arterial and venous vascular occlusion has been the use of various forms of photo-coagulative lasers like the diode, Argon and Frequency Doubled YAG laser.<sup>1</sup> However the use of thermal laser, in these disorders, is associated with serious ocular complications due to the loss of retinal tissue secondary to laser burns.<sup>2</sup>

This manifest itself as loss of visual function; both central visual acuity and visual field loss which adversely affects the quality of life of the patients.<sup>2,3</sup> Specific forms of complications of retinal vascular pathologies which lead to the development of choroidal neovascularization with or without associated intra-retinal neovascularization can be treated with non-thermal form of laser utilizing photodynamic therapy.<sup>4</sup> However while it may be possible to manage these conditions with this treatment modality, it only to stabilize vision and offers no improvement in visual function of the patients.<sup>4,5</sup>

Ranibizumab is now being used to manage a wide range of retinal vascular disorder and their associated complications. Though it is associated with a higher initial and recurring incurred cost to the patient, it results in improvement in the visual function.<sup>6</sup> This brings about direct economic benefit to the patient (and his or her family) in terms of being able to successfully continue working. Bevacizumab is an alternate form of anti-vascular endothelial growth factor treatment that is incurs comparatively lower end-user expense while producing results that are similar to the more expensive Ranibizumab.<sup>7-9</sup> While evidence shows that they are safe from the blinding effects associated with the use of photo-coagulative laser when used in treatment of retinal vascular disorder, the use of these drugs has been shown to be associated with a resultant, short-term in rise in intra-ocular pressure.<sup>10</sup> The purpose of our study is to investigate whether this short-term rise persists in patients receiving injections of Bevacizumab.

## MATERIAL AND METHODS

Approval for this study was taken from the institutional review board. The sample size was calculated using sample size calculator located at: <http://www.surveysystem.com/sscalc.htm>. Keeping confidence level of 95%, confidence interval of 5 and population of 130 (based on incidence of the

pathologies that cause vascular endothelial cell growth factor induced neo-vascularization) results in a sample size of 97. Based on this calculation, one hundred eyes of 100 patients were enrolled from Shifa Foundation Community Health Centre between January and December 2014. Inclusion criteria was a requirement of intra-vitreous injection of Bevacizumab for diabetic macular oedema, while the exclusion criteria included patients with glaucoma, ocular hyper-tension, known allergy or had prior injections of Bevacizumab. Patients with active ocular inflammation only eyed patients and patients with family history of glaucoma were also excluded.

A full disclosure of the study was made to the patients and informed consent was taken from them. Explanations concerning the drug, its route of administration, the procedure of administration as well as potential side effects were explained to the patient to his or her satisfaction. Explanation concerning the significance and measurement of Intra-Ocular Pressure (IOP) after the injection was provided to all the patients.

The IOP of the patients was measured using a Goldmann Applanation Tonometer (GAT) by a separate investigator who was blind to the study. Data was collected during morning hours to reduce the bias of time based variation of IOP. After proper sterilization of the GAT head, the eye was anesthetized with topical 1% Proparacaine eye drops. The tear film was stained using a commercially available Fluorescein dye strip. The pressure of the eye to be injected was then measured and recorded in millimetres of Mercury (mmHg). The IOP was measured prior to the injection, and then at six months and twelve months following the injection

Prepared, ready to use injection of the anti- Vascular Endothelial Growth Factor (anti-VEGF) agent Bevacizumab at a concentration of 1.25 mg/0.05 ml was used in all our patients. A 0.5% commercial preparation of proparacaine topical eye drops was instilled in the eye as anaesthesia. The eye and eyelids were disinfected with povidone solution. The drug was injected 4.0 mm posterior to the corneal limbus in the vitreous cavity in a sterile environment ensuring asepsis. Sterile cotton tipped applicator was used after the injection to prevent reflux. All patients were prescribed Moxifloxacin eye drops QID for five days. All the patients recruited for the study received one injection every 4 weeks for a total of 4 injections. The patients were asked to follow up for monitoring of IOP six months and at twelve months.

Univariate analysis (mean±standard deviation) was performed for age, IOP (pre-operative, at six months and at twelve months) and

for gender of all the patients. Frequency distribution and test of significance were applied to the data to see whether there was significant change in intra-ocular pressure after the injection.

## RESULTS

A total of 100 eyes of one hundred patients (67 males and 33 females) were enrolled in our investigation. The mean age of the patient was 56.97 years (±14.91). The mean age, pre- and post- injection IOP at six and twelve months is shown in table-1.

Table-2 lists the complications seen after injection in the patients. The most common complication was reactive hyperaemia of the conjunctiva. No sight threatening complications were observed in the patients.

There was no significant difference in the ages of male and female population in this study ( $p=0.1$ ).

The mean intra-ocular pressure was 13.86±3.16 mmHg before injection, while post-injection mean IOP was 14.21±3.12 mmHg and 13.79±3.07 at six and twelve months respectively.

Paired t-test was used to analyse the pre- and post- injection IOP data. The level of significance was set at 5%;  $p<0.05$  was taken to be significant.

Between baseline and six months there was a statistically significant difference in intra-ocular pressure ( $p=0.03$ ), while no significant difference existed in the IOP between baseline and twelve months ( $p=0.92$ ). The IOP was higher six months after injection as compared to baseline (13.86±3.16 mmHg vs 14.21±3.12 mmHg). At twelve months the IOP was comparable to baseline, pre-injection IOP (13.86±3.16 mmHg vs 13.79±3.07).

**Table-1: Mean age, pre- and post- injection Intra-ocular pressure in patients**

Mean Age	Pre-Injection intra-ocular pressure	Intra-ocular pressure at six months	Intra-ocular pressure at twelve months
56.97±14.97	13.80±3.16	14.21±3.12	13.79±3.08

**Table-2: Complication after intra-vitreous injection of Bevacizumab**

Complication	Frequency	Percentage (%)
Subconjunctival haemorrhage	31	64.58%
Conjunctival chemosis	14	29.17%
Drug reflux	3	6.25%

## DISCUSSION

The study was carried out to explore the long term outcomes on IOP of intra-vitreous injection of Bevacizumab. To our knowledge this is the only study originating from this region that studies the impact of this drug on IOP, in the long term, on patients receiving injections for diabetic macular oedema.

Bevacizumab has been in use for several years for treatment of many retinal vascular disorders.<sup>11-14</sup> Initial reports on their use did not always include the association of injection to a rise in intra-ocular pressure.

We saw a statistically significant rise of the IOP in our patients at six months as compared to the base line IOP. Rise in IOP after multiple injections of Bevacizumab have been reported in literature in patients with no history of glaucoma.<sup>15</sup> Our findings are in agreement with this study; all our patients received four injection at 4 weeks interval.

Literature review reveals that the evidence regarding delayed elevation of IOP after injection(s) of Bevacizumab is disparate.<sup>15-18</sup> The rise in IOP, at times, is correlated to the number of injections received<sup>15,16</sup>, and at other times this has shown not to be the case<sup>17,18</sup>.

The majority of the evidence, however, shows no delayed rise in IOP or over-all elevation of the intraocular pressure after injection of Bevacizumab.<sup>19-22</sup>

Our study is in agreement with the results of these investigations. We noticed that the IOP was comparable to the baseline, pre-injection IOP at twelve months. None of our patients required any medication to control IOP after the injections; the post injection rise seen at six months was still within the normal acceptable range for IOP. There have been occasions where surgical intervention has been required to control IOP after injection.<sup>18</sup>

No cause has yet been determined for rise in IOP seen after anti-VEGF injections. However several hypotheses have been put forward. Out-flow channel obstruction has been assumed to cause a rise in IOP.<sup>23</sup> Other hypothesis include underlying inflammatory response<sup>24</sup>, trauma (in the form of disruption of anterior vitreous face) due to repeated injections<sup>25</sup>, implication of syringes<sup>26</sup> and silicone used to lubricate these syringes<sup>27</sup>. It has been shown that patients receiving  $\geq 29$  injections were at a greater risk of developing a rise in IOP.<sup>28</sup> This rise in IOP is blind to the drug received; it is seen in patients who receive Ranibizumab instead of Bevacizumab for retinal vascular disorders.<sup>29</sup> This implies a common end-point mechanism for rise in IOP after injection of either anti vascular endothelial growth factor drug. Injection techniques have also been implicated in the IOP rise seen after injections.<sup>30</sup> A scleral tunnelled is associated with a significantly greater rise in IOP. All our patients received the drug through a non-tunnelled straight scleral injection.

Patients who exhibit a higher reflux at the site of injection have a lower tendency to develop a raised IOP.<sup>31</sup> This is probably due to an over-all reduction or maintenance of vitreous volume

following the injection, but can only explain short-term changes in IOP associated with anti-VEGF injections.

The complications seen in our patients are listed in table-2. Conjunctival hyperaemia at the injection site was the most common observed complication. This did not require any intervention and settled on its own. None of the complications observed in our study were sight threatening. These are largely posterior segment complications and have been reported in the literature.<sup>32</sup> Patient factors, sample size, indications for injection are predictors for complications seen in patients.

## CONCLUSION

There is a statistically significant rise in IOP after an intra-vitreous injection of Bevacizumab at six months which is not seen at twelve months. The Intra-ocular pressure is comparable to baseline at this point in time. Clinicians should be alert to this fact and in light of the findings of our study offer a prophylaxis to their patients or aggressively manage the IOP if the rise is persistent.

## AUTHOR'S CONTRIBUTION

SJ, AT, ZIM conceived the study design, supervised the study, write up and proof reading. AM, RN did data collection and statistical analysis.

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