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Original Article

Effect of Intra Vitreal Injection of Bevacizumab on Intra-Ocular Pressure.

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Abstract

Background **To evaluate the effect of intra-vitreal injection of Bevacizumab on Intra-ocular pressure**

Methods: **In this descriptive study sixty six patients who required intra-vitreal injection of Bevacizumab were enrolled. Patients with prior history of glaucoma, ocular hyper-tension, known allergy to Bevacizumab or who had prior injections of Bevacizumab were excluded from the study. Intra-ocular pressure was measured in the eye, using a Goldmann applanation tonometer, prior to the injection and for the purpose of this study seven days after the injection. The pre- and post- injection Intra-ocular pressure was entered into the database.**

Results: **The mean age of the patient was 56.97 years (±13.805). The mean pre-injection intra-ocular pressure was 13.86 (±3.656) mmHg, while post-injection mean IOP was 15.43 (±5.498) mmHg. There was a statistically significant rise in intra-ocular pressure after injection of Bevacizumab (p=0.01).**

Conclusion: **Intra-vitreal injection of Bevacizumab is associated with a statistically significant rise in intra-ocular pressure.**

Key Words: **Bevacizumab, Intra-ocular pressure, Intra-vitreal, Injection**

Introduction

The treatment of retinal vascular disorders associated with neo-vascularization has traditionally been managed with some form of laser treatment.[1] Use of this form of treatment results in retinal tissue death which while reducing growth of neo-vascularization also diminishes visual function[2]. The treatment of other retinal disorders where photo-coagulation was employed to reduce vascular leakage like macular edema secondary to diabetes, vascular occlusion and vasculitis also produces some reduction in patient's quality of vision[3]. Wet age related macular degeneration has also been managed with photo-coagulative laser therapy[4] as well as photodynamic therapy.[4,5] Laser therapy was employed to control the spread of the disease[6] while photodynamic therapy tended to stabilize the disease process often resulting in marginal improvement or stasis of visual function.[6,7] Monoclonal antibody, Ranibizumab, targeting neo-vascular membrane in wet age-related macular degeneration not only stabilizes the disease process but also regresses the neo-vascularization resulting in significant improvement in vision[8]. However the prohibitive cost of treatment of treatment has kept the wide spread acceptance of treatment not only in developing but developed world as well.[9] A closely related drug to Ranibizumab is Bevacizumab which is used for metastatic colo-rectal tumors.[10] This drug has also been in the eye via an intra-vitreal route for controlling neo-vascularization of retinal or choroidal origin as well as reduced visual function secondary to macular edema.[11,12] The clinical outcomes of both of these drugs have been reported to be similar.[13] Recent reports reveal that use of either of these drugs can result in rise in intra-ocular pressure.[14]

Patients and Methods

A total of 66 eyes of 66 patients were recruited from the out patients department of Shifa Foundation Community Health Center between January and December 2012. Inclusion criteria for recruitment was any applicable indication for injection of Bevacizumab, while the exclusion criteria included patients with prior history of glaucoma, ocular hyper-tension, known allergy to Bevacizumab or had prior injections of Bevacizumab. Patients with active ocular inflammation only eyed patients and patients with family history of glaucoma in first degree relatives were also excluded from the study.

Goldmann Applanation Tonometer was used to measure intra-ocular pressure (IOP) in all the patients by a single investigator who was blind to the study during morning hours to reduce the bias of time based variation of intra-ocular pressure[15]. After proper sterilization of the GAT head, the patient was seated comfortably in front of the slit lamp. The eye to be examined was anesthetized with topical 1% procaine

eye drops. The tear film was stained using a commercially available fluorescein strip. The patient was then asked to blink twice so as to uniformly spread the fluorescein dye. The pressure of the eye under examination was then measured. A total of three readings were taken and the average recorded.

The intra-vitreal injection of Bevacizumab was obtained in a prepared form (diluted to proper strength) for use in our patients. A dose of 1.25mg/0.05ml of Bevacizumab was used in all our patients. Proparacaine (0.5%) topical eye drops were instilled in the eye as topical anesthesia. The eye and eyelids were disinfected with povidone solution. The drug was injected 4.0mm 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 patients were asked to follow up 1 week after the injection for measurement of IOP in a manner similar to what has been described above.

Results

A total of 66 eyes of sixty six patients (40 males and 26 females) were recruited for this study. The mean age of the patient was 56.97 years (±13.805),with a range of 3 to 82 years. Most common indication being clinically significant macular edema associated with diabetes mellitus (n=53), while the least common indication was Neo-vascular glaucoma associated with vein obstruction (n=1) (Table 1).Reactive conjunctival hyperemia was by far the most common complication (Table 2). The pre-injection mean IOP was 13.86 (±3.656), while post-injection mean IOP was 15.43 (±5.498) mmHg. Paired t-test was used to analyze the pre- and post- injection IOP data. The level of significance was set at 5%; p <0.05 was taken to be significant.The pre- and post- injection IOP was found to be significantly different (p=0.01), with the post injection IOP being higher (Table 3).

Table 1: Indications for intra-vitreal injection of Bevacizumab

Indication	No(%)
Macular edema associated with diabetes mellitus without proliferative changes	53(80.3)
Proliferative diabetic retinopathy	5(7.5)
Wet Age Related Macular Degeneration	4 (6.0)
Macular edema associated with venous obstruction	3(4.5)
Neo-vascular glaucoma secondary to venous obstruction	1(1.5)

Table 2: Complication after intra-vitreal injection of Bevacizumab

Complication	No(%)
Subconjunctival hemorrhage	23(34.8)
Conjunctival chemosis	10(15.1)
Drug reflux	2(3.0)

Table 3: Mean pre- and post- injection Intra-ocular pressure in patients

	Pre-injection Intraocular pressure in mmHg	Post-injection Intraocular pressure in mmHg
Mean	13.86	15.43
Std. Deviation	3.656	5.498
Minimum	7	7
Maximum	23	33

Discussion

Bevacizumab has been in use for several years for treatment of many retinal vascular disorders.[16-19] Initial reports on their use did not always include the association of injection to a rise in intra-ocular pressure. We report a statistically significant (p=0.01) rise in intra-ocular pressure in our study population one week after an injection of Bevacizumab. Adelman reported a persistent rise in intra-ocular pressure after injection of Bevacizumab in patients with no prior history of glaucoma or ocular hypertension.[20] They reported that most of their cases developed a persistent rise after multiple injections. Our findings are in agreement with those of Adelman with the stipulation that in our patients the rise was seen after a single injection.

The delayed rate of intra-ocular elevation has also been investigated.[21] Contrary to early rise in intra-ocular pressure as shown in our study, this study shows that a delayed elevation of IOP does not occur after injections of Bevacizumab. Factor behind the rise of IOP after injecting Bevacizumab have been looked into as well.[22.] Their study shows that patients receiving ≥29 injections were at a greater risk of developing a rise in IOP as compared to patients ≤12 injections.

The rise in IOP has also been seen in patients who receive Ranibizumab instead of Bevacizumab for retinal vascular disorders[23]. This implies a common

end-point mechanism for rise in IOP after injection of either anti vascular endothelial growth factor drug. One explanation given for the rise in IOP is the variation in injection technique. It has been shown that a tunneled scleral injection is associated with a significantly greater rise in IOP[24]. Tunneled injections are employed to prevent reflux after injection[25]. All our patients received a straight scleral injection and we noticed a significant rise in IOP after the injection. Perhaps the rise in IOP would have been of a greater magnitude if we had employed a tunneled technique.

Another variable that has been shown to be responsible for rise in IOP is reflux at the injection site after the injection. It has been shown that patients with greater reflex have a lower tendency to develop a raised IOP as compared to patients in whom the reflux was smaller[26]. We did not observe nor categorized the reflux in our patients and as such cannot comment on how this related to patients in our study.

Although the volume of the vitreous does increase after the injection of Bevacizumab the rise in IOP caused by this alone is reported to transient dropping to near pre-injection levels with an hour after the injection[27]. We noticed a persistent rise in IOP at one week interval that cannot be explained alone on the basis of a rise in volume of the vitreous. The packaging and disbursement of the drug has also been implicated, but not proven to be causative in the rise of IOP[28].

In all our patients the rise in IOP was controlled with topical administration of topical aqueous suppressants. They have been shown to be effective in controlling rise in IOP after intra-vitreal injections[28]. In rare cases trabeculectomy surgery has also been carried out to control a persistent rise in IOP[29]. None of our patients required surgery for return to normal levels of IOP. Combination of an alpha-agonist and beta-blocker has been shown to be effective in prophylaxis of IOP rise associated with injections of Bevacizumab[30].

Bevacizumab was initially employed for use in wet ARMD, it now sees wide spread use in many retinal and even anterior segment ocular pathologies[31]. Our indications were limited to posterior segment pathologies which correlate well with those of other locally published results[32].

In present study conjunctival hyperemia was a common complication, though it was transient and resolved on its own without sequlae. No treatment was required for other complications as well; all of them settled on their own. In our study we did not experience posterior segment complications which have been reported in literature.[33] Patient factors, sample size, indications for injection are predictors for complications seen in patients. A regional study by Fasih et al also noticed a majority of anterior segment complications and vitreous hemorrhage in one patient (n=150). [32]

Conclusion

There is a statistically significant rise in IOP after an intra-vitreal injection of Bevacizumab. Clinicians should be alert to this complication and in light of the findings of and quoted in our study offer a prophylaxis to their patients or aggressively manage the IOP if the rise is persistent.

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