ORIGINAL ARTICLES

MEASUREMENT OF INTRAOCULAR PRESSURE FOLLOWING 0.05 ML (1.25MG) INTRAVITREAL INJECTION OF BEVACIZUMAB (AVASTIN) TO DETERMINE THE RATIONALE OF USING POST-INJECTION IOP LOWERING MEDICATION

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ABSTRACT

Objective: To determine the change in intraocular pressure in eyes injected with 0.05 ml of intravitreal Bevacizumab (Avastin) to ascertain the need of prescribing post injection IOP lowering medications.

Type of Study: A quasi-experimental study.

Place and duration of study: Armed Forces Institute of Ophthalmology, from Jan 2010 to April 2010.

Patients and Methods: Fifty two eyes of 47 patients who were given 0.05 ml (1.25 mg) of intravitreal Avastin for retinal diseases reporting at Armed Forces Institute of Ophthalmology Rawalpindi, were included in the study. The IOP was checked prior to injection, 24 hours post injection and at 7 days on air puff computerized konometer (Topcon ct-80) to rule out operator bias and other factors like sclera rigidity. Reflux during injection was noted. All patients were given post injection antibiotic drops only. Topical steroids and topical / systemic anti glaucoma medications were not given. Patients with glaucoma and vitreous hemorrhage were excluded.

Results: Baseline mean IOP was 16.05 mm Hg, with range from 8 mm Hg to 23 mm Hg. At 24 hour post injection, 20 (38.5%) eyes showed no or ±1 mmHg change from pre injection IOP, 22 (42.3%) showed an increase of ≥2mmHg, while 10 (19.2%) eyes showed a decrease in IOP of ≤2 mmHg. On 7th day, 18 (40.0%) eyes showed either no change from pre injection reading of IOP or the change was +/- 1 mm of Hg. Fourteen patients (31.1%) had a rise of 2 mm Hg or more, 13 (25.0%) had a decrease of 2 mmHg or more as compared to pre injection reading out of which 6 (13.63%) eyes were those in which reflux had occurred.

Conclusion: Topical IOP lower agents are given routinely for 2 weeks post injection.. Our result showed significant difference in IOP 24 hour post injection but the results were not significant for 7th day. Based on our results it was suggested that long term post injection anti glaucoma agents are not required except in known cases of glaucoma.

Keywords: Intraocular pressure, Bevacizumab, Intravitreal injection.

INTRODUCTION

Ocular neovascularization and increased vascular permeability have been associated with Vascular Endothelial Growth Factor (VEGF), a diffusible cytokine that plays a key role in the process of normal and pathologic angiogenesis[1]. Animal studies have demonstrated that VEGF expression is able to promote neovascularization in the eye, whereas its inhibition reduces its effect. In addition, the presence of VEGF is temporally and spatially correlated with ocular angiogenesis in the primate model. Increased intravitreal levels of VEGF have been observed in many retinovascular diseases such as proliferative diabetic retinopathy, age-related macular degeneration, retinopathy of prematurity and retinal vein occlusion.

One possible therapeutic approach to the development of abnormal blood vessels in proliferative diabetic retinopathy and central retinal vein occlusion, choroidal neovascularization secondary to age related macular degeneration, and macular edema

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associated to various retinovascular diseases is to inhibit VEGF activity with a VEGF-blocking drug.

Bevacizumab (Avastin; Genentech) is a full-length humanized murine monoclonal antibody against VEGF approved by the Food and Drug administration for treating metastatic colorectal cancer. It is usually administered intravenously, and stops tumour growth by preventing angiogenesis.

Intravitreal Bevacizumab has been described for the treatment of proliferative diabetic retinopathy complicated by vitreous hemorrhage[2], macular edema in central retinal vein occlusion[3], and neovascular age-related macular degeneration[4]. Initial treatment results showed a significant regression of neovascularization, decrease in macular edema, and improvement in visual acuity. However till now this is an "off label" use of Avastin not yet approved by FDA for intravitrteal use. Like all intravitreal injections Avastin when given intravitreally cause an acute volume based rise in IOP. Few studies carried in this regard[5,6] concluded that this acute rise in IOP was transient and did not cause any subsequent damage. However our study was aimed to ascertain if there was a sustainable rise in IOP following intravitreal injection of Avastin and if there was a rationale to prescribe topical / systemic IOP lowering agents post injection.

PATIENTS AND METHODS

Our study included 52 eyes of 47 patients who were given 0.05 ml (1.25 mg) of intravitreal Avastin for retinal disorders. The patients included were those with diabetic retinopathy, choroidal neovascularization, central / branch retinal vein occlusion and Eale's disease. Forty four eyes were given the first injection while 8 eyes had already been injected previously but not less than 4 weeks gap. Patients excluded from the study were those who were known cases of glaucoma, patients with an IOP reading of 24mm Hg or more prior to injection and those with vitreous haemorrhage.

After patient selection and registration, the IOP was checked prior to giving the injection on air puff computerized tonometer (Topcon ct-80). The patient was prepared for intravitreal injection under stringent aseptic conditions. The area around the eye was cleaned with 10% povidone iodine and spirit after which it was draped. Povidone iodone 5% solution was instilled in the eye through a canula. The eye was then washed with balanced salt solution. Avastin 0.05 ml (1.25 mg) was then injected in the suprotemporal quadrant with a 27 gauge insulin syringe. The site was pinched with toothed forcep as soon as the needle was released to prevent reflux. Any reflux was noted and put on record. An antibiotic drop was instilled at the end. None of the eyes were padded post injection and the patient was prescribed an antibiotic drop only. No topical steroids or topical / systemic IOP lowering agents were prescribed. The patient's were advised to report next day.

The patients were examined on slit lamp after 24 hours of injection to look for any signs of inflammation in the anterior chamber. The IOP was taken on air puff computerized tonometer (Topcon ct-80) and readings were noted. The patients were advised to continue topical antibiotic drops and report to OPD after 06 days. In case of signs of inflammation in anterior chamber topical steroids were started and the patient's name was removed from the study.

The same protocol was followed on 7th day of followup and the IOP reading was noted. The topical antibiotic drops were discontinued and the patient was briefed regarding further treatment and followup of his retinal disorder. IOP in 8 eyes could not be recorded as those patients did not report for followup on 7th post injection day.

RESULTS

A Total of 52 eyes were included in the study out of which 5 patients had injection in both eyes. The average age of the patients was 58 years. There were 32 male and 15 female patients. The average age of the patients was 58 years. Out of 52 eyes injected, 29 had diabetic retinopathy with clinically significant macular

oedema, 11 had choroidal neovascularization, 4 had cental retinal vein occlusion, 5 had branch retinal vein occlusion, 2 were suffering from Eales' disease and one patient has a pigment epithelial detachment. All the patients reported next day for IOP checkup but 6 patients did not report for followup after 7 days.

Table-1: Age of patients

Min	Max	Average
22 years	78 years	58 years

Table- 2: Diagnosis

DME	CNV	CRVO	BRVO	Eales Disease	Other
29	11	4	5	2	1

Table- 3(a): Pre Injection IOP

Min	Max	Average
8	23	16.1

The variables (pre-injection IOP, 24 hour post injection IOP and 1 week post injection IOP) were normally distributed and hence Paired t-test was applied to assess the difference in intra-occular pressure before and after intravitreal injection.

Mean difference between pre-injection IOP and 24 hour post injection IOP was 1.01 (3.48) and this difference was found to be significant at 5% level of significance (p=0.04). The mean difference between pre-injection IOP and 1 week post injection IOP was -0.22 (3.25) but this difference was not significant at 5% significance level (p=0.964).

Pre-op IOP ranged between 8 and 23 mm of Hg with an average IOP of 16.05 mm of Hg. Reflux occurred in 8 (15.38%) eyes and was noted as a factor that would cause a volume based decrease in IOP. Two eyes developed subconjuctunctival haemorrhage and both the patients were removed from the study.

At 24 hour post injection, 20 (38.5%) eyes showed no or ±1 mmHg change from pre injection IOP, 22 (42.3%) showed an increase of ≥2mmHg, while 10 (19.2%) eyes showed a decrease in IOP of ≤2 mmHg. The maximum rise in IOP at 24 hours was noted to be 10 mm of Hg which remained at that level on 7th day. Eight eyes showed a rise of 5 mm Hg or more but the IOP was within normal limits except for one eye (which was started on topical anti glaucoma medication). Out of the 10 (19.2%) eyes that showed a decrease in IOP, a decrease of ≤-5mmHg was noted in only 2 eyes. Among them only 2 eyes were those in which reflux had occurred.

One week post injection, IOP measurements could not be taken for 7 eyes hence the calculations were done on 45 instead of 52 eyes. On 7th day, 18 (40.0%) eyes showed either no change from pre injection reading of IOP or the change was +/- 1 mm of Hg. Forteen (31.1%) had a rise of 2 mm Hg or more. The maximum rise in IOP on 7th day was 2 mm of Hg more than the reading at 24 hours post injection. Thirteen (25.0%) eyes had a decrease of 2 mmHg or more as compared to pre injection reading.

Out of 8 eyes that had reflux, the average decrease in IOP due to volume loss at 24 hours was 2.87 mm Hg (with a maximum decrease of 11 mm Hg) and on 7th day it was 1.33 mm Hg. The maximum decrease in IOP was 9 mm Hg at 24 hours which returned to a (-) 3 mm Hg change at 7th day as compared to baseline reading.

DISCUSSION

Intravitreal injections of air were first used in 1911 for the purpose of repairing retinal detachments[7]. Since that time, intravitreal injections have been used for treatment of a variety of conditions, including endophthalmitis, submacular hemorrhage, vitreous hemorrhage, neovascular age-related macular degeneration (AMD) and diabetic retinopathy. The primary benefit of intravitreal injection is that the therapeutic agent is targeted in the eye while minimizing systemic absorption.

Enhanced use of intravitreal injections in the early 2000s was fueled by clinical trials and technology assessments demonstrating the safety and effectiveness of antivascular endothelial growth factor (VEGF) agents for the treatment of neovascular AMD. Agents

approved by the FDA for intravitreal injection to treat neovascular AMD include ranibizumab (Lucentis: Genentech, South San Francisco, CA) and pegaptanib sodium (Macugen; Eyetech Pharmaceuticals, New York, NY). In addition, intravitreal bevacizumab (Avastin: Genentech, South San Francisco, CA) is used widely in an off-label application for treatment of above mentioned clinical conditions since 2005. As it is of much lower cost than either Lucentis and Macugen (FDA approved anti-VEGF), it is being widely used specially in our setup as our patients are unable to afford the other expensive anti VEGF agents.

There is individual variation in IOP elevation after the injection of the same amount of drug. This variation is due to relative inaccuracy of dosing exactly the intended amount in a clinical setting. In addition, scleral rigidity differs between patients. Another source of variation is whether there is reflux from the injection site after the needle is withdrawn[8,9]. Larger needles may allow more reflux from the injection site, and therefore a lower immediate IOP. We used 29-gauge needles to inject bevacizumab to minimize the chances of reflux in line with a study carried out in Canada in 2007 to assess the immediate change in IOP following intravitreal injection of Avastin[9]. Another study describes the IOP fluctuations in 38 eyes after intravitreal triamcinolone[10], but the authors did not separate patients into groups depending on whether they had glaucoma. A 2007 national survey in the United Kingdom found that the rate of severe IOP increase following intravitreal injection of triamcinolone acetonide was 1.1% (45/3899), necessitating either laser or surgery to control IOP[11]. As seen in studies carried out to assess the acute rise in IOP following intravitreal injection it was seen that Intravitreal Avastin is safe with respect to short-term IOP changes, as almost all patients' IOP returned to a safe range (<25 mm Hg) within 30 minutes[9].

Table-3(b): 24 Hours post injection IOP

Change less than ± 2 mm Hg n(%)	Increase by 2 mm Hg or moren(%)	Decrease by 2 mm Hg or moren(%)	Average change in IOP
20 (38.5)	22 (42.3)	10 (19.2)	1.01 (± 3.48)

Table-3(c): 7 days post injection IOP (N= 45)

Change less than +/- 2 mm Hg n(%)	Increase by 2 mm Hg or more n(%)	Decrease by 2 mm Hg or more n(%)	Average change in IOP n(%)
18 (40.0)	14 (31.1)	13 (28.9)	(-) 0.02 (±3.25)

Table-4: Reflux Factor at 24 hours reading (8 eyes)

Change less than +/- 2 mm Hg	Increase by 2 mm Hg or more	Decrease by 2 mm Hg or more	Average change in IOP
1 (12.5%)	2 (25%)	5 (62.5%)	(-) 2.75

Currently used intravitreal drugs for the treatment of retinal diseases include triamcinolone acetonide (Kenalog-40, Bristol-Myers Squibb, Peapack, NJ, USA), pegaptanib sodium (Macugen, Eyetech-OSI, New York, USA), bevacizumab (Avastin, Genenetech, San Francisco, CA, USA), and ranibizumab (Lucentis, Genentech, San Francisco, CA, USA). The most commonly used doses are 0.1 ml (4 mg) of triamcinolone, 0.09 ml (0.3 mg) of pegaptanib, 0.05 ml (1.25 mg) of bevacizumab, and 0.05 ml (0.5 mg) of ranibizumab. Injecting fluid into the eye transiently increases the intraocular pressure (IOP). The current recommendation for performing intravitreal injections advises against performing a paracentesis[12]. However, in patients who suffer from glaucoma or optic nerve damage, there is a concern that a transient high IOP elevation may further damage the ganglion cells in the

optic nerve. It is important to know the transient IOP elevations that patients are subjected to after such intravitreal injections for several reasons, such as to assess whether a paracentesis is necessary, whether IOP monitoring is necessary after the procedure, and to reassess, when manufacturing a new drug, the optimum amount of fluid to be injected into the eye.

Additional infrequent complications include hypotony, sustained increase in IOP after injection with triamcinolone acetonide, angle closure, hemiretinal vein occlusion, retinal pigment epithelial tears, iritis/uveitis, optic disc atrophy, corneal epitheliopathy, maculopathy, and anaphylactic reaction to the agent injected in the vitreous[13-16].

CONCLUSION

Our study was aimed at assessing the changes in IOP in longer duration upto 1 week, to justify the need for prescribing topical IOP lowering medications in every patient. However based on the results it is suggested that there is no indication of topical or systemic IOP lowering medications in patients injected with 0.05 ml of intravitreal Avastin except for those who have glaucoma. Close monitoring of patients undergoing intravitreal injections is however imperative. Considering the magnitude of intravitreal use of this drug it is suggested that further prospective studies are needed to verify the results and better understand the implications of these findings.

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