

Ocular Complications of Intravitreal Bevacizumab in Posterior Segment Diseases

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Abstract

Background: To study the rate of different complications of intravitreal Bevacizumab while treating patients of different posterior segment diseases.

Methods: A prospective study of 60 patients having different retinal diseases like diabetic retinopathy, wet age related macular degeneration (AMD), retinal vein occlusion (RVO), was carried out. Patients were given intravitreal Bevacizumab injection under full sterile conditions in operation theatre. The patients were rechecked during their follow up visits for the known complications of intravitreal injection i.e. subconjunctival haemorrhage, cataract, endophthalmitis, uveitis, rise of intraocular pressure (IOP), rhegmatogenous retinal detachment and vitreous haemorrhage.

Results: A total of 60 patients (60 eyes), 20 males and 40 females, having age range 40-65 years, were included in the study. There were 25 eyes (41.7%) with diabetic macular edema (DME) with non-proliferative diabetic retinopathy, 20 eyes (33.3%) with proliferative diabetic retinopathy (PDR) with or without diabetic macular edema, 10 eyes with wet AMD (16%) and 5 RVO (8.3%). Post-intravitreal complications were sub-conjunctival haemorrhage in 20 eyes (19.6%), raised IOP in 3 (2.9%), cataract formation in 2 eyes (1.9%), endophthalmitis in 1 eye (0.9%). No case of rhegmatogenous retinal detachment, retinal pigment epithelial detachment, retinal tear, uveitis, central retinal artery occlusion and vitreous haemorrhage was seen in our study.

Conclusion: The complications are negligible if good disinfection and proper technique is observed

Key Words: Intravitreal Bevacizumab, Posterior Segment Diseases

antibody against VEGF-A that is used widely off-label to treat these diseases.² Because it is not provided by the manufacturer in individual doses, it is routinely aliquoted into ready-to-use syringes by compounding pharmacies or at the institution of administration.² The drug acts by reducing the size and number of new vessels.³

Currently, several anti-VEGF drugs, including Pegaptanib, Ranibizumab, Bevacizumab, and Aflibercept, are available.^{2, 3} Intravitreal injection of anti-vascular endothelial growth factor (anti-VEGF) agents has revolutionized the treatment of common retinal diseases including neovascular age-related macular degeneration, diabetic retinopathy, and retinal vein occlusions^{4,5}. Encouraging results were reported with intravitreal injection of anti-VEGF agents for other ocular diseases, such as neovascular glaucoma, retinopathy of prematurity (ROP), and intraocular tumors.^{4,5}

Intravitreal anti-VEGF therapy is not without risks. The systemic administration of Bevacizumab had the potential to cause systemic side effects, that's why, instead of systemic administration, local administration of this drug spread worldwide so rapidly.⁸ However, not only the potential ocular adverse events like endophthalmitis, retinal detachment, retinal tear, vitreous haemorrhage, raised intraocular pressure (IOP), central retinal artery occlusion and lens damage but also the possible drug-related systemic adverse events including hypertension and cerebral vascular accidents have been reported recently.^{6,7,8,9,10} Although well-designed randomized clinical trials have shown the effectiveness of these agents in various retinal diseases, each intravitreal injection poses the risk of post-injection adverse reactions.¹¹

Introduction

Neovascularization of the choroidal and retinal tissues are the leading cause of blindness in developed countries.¹ Vascular endothelial growth factor (VEGF) has been identified as a major angiogenic stimulus of neovascularization.¹ Bevacizumab is a full monoclonal

Patients and Methods

This descriptive study was carried out at Benazir Bhutto hospital Rawalpindi from 1st Jan 2014 to 31st Dec 2014. A total of 60 eyes were enrolled in the study. These eyes received one intravitreal injection of Bevacizumab each. Inclusion criteria encompasses

patients of any age and any gender, proliferative diabetic retinopathy with or without diabetic macular edema, diabetic macular edema with non-proliferative diabetic retinopathy, choroidal neovascularization (wet AMD) and retinal vein occlusions. Any ocular conditions, presented along with the diseases of inclusion criteria, which can affect the vision and safety, like glaucoma, uveitis, retinal dystrophies, patients already having findings which are mentioned as complications, patients not giving consent were exclusion criteria. Baseline assessment included anterior segment examination using a slit lamp, intraocular pressure measurement with Goldman applanation tonometer, dilated fundus examination using slit lamp with +90 diopters lens and indirect ophthalmoscope with +20D lens. An authentic pharmacy prepared 1.25mg (0.05 ml) injections(in an insulin syringe for each patient) from commercially available 4 ml vial of Bevacizumab (25mg/ml) under aseptic techniques was given. Intravitreal injections were given in operation theater under full aseptic measures. The eye was draped and topical anesthesia was administered using proparacaine hydrochloride 1% ophthalmic drops. The site of the injection was measured with the help of a caliper. Using a 29 –gauge needle, 0.05ml of Bevacizumab was injected intravitreally through the pars plana, 4mm from the limbus in phakic, 3.5 mm in pseudophakic and 3mm in aphakic eyes. After injection, needle was taken out followed by immediate pinching of entry site with an artery forcep for few seconds to prevent any regurgate. After the injection, slit lamp examination was performed and intraocular pressure was measured. Patients were instructed to use topical moxifloxacin 0.5% four times a day for one week. Patients were followed at day one, week 1 and week 4 after the injection. At each visit, slit lamp examination of the anterior segment, intraocular pressure measurement and dilated fundus examination with both slit lamp and indirect ophthalmoscope, was done with special emphasis on ocular complications. Patients were asked to report immediately if they experienced ocular pain or acute visual loss. Assessment at the end of 1 month was taken as final score. Paired t-test was used to compare the mean IOP pre and post operatively. p < 0.05 was considered level of significance.

Results

Mean age of the patients was 54 (±SD =5.57) years, (Range = 40-65 years). Out of 60 patients, 20 were males (M: F = 1:2). The most common indication of

intravitreal Bevacizumab were diabetic macular edema 25 eyes(41.7%)(Table1).Of the 60 eyes, complications were seen in 26 eyes (43.3%). Of the 43.3% complications, Sub-conjunctival hemorrhage(noted on day 1) was the most common but least serious complication found in 20 eyes(33.3%, followed by raised IOP(noted on day 1) in 3 patients(5%), cataract formation(noted on week 1) in 2 patients (3.3%) and endophthalmitis (noted on week 1) in 1patient (1.7%) (Table 2).Insignificant increase was seen in IOP postoperatively (p-value =.002)(Table 2).No case of, uveitis,rhegmatogenous retinal detachment, retinal tear or vitreous haemorrhage was seen in our study.

Table 1: Intravitreal Bevacizumab in posterior segment diseases-Indications (n=60)

Complications	No (%)
Diabetic macular edema	25(41.66)
Proliferative diabetic retinopathy	20(33.33)
Wet age related macular degeneration	10(16.7)
Retinal vein occlusion	5(8.3)

Table 2: Intravitreal Bevacizumab-Complications (n=26/60)

Complication	No(%)
Sub-conjunctival haemorrhage	20(33.3)
Raised intraocular pressure	3(5.0)
Lens injury	2(3.3)
Endophthalmitis	1(1.7)

Table 3: Comparison of intra ocular pressure pre and post operatively

IOP	Mean	Standard deviation	p-value
Pre- operative	15.92	1.124	.002
Post-operative	17.12	2.662	

Discussion

Bevacizumab has been used on “off-label” basis since 2005. Since it is cost effective as compared to Lucentis and Macugen (FDA approved antiVEGFs’), so it is used as first line treatment in most macular degeneration patients. The most common indications of Bevacizumab in one paper by Lihteh Wu et al were diabetic retinopathy and Choroidal neovascularization of several etiologies. ¹¹ The main indications in our study were also diabetic retinopathy. In present study sub-conjunctival hemorrhage was (19.60%) which is comparable to Lihteh Wu et al’s study¹¹ who reported 19.47% and Khan A et al’s study where it is 6%.^{11,1} Fung AE et al experienced this

complication in 0.03% of the patients. It was procedure related and resolved in 10 to 14 days without any consequences. ¹¹Bevacizumab injection is said to cause volume related rise in IOP. In our study there was raised IOP in 3 cases (2.9%) which returned to normal after pressure lowering topical medication. In a study of Khan et al ¹ there were 2 cases, which did return to normal with anti-glaucoma medication.

Traumatic cataract is a risk of intravitreal injection if the needle contacts or penetrates the lens capsule. Cataract formation, dislocation of lens and zonular tears are a possibility. Improper technique, inexperienced surgeon and patient's head movement at the time of the injection can be the reasons. We experienced 2 cases (1.9%) of traumatic cataract. Khan A et al ¹ observed 1% procedure related lens injury resulting in cataract formation. Fung AE et al and Shima C et al reported 0.14% and 0.01% lens injury respectively. ^{11,12}

Most dreadful complication of intravitreal Bevacizumab injection is bacterial endophthalmitis which causes profound visual loss. Prompt recognition and treatment is the key in maximizing good visual outcomes in patients who developed endophthalmitis after intravitreal injection of Bevacizumab. We did observe this complication in only 1 of our case (0.9%). Lihteh Wu et al⁴ have observed this complication in 0.16% of patients and Artunay O et al reported 0.066% of cases,^{13,14} A case report of a 52 years old male who received intravitreal Bevacizumab and developed culture positive endophthalmitis. Vitreous culture indicated that endophthalmitis was caused by Staphylococcus epidermidis.¹⁴ Khan P et al reports the occurrence of cluster endophthalmitis following multiple intravitreal Bevacizumab injections from a single vial.¹⁵

The complications associated with intra-vitreous Bevacizumab injection such as retinal detachment, retinal tear, central retinal artery occlusion, mild surface discomfort, progressive sub retinal hemorrhage, vitreous haemorrhage, transient hypotony and corneal abrasion were observed in studies of Khan A et al, Lihteh Wu et al and Fung AE et al. ^{1,4,11} None of these complications were observed in our study. Many of the studies reviewed are retrospective and lack randomization or controls, resulting in under reporting of the true prevalence of any given complications.

Conclusion

1. Anti-VEGF therapy is the mainstay of treatment for many retinal diseases. Despite its promising efficacy in halting the diseases and improving the vision for the

patients, intravitreal route of anti-VEGF agents may be associated with significant ocular complications.

2. Ophthalmologists, who employ anti-VEGF agents for their patients, should consider the potential systemic and ocular risks and benefits of intravitreal anti-VEGF therapy and closely monitor the patients for adverse effects that may occur in the immediate or subsequent periods after administration of the drugs.

References

1. Khan A, Mahar PS, Hanfi AN, Qidwai U. Ocular Complications after Intravitreal Bevacizumab Injection in Eyes with Choroidal and Retinal Neovascularization. *Pak J Ophthalmol* 2010;26:205-09.
2. Sigford DK, Reddy S, Mollineaux C, and Schaal S. Global reported endophthalmitis risk following intravitreal injections of anti-VEGF: a literature review and analysis. *Clin Ophthalmol*. 2015; 9: 773-81.
3. Shalaby KAG. Ocular Complications after Intravitreal Bevacizumab (Avastin) in Patients with Diabetic Retinopathy. *Journal of American Science* 2012;8(12):1121-26.
4. Falavarjani KG, Nguyen QD. Adverse events and complications associated with intravitreal injection of anti-VEGF agents: a review of literature. *Eye*. 2013; 27(7): 787-94.
5. Lihteh Wu, Maria A, Martinez- Castellanos, Quiroz-Mercado H, Arevalo JF, Maria H et al. 12 month safety of intravitreal injection of bevacizumab results of Pan- American Collaborative Retina Study Group (FACORES). *Graefes Arch Clin Exp Ophthalmol* 2008; 246: 81-87
6. Fasih U, Shaikh N, Rahman A, Sultan S, Fehmi MS, Shaikh A.A one-year follow-up study of ocular and systemic complications of intravitreal injection of bevacizumab (Avastin). *J Pak Med Assoc*. 2013 ;63 (6):707-10.
7. Avery RL, Pearlman J, Pieramici DJ, Rabena MD, Castellarin AA. A one-year follow-up study of ocular and systemic complications of intravitreal injection of bevacizumab (Avastin). *Ophthalmology* 2006; 113: 1695.e1-15.
8. Spaide RF, Laud K, Fine HF, Klanclnik JM Jr, Meyerle CB. Intravitreal bevacizumab treatment of choroidal neovascularization secondary to age-related macular degeneration. *Retina* 2006; 26: 383-90.
9. Rich RM, Rosenfeld PJ, Puliafito CA, Dubovy SR, Davis JL. Short-term safety and efficacy of intravitreal bevacizumab (Avastin) for neovascular age-related macular degeneration. *Retina* 2006; 26: 495-511.
10. Meyer CH, Mennel S, Schmidt JC, Kroll P. Acute retinal pigment epithelial tear following intravitreal bevacizumab (Avastin) injection for occult choroidal neovascularization secondary to age related macular degeneration. *Br J Ophthalmol* 2006; 90: 1207-08.
11. Fung AE, Rosenfeld PJ, Reichel E. The international intravitreal Bevacizumab Safety Survey. *Br J Ophthalmol*. 2006; 90(11): 1344-49.
12. Shima C, Sakaguchi H, Gomi F, Kamei M, Ikuno Y. Complications in patients after intravitreal injection of bevacizumab. *Acta Ophthalmol*. 2008;86(4):372-376.
13. Artunay O, Yuzbasioglu E, Rasiar R, Sengül A, Bahcecioglu H. Incidence and management of acute endophthalmitis after intravitreal bevacizumab (Avastin) injection. *Eye (Lond)*. 2009;23(12):2187-93.
14. AlRashaed S and Rushood A. Acute bacterial endophthalmitis after intravitreal bevacizumab injection: Case report and literature review. *Saudi journal of ophthalmology*. 2013; 27(1): 55-57.
15. Khan P, Khan L, Mondal P. Cluster endophthalmitis following multiple intravitreal bevacizumab injections from a single use vial. *Indian journal of ophthalmology*. 2013;32: 65-68