Original Article

Ocular Complications after Intravitreal Bevacizumab Injection in Eyes with Choroidal and Retinal Neovascularization

Aimal Khan, P.S Mahar, Azfar Nafees Hanfi, Umair Qidwai

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See end of article for authors affiliations

Correspondence to:
Aimal Khan
Isra Postgraduate Institute of Ophthalmology
Al – Ibrahim Eye Hospital
Malir, Karachi

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Purpose: To assess the ocular complications after intra-vitreal Bevacizumab (Avastin) injection in eyes with choroidal and retinal neovascularization.

Materials and Method: This study was conducted in Isra Post-graduate Institute of Ophthalmology, Al-Ibrahim Eye Hospital, Karachi. The patients were selected through simple random sampling. This was a quasi experimental study. It was conducted from 21.07.2007 to 20.07.2008.

All the 200 patients with neovascularization who fulfilled the inclusion criteria, were selected on outpatient basis and were treated with intravitreal bevacizumab on day care basis. They were re-examined the next day and evaluated for complications. Data was collected according to proforma and analysis was done using SPSS version 17.0.

Results: Study was conducted on 200 patients with choroidal and retinal neovascularization. Average age of patients was 53.7 with (±SD =11.7) years (Range = 25 – 83 years). The most common indication of intravitreal bevacizumab was diabetic retinopathy found in 110 (55%) patients. Complications were seen only in 24 (12%) patients. Sub Conjunctival hemorrhage was the most common but least serious complication found in 12 (50%) patients, followed by Corneal Abrasion in 4 (16.7%), while raised IOP, Vitreous Hemorrhage, Transient mild uveitis and lens Injury was seen in only 2 (1%) patients.

Conclusion: Adverse effects of intravitreal Bevacizumab are mostly procedure related but few may be drug related. The procedure is generally safe but there are risks involved. To minimize the risk careful attention to injection technique and appropriate post injection monitoring are essential.
The short term results suggest that intravitreal Bevacizumab is safe procedure.

Neovascularization of the choroidal and retinal tissue are the leading cause of blindness in developed countries[1]. Vascular endothelial growth factor has been identified as a major angiogenic stimulus in variety of retinal and choroidal neovascularization[2].

Vascular Endothelial Growth Factor is homodimeric glycoprotein and is a growth factor specific for endothelial cells[3]. Not only it promotes the growth and survival of vascular endothelial cells, but it also causes conformational changes of tight junctions of retinal vascular endothelial cells leading to increased vascular permeability[4].

Advances in our understanding of pathogenesis of Choroidal and retinal neovascularization have facilitated the development of drugs specifically directed against Vascular Endothelial Growth Factor.

Bevacizumab (Avastin) is a humanized monoclonal antibody to Vascular Endothelial Growth Factor approved for the treatment of colorectal cancer. It has

been used systemically and intravitreally for the treatment of retinal and choroidal neovascular diseases since July 2005. However, systemic administration of Bevacizumab has a small but significant risk of thromboembolism in patients with cancer[5]. Several studies have not shown any evidence of ocular toxicity after the use of intravitreal Bevacizumab at or beyond the therapeutic levels expected with the standard dose of intravitreal bevacizumab used in routine care of patients[6].

Few of the self-reported adverse events from various institutions in an internet-based survey were corneal abrasion, lens injury, endophthalmitis, retinal detachment, inflammation or uveitis, cataract progression, acute vision loss, central retinal artery occlusion, sub retinal hemorrhage, retinal pigment epithelium tears but none of the adverse event rate exceeds 0.12%[7].

Since no work has been carried out before on this issue in our local setup, this study would be important in decision making regarding the safety of intravitreal Bevacizumab in choroidal and retinal neovascular disorders.

MATERIAL AND METHOD

The study was carried out at Al-Ibrahim Eye Hospital, Malir, Karachi from 21.07.2007 to 20.07.2008. Two hundred patients with clinical evidence of choroidal and retinal neovascularization were included in the study. It was a Quasi experimental study and sampling was done by non-Probability purposive sampling technique. Patients who with diagnosed choroidal and retinal neovacular, and age 30 years or older were included in the study. Patients who had any ocular conditions other than neovascularization in the study eye that can affect the vision and/or safety e.g. glaucoma, corneal dystrophy, uvietis, retinal detachment were excluded from the study.

Informed and written consent was taken after thorough discussion of possible benefits and complications. Baseline assessment included best corrected visual acuity (BCVA) using Snellen acuity chart, anterior segment examination using a Slit lamp; intraocular pressure with Goldman applanation tonometer, dilated fundus examination using slit lamp with +90 diopters lens and indirect ophthalmoscope with +20D lens.

The Aga Khan University hospital 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.

The eyes to be treated were prepared with 5% povidone-iodine solution. 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 27 –gauge needle, 0.05ml of Bevacizumab was injected intravitreally through the pars plana 3.5 mm from the limbus.

After the injection, intraocular pressure was measured along with the slit lamp examination of anterior segment. Patients were instructed to use topical ciprofloxacin 0.3% four times a day for one week.

Patients were followed at 1, 4, 8 and 12 weeks after the first injection. At each visit, BCVA was measured along with the slit lamp examination of the anterior segment, intraocular pressure measurement and dilated fundus examination with both slit lamp microscope and indirect ophthalmoscope, with special emphasis on ocular complication. Subsequent injections were given at monthly intervals (maximum three injections) depending upon response of choroidal or retinal neovascularization.

Statistical analysis was carried out with SPSS version10.0. Frequencies and percentages were computed for qualitative variables like gender, complications, diagnosis, visual acuity and age groups. Mean and standard deviation was computed for quantitative variables like age, acute vision loss and IOP. Sign test was used to compare the proportions of pre and post-operative visual acuity. Chi- Square test was used to compare the proportions of pre and post-operative complication (presence or absence of a complication). Paired t-test was used to compare the mean IOP pre and post operatively. Independent sample t-test was used to compare the mean age between genders. $P < 0.05$ was considered level of significance.

RESULTS

A total of 200 patients with choroidal and retinal neovascularization disorders were included in this study. Mean age of patients was 53.7 (±SD =11.7) years, (Range = 25 – 83 years). Out of 200 patients, 140 (70%) were males and 60 (30%) were females (M: F = 1: 0.4). The most common indication of intravitreal bevacizumab were diabetic retinopathy found in 110 (55%) patients, followed by exudative ARMD in 52

(26%) patients, BRVO in 12 (6%) patients, Myopic CNV and CRVO found in 8 (4%) patients, Eale's disease in 6 (3%) patients while Angoid Streak and CNV sec. to CSCR was found in only 2 (1%) patient.Table-1. Of the 200 patients, 88 (44%) patients with right eye affected, 74 (37%) patients with left eye affected, and both eyes involved in 38 (19%) patients.

Significant improvement was seen in visual acuity after intravitreal bevacizumab injection. Out of 200 patients improvement was seen in 132 (66%) patients which is significantly high (p-value < 0.0001), decreased in 20 (10%) patients while 48 (24%) patients remained stable (Fig. 1).

Insignificant complications were seen after intravitreal bevacizumab injection. Of the 200 patients, complications were seen only in 24 (12%) patients. (Fig.2). Of the 12% complications, Sub-conjunctival hemorrhage was the most common but least serious complication, found in 12 patients, followed by Corneal Abrasion in 4, raised IOP in 2 patients, Vitreous Hemorrhage in 2 patients, Transient mild uveitis was seen in 2 patients and Lens Injury was seen in 2 patients as well (Table 3).

Insignificant increase was seen in IOP post operatively (P-value = 0.083). Pre-operative mean IOP was 15.46± 2.57 and post-operative mean IOP was 15.27± 2.7 (Table 3)

Neovascularization of the choroidal and retinal tissue are the leading cause of blindness in developed countries.[1]Vascular endothelial growth factor has been identified as a major angiogenic stimulus in variety of retinal and choroidal neovascularization[2].

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Few of the self-reported adverse events from various institutions in an internet-based survey were corneal abrasion, lens injury, endophthalmitis, retinal detachment, inflammation or uveitis, cataract progression, acute vision loss, central retinal artery occlusion, sub retinal hemorrhage, retinal pigment epithelium tears but none of the adverse event rate exceeds 0.12%[7].

Since no work has been carried out before on this issue in our local setup, this study would be important in decision making regarding the safety of intravitreal Bevacizumab in choroidal and retinal neovascular disorders.

Table 1: Diagnosis

	No. of patients n (%)
DR	110 (55)
ARMD	52 (26)
Myopic CNV	8 (4)
CRVO	8 (4)
BRVO	12 (6)
Eale's Disease	6 (3)
CNV secondary to CSCR	2 (1)
Angoid Streak	2 (1)

Table 2: Distribution of complications n = 200

	No. of patients n (%)
S.C.H	12
Corneal Abrasion	4
Raised IOP	2
Vitreous H	2
Transient mild uveitis	2
Lens Injury	2

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

IOP	Mean	Standard Deviation	P-value*
Pre-Operative	15.46	2.57	0.083
Post Operative	15.27	2.7	

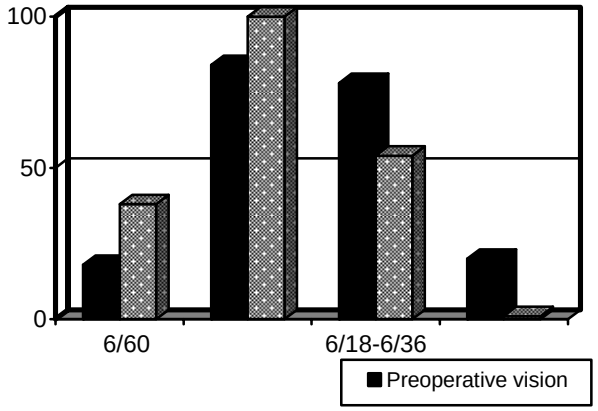

Fig. 1: Pre and Post injection visual acuity distribution N = 200

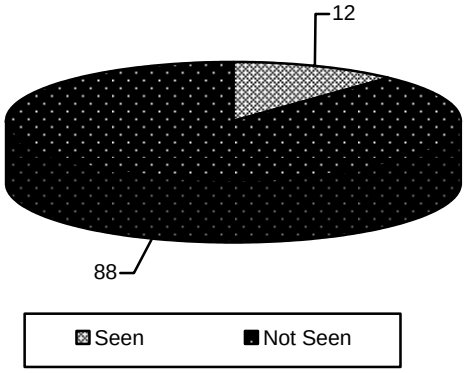

Fig. 2: Complications Chi-square value = 112.5, (DF = 1) P-value < 0.0001

Chi-square value = 112.5, (DF = 1) P-value < 0.0001

DISCUSSION

Bevacizumab has been used on "off-label" basis since the fall of 2005. Since it is of much lower cost than either Lucentis and Macugen (FDA approved anti-VEGF), it is used as first line treatment in most macular degeneration patients.

Since no work has been carried out before on this issue in our local setup, this study would be important in decision making regarding the safety of intravitreal bevacizumab in choroidal and retinal neovascular disorders.

The most common indications of Bevacizumab in one paper by Lihteh Wu et al[9] were diabetic retinopathy and CNV of several etiologies. The main indications in our study were diabetic retinopathy (55%) followed by CNV (31%) of various etiologies as well.

In our study sub-conjunctival hemorrhage was 6% as compared to Lihteh Wu et al[9] who reported 19.47%. It was procedure related and resolved in 8 to 10 days without any consequences. A E Fung et al[7] experienced the complication in 0.03% of patients.

Another procedure related complication faced was corneal abrasion in 2% cases which spontaneously resolved in 2 to 3 days with the use of lubricants. A E Fung et al[7] and Shima C et al[10] has reported this complication in 0.15% and 0.28% cases respectively.

Avastin injection caused a rise in IOP, which was a probably volume related. It never occluded the central retinal artery and it fell to below 30 mmHg in all eyes spontaneously within 15 minutes[11,8]. In our study there were just 2 cases of raised IOP which did return to normal with glaucoma medication thus necessitating checking IOP after injection as a precaution.

Vitreous hemorrhage is a risk of intra-vitreal injection. The etiology was unclear. It was probably attributable either to procedure or the underlying pathologic condition for which the injection was administered like proliferative diabetic retinopathy. 1% of our patients suffered the complication of vitreous hemorrhage which was managed by pars plana vitrectomy. Lihteh Wu et al[9] has reported the complication in only 0.02% cases.

We experienced inflammatory response in the form of mild uveitis in 1% of cases who responded well to corticosteroids. In the study of Kiss C et al[12], no inflammatory response was detected clinically. The slight reduction in anterior chamber flare was due to anti-inflammatory effect of Anti-VEGF therapy. On the other hand another study by Lihteh Wu et al,[9] have reported 0.09% uveitis.

Iatrogenic traumatic cataract is a risk of intra-vitreal injection if the needle contacts or penetrates the lens capsule. We observed 1% procedure related lens injury resulting in cataract formation. Shima C et al[10] and Fung et al[7] reported 0.14% and 0.01% lens injury respectively.

Bacterial endophthalmitis is an expected and dreadful complication of intra-vitreal injection. We did not observe this complication at all. Lihteh Wu et al[9] have observed this complication in 0.16% of patients.

There are several other complications associated with intra-vitreal bevacizumab injection such as retinal detachment, retinal pigment epithelial tear, acute vision loss, central retinal artery occlusion, mild surface discomfort, progressive sub retinal hemorrhage, cataract progression, transient hypotony which were observed in studies of Lihteh Wu et al[9] and A E Fung et al.[7] 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. Main limitations of our study were that it was a short term study, it lacks randomization and there were no controls.

CONCLUSION

Complications of intra-vitreal Bevacizumab are mostly procedure related but few may be drug related. The procedure is generally safe but there are risks involved. To minimize the risk careful attention to injection technique and appropriate post injection monitoring are essential.

The short term results suggest that intra-vitreal Bevacizumab is safe, but long term randomized control trial is recommended.

Author's affiliation

Dr. Aimal Khan
Isra Postgraduate Institute of Ophthalmology
Al – Ibrahim Eye Hospital, Malir
Karachi

Prof. P.S Mahar
Isra Postgraduate Institute of Ophthalmology
Al – Ibrahim Eye Hospital, Malir,
Karachi

Dr. Azfar Nafees Hanfi
Isra Postgraduate Institute of Ophthalmology
Al – Ibrahim Eye Hospital, Malir,
Karachi

Dr. Umair Qidwai
Isra Postgraduate Institute of Ophthalmology
Al – Ibrahim Eye Hospital, Malir
Karachi

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