

EVALUATION OF VISUAL OUTCOME OF INTRAVITREAL INJECTION AVASTIN (BEVACIZUMAB) IN PROLIFERATIVE DIABETIC RETINOPATHY WITH VITREOUS HEMORRHAGE

¹NISAR SHAIKH, ²UZMA FASIH, ³M.S.FEHMI, ⁴WAQAR UL HUDA

¹Eye Dept(Unit 1).Karachi Medical & Dental College, Abbasi Shaheed Hospital Karachi. ²Eye Dept.(Unit 2)Karachi Medical & Dental College, Spencer Eye Hospital. ³Eye Dept(Unit 2).Karachi Medical & Dental College, Spencer Eye Hospital.

⁴Resident Trainee Eye Dept. Abbasi Shaheed Hospital, Karachi

ABSTRACT

Objective of Study:

To report the visual outcome after intravitreal injection Avastin(Bevacizumab) in proliferative diabetic retinopathy with vitreous heamorrhage with 1 year followup. It was analytical observational type of study.

The study was carried out at Eye department Abbasi Shaheed Hospital from July 2008-June 2010.

Materials & Methods:

100 patients were selected through non-probability cosecutive sampling technique from the diabetic eye clinic who presented with proliferative diabetic retinopathy and vitreous hemorrhage .Patients with vitreous hemorrhage in one eye and proliferative diabetic retinopathy or bilateral vitreous hemorrhage were included in the study.B scans were done in dense vitreous hemorrhage to exclude tractional retinal detachment. History was taken regarding duration of diabetes and decreased vision.Detailed ocular examination including visual aquity, intraocular pressure , detailed anterior segment examination on slitlamp and direct and indirect ophthalmoscopy was done.Other eye was also examined to exclude proliferative diabetic retinopathy in that eye.Patients were counselled for intravitreal injection Avastin (Bevacizumab). After detailed examination patients were admitted in the ward and Intravitreal injection Avastin 1.25mg/0.05 ml was given in sterile environment in the operation theatre using fully aseptic technique. Patients were discharged on moxifloxacin eye drops and steroid antibiotic combination ointment at night time.Patients were followed up very next day, after 1 week, 6 weeks,3 months, six months and 1 year.Snellens best cor-

rected visul aquity was recorded at each visit along with fundus biomicroscopy and fundus flourescine angiography wherever possible. Other eye was also treated with intravitreal injection Avastin-(Bevacizumab), grid or focal laser treatment or panretinal fundus photocoagulation as and when required.

Results:

140 eyes of 100 patients were treated with intravitrea linjection Avastin(Bevacizumab) Followup ranged from 1st postoperative day to 1 year.Baseline visual aquity was PL/PR –perception of hand movement in 99 eyes, finger counting-6/60 in 27 eyes and 6/36 in 14 eyes.Improvement of vision was observed at 2 weeks. VA finger counting -6/60 was seen in 43 eyes, 6/36-6/18 in 63 eyes and there was no improvment in 14 eyes.After 6 month follow up FC-6/60 was seen in 18 eyes ,6/36-6/18 in 88 eyes, 6/12-6/9 was seen in 20 eyes .There was still no improvment in 14 eyes due to exudative maculopathyin 10 eyes and ischeamic maculopathy in 4 eyes.At one year followup VA finger counting-6/60 was seen in 14 eyes ,6/36- 6/18 in 87 eyes and 6/12-6/9 in 25 eyes .There was still no improve-ment in 14 eyes due to the above mentioned reasons.Vitreous hemorrhage resolved completely in 44 eyes, while 16 eyes had residual vitreous heamorrhage. Regression of neovascularization was observed in 120 eyes. Intravitreal injection Avastin (Bevacizumab) was repeated twice or thrice 6 weeks apart in patients with residual vitreous hemorrhage11.4%(16 patients) and in patients with neovascularization at disc or elsewhere after 6 weeks of first injection30%(42 patients). Some visual improvement was observed after repetition of the injection.Complications like cells in anterior chamber were seen in 5% of the eyes.Acute rise of intraocular pressure was seen in 15% eyes sub-

conjunctival hemorrhage in 30% eyes. All the complications were managed successfully .

Conclusion:

It was concluded that Avastin is a promising drug for proliferative diabetic retinopathy .It is a very helping and simple procedure keeping in mind the long periods of absorption of vitreous hemorrhage and avoiding vitrectomy. Panretinal photocoagulation is recommended after clearance of vitreous hemorrhage.

Key Words:

VA Visual acuity, PDR: proliferative diabetic retinopathy, RN: retinal neovascularization, PRP: panretinal fundus, photocoagulation, BCVA: best corrected visual acuity.

INTRODUCTION

Diabetic retinopathy remains a major threat to sight in the working age population in the developed world. Furthermore, it is increasing as a major cause of blindness in other parts of the world especially in developing countries¹. Proliferative diabetic retinopathy (PDR) is a major cause of visual loss in diabetic patients. In PDR, the growth of new vessels from the retina or optic nerve, is thought to occur as a result of vascular endothelial growth factor (VEGF) release into the vitreous cavity as a response to ischaemia²⁻⁴. VEGF has been shown to play a major role in retinal neovascularization, but other factors may be involved as well, Anti-VEGF treatments have been hypothesized as an alternative adjunctive treatment for retinal neovascularization.⁵⁻⁸ Avastin (Bevacizumab) is a humanized mouse anti vascular endothelium growth factor antibody approved for intravenous use as an adjuvant in treatment of colon cancer.⁹ In case series, it has been reported to be effective in diabetic retinopathy, retinal vein occlusion and neovascular glaucoma when given through intravitreal route.¹⁰⁻¹² Angiogenesis in proliferative diabetic retinopathy is driven by vascular endothelial growth factor (VEGF). Studies have shown that vitreous fluids in eyes with severe PDR contain high levels of VEGF and is reduced by PRP and vitrectomy .

The rationale for anti VEGF therapy Avastin (Bevacizumab) is to reduce VEGF. Its primary goal is in decreasing preretinal fibrovascular proliferation in PDR or as a preoperative treatment to facilitate removal of fibrovascular tissues, intraoperatively

during vitrectomy and postoperatively to reduce vitreous hemorrhage. Because of its significant effect on reducing vascular permeability in retina, it may also be used to reduce intraretinal macular edema, which directly improves postoperative visual acuity.³ Based on vitrectomy samples after intravitreal injection avastin, intraocular half life in humans is approximately 3 days.^{13,14} Peak serum concentration is reached 6 days after the injection and then dropping to 45 % on 28 days after the injection.¹³ It is expected that some systemic VEGF inhibition must be expected after intravitreal injection for diabetic retinopathy as there is a clinical observation that after unilateral intravitreal injection avastin, (Bevacizumab) the contralateral eye also shows some anti-VEGF effects.¹⁰

MATERIALS & METHODS

Institutional ethical committee approval and written informed consent was taken from each patient.

Setting:

The study was carried out at eye department of Abbasi Shaheed Hospital from July 2008 to June 2010.

Sampling Technique:

A total of 100 patients were selected through nonprobability consecutive sampling technique from the diabetic eye clinic who presented with proliferative diabetic retinopathy with vitreous hemorrhage.

Inclusion Criteria:

We selected patients with mild to moderate or dense vitreous hemorrhage in unilateral or bilateral eyes with proliferative diabetic retinopathy.

Exclusion Criteria:

We excluded patients with history of any surgical procedure or previous laser treatment, glaucoma, uveitis, retinal detachment, burnt out stage of diabetic retinopathy, dense cataract or significant corneal opacity. We also excluded patients in whom B scans showed tractional retinal detachment.

Procedure:

History was taken regarding duration of diabetes and decreased vision from each patient.

Detailed ocular examination including visual acuity, intraocular pressure, detailed anterior segment examination on slitlamp and direct and indirect funduscopy was done. Other eye was also examined to exclude proliferative diabetic retinopathy in that eye. All the patients were counselled for intravitreal injection Avastin (Bevacizumab). After examination in the clinic, patients were admitted in the ward and Intravitreal injection Avastin 1.25 mg/0.05 ml was given in sterile environment in the operation theatre using fully aseptic technique. Patients were discharged on moxifloxacin eye drops and steroid antibiotic combination ointment at night time.

Follow Up:

All patients were then followed up in clinic on the very next day, after 2 weeks, 6 weeks, 3 months, 6 months and 1 year. Snellens best corrected visual acuity was recorded at each visit along with fundus biomicroscopy and fundus fluorescein angiography where possible. Disease progression and effect of treatment were documented by fundus photography. Other eye was also treated with intravitreal injection Avastin, (Bevacizumab) grid or focal laser treatment or

panretinal fundus photocoagulation as and when required. Intra vitreal injection Avastin was repeated twice or thrice 6 weeks apart in 11.4%¹⁶ eyes which showed residual vitreous hemorrhage after 6 weeks of first injection or in eyes with neovascularization at disc or elsewhere after 6 weeks of first injection.

RESULTS

140 eyes of 100 patients were included in the study. Mean age of the patients included in the study was 45 years. 62 % of patients included in the study were male. Visual acuity of patients at the start of study and visual improvement at 2 weeks, 2 months, 6 months and 1 year can be shown in table 1. There was no improvement at all in 14 (10%) eyes, out of which exudative maculopathy could be the cause in 10 (7.1%) eyes and ischemic maculopathy in 4 (2.8%) eyes. Vitreous hemorrhage resolved completely in 44 (31 %) eyes, while 16 (11.4%) eyes had residual vitreous hemorrhage. Regression of neovascularization was observed in 120 (85%) eyes. Intravitreal injection Avastin was repeated twice or thrice 6 weeks apart in 16 (11.4 %) patients with residual vitreous hemorrhage. It was repeated after 6 weeks of first injection.

TABLE NO:1
FOLLOW UP OF VISUAL ACUITY AT VARIOUS INTERVAL

Time of follow up	PL/ PR-HM	FC-6/60	Visual acuity 6/36-6/18	6/12-6/9	No improvement
Baseline	71 (99patients)	19%(27patients)	10%(14patients)	----	----
2 weeks	-----	46.4 %(65patients)	18%(25patients)	----	35.6%(50patients)
6 weeks	-----	31%(43patients)	45%(63patients)	14%(10patients)	10%(14patients)
6 months	-----	13%(18patients)	63%(88patients)	14%(10patients)	10 %(14patients)
1 year	-----	13%(18patients)	63%(88patients)	14%(10patients)	10 %(14patients)

TABLE:2
COMPLICATIONS OF INTRAVITREAL INJECTION AVASTIN(BEVACIZUMAB)

Complications	Incidence
Cells in anterior chamber in first week (0-2 seen by 1*1 beam of slit lamp)	7 eyes (5%)
Acute rise of intra ocular pressure on first post injection day and for first few days	21 eyes (15%)
Subconjunctival hemorrhage.	21 eyes (15%)

tion in 42 (30 %) patients with neovascularization at disc or elsewhere. No significant visual improvement was seen after repetition of the injection.

A number of complications were also noted after these injections as can be shown in table 2. All these complications were managed successfully. For cells in anterior chamber, steroid antibiotic combination was prescribed. Mild rise of intraocular pressure was managed by topical beta blockers. Subconjunctival hemorrhage subsided itself within two to three weeks. No signs of infection were observed and no retinal detachment were seen after the injection. Patients were observed for chest pain, blood pressure and thromboembolic phenomena but no such incidence was reported.

DISCUSSION

Although retinal neovascularization actually may be due to more than one cytokine, VEGF is an important, if not the most important cytokine involved.¹⁵ Activation of the VEGF receptor pathway triggers a network of signalling processes that promotes endothelial cell growth, migration, survival from pre-existing vessels, differentiation, and mobilization of endothelial progenitor cells from the bone marrow into the peripheral circulation¹⁶⁻¹⁷. Furthermore, VEGF increases vessel permeability leading to deposition of proteins in the interstitium that facilitate the process of angiogenesis¹⁸.

There are five case reports on the use of intravitreal bevacizumab in RN in diabetic retinopathy demonstrating regression of RN in PDR^{19,20, 21,22,23}.

A somewhat similar study was presented at American Academy of Ophthalmology Subspecialty meeting in October 2005 and Royal Hawaiian Eye Meeting in January 2006 which included 45 eyes Of 32 patients with retinal vascularization secondary to diabetes mellitus .These patients were treated with intravitreal Avastin(Bevacizumab). 44 (99.9)%eyes showed almost complete reduction of retinal neovascularization and visual improvement of 1-2 lines of Snellens Chart within 2 weeks (24) as compared to results of our study where visual status at Visual status 2 weeks after the intravitreal injection avastin (Bevacizuab)was FC-6/60 46 eyes(32.8%) 6/36-6/18 74 eyes(53%) 6/12-6/9- No improvement 20 eyes(14.2%).

Another study presented in part at the 2006 Joint Meeting of the American Society of Retinal

Specialists-European Vitreoretinal Society, Cannes, France, September 2006 showed that similar doses of intravitreal injection avastin were used for treatment of proliferative diabetic retinopathy.

They reviewed the clinical records of 33 consecutive patients (44 eyes) with PDR injected with intravitreal bevacizumab. Patients had a mean follow-up of 28.4 weeks and final BCVA analysis demonstrated that 12 eyes (27.3%) remained stable, 29 eyes (65.9%) improved two or more lines of BCVA, and three eyes (6.8%) decreased two or more lines of BCVA.

Twenty-seven eyes (61.4%) showed total regression of RN on fundus examination, 15 eyes (34.1%) demonstrated partial regression of RN on fundus examination , and two eyes (4.5%) of two patients showed no regression of RN (25) as compared to our study where Visual status 1 year after the intravitreal injection avastin(Bevacizumab) was FC-6/60 8 eyes(5.7%) 6/36-6/18 95eyes(67.8%) 6/12-6/9 23 eyes(16.4%).There was still no improvement in 14eyes(10%) due to exudative maculopathy in 10 eyes and ischemic maculopathy in 4 eyes. Vitreous hemorrhage resolved completely in 44 eyes (31.4%),while 16 eyes(11.4%) had residual vitreous heamorrhage.Regression of neovascularization was observed in 120 eyes(85.7%).

No complications were noted in all eyes after clearance of vitreous heamorrhagehere.Although no serious complications were seen in our study further studies are needed to assess the efficacy and safety of intravitreal Avastin(Bevacizumab) in the management of PDR.

CONCLUSION

Intravitreal bevacizumab seems to be a promising treatment for PDR, minimizing the risk for exudative complications, progression of RN, vitreous haemorrhage, and decreased vision caused by macular oedema. Intravitreal Avastin(Bevacizumab) may potentially be used as an adjuvant agent to PRP for PDR. It is a very helping and simple procedure keeping in mind long periods of absorption of vitreous hemorrhage and avoiding vitrectomy.

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