Original Article

Intravitreal Bevacizumab (Avastin) for post-vitrectomy diabetic vitreous hemorrhage

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ABSTRACT

Objective: To evaluate the efficacy of intravitreal bevacizumab injection in treating vitreous haemorrhage after diabetic vitrectomy.

Methodology: This interventional study was conducted at Al-Ibrahim Eye Hospital, Karachi, between July 2008 and Sept'2009. Selected patients having vitreous hemorrhage, after diabetic vitrectomy, were given intravitreal bevacizumab 1.25mg.Main outcome measures were Vitreous clear-up time and change in vitreous hemorrrhage scale at baseline and at four weeks and three months after injection.

Results: After intravitreal bevacizumab in 16 eyes, vitreous hemorrrhage cleared in 13(81%) eyes within four weeks. Mean vitreous clear-up time was 2.9 weeks. At baseline, mean vitreous hemorrrhage scale was 2.5±0.52; this improved to 0.81±1.0(p=<0.001) and 0.53±0.45(p=<0.001) at four weeks and three months, respectively. At the end of three months, 10(71%) of 13 eyes maintained vitreous hemorrrhage-free condition while 3(23%) developed recurrent vitreous hemorrrhage.

Conclusion: Intravitreal bevacizumab is quite effective in clearing post-operative vitreous haemorrhage after diabetic vitrectomy.

KEY WORDS: Bevacizumab intravitreal, Diabetic vitreous haemorrhage, Post vitrectomy vitreous haemorrhage.

Pak J Med Sci October - December 2011 Vol. 27 No. 5 1164-1168

How to cite this article:

Memon AF, Aziz-ur-Rehman, Shaikh FF. Intravitreal Bevacizumab (Avastin) for post-vitrectomy diabetic vitreous hemorrhage. Pak J Med Sci 2011;27(5):1164-1168

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* Received for Publication: June 15, 2011
* 1st Revision Received: July 12, 2011
* 2nd Revision Received: August 9, 2011
* Final Revision Accepted: August 20, 2011

INTRODUCTION

Post-operative vitreous hemorrhage following Pars Plana Vitrectomy for complications of proliferative diabetic retinopathy has been reported in upto 75% of patients[1]; while most clear spontaneously, reoperation for non-clearing vitreous haemorrhage may be required in about 38% of cases.[2]

The causes of recurrent vitroeus hemorrhage are hemolysis of remaining blood clots, reactivation of retinal neovascularization sites, anterior hyaloidal fibrovascular proliferation, or neovascularization at the sclerotomy sites.[3,4] This condition is usually managed by air-fluid exchange or vitreous cavity lavage.[5,6] Recent treatment modalities proposed for post-vitrectomy vitreous haemorrhage include intravitreal Anti-Vascular Endothelial Growth Factor (VEGF) injection[7] and intravitreal triamcinolone[8] injection. One of the anti-VEGF agents being used world-wide is Bevacizumab (Avastin, Genentech

Inc., San Francisco, CA); it is a full-length antibody that blocks all isoforms of VEGF-A. Intravenous administration of bevacizumab is approved for the treatment of metastatic cancers. Intravitreal bevacizumab is being used for retinal vein occlusion[9], age-related macular degeneration[10] and proliferative diabetic retinopathy as an off-label treatment[11]; its use has risen sharply, mainly because of its efficacy and lower cost.

As intravitreal bevacizumab results in the dissolution of vitreous haemorrhage due to proliferative diabetic retinopathy, we assessed its efficacy in the management of vitreous haemorrhage, after vitrectomy, in order to avoid repeated vitreous surgery.

METHODOLOGY

Sixteen eyes of as many patients were given off-label intravitreal bevacizumab. The study was approved by the institutional review board. The inclusion criteria were eyes having post-operative vitreous haemorrhage, after diabetic vitrectomy and having attached retina on B-scan ultrasound. Post-operative vitreous haemorrhage was defined as vitreous haemorrhage that obscured the retinal details (grade 2 or above in Diabetic Retinopathy Vitrectomy Study) and persisted for more than two weeks. Exclusion criteria included best-corrected visual acuity of 20/80 or better, diabetic tractional retinal detachment, pregnancy, intra-operative use of gas or silicone oil, simultaneous intraocular surgery, and use of anti-coagulants. All these patients had undergone 3-port (20 guage) vitrectomy with detachment of the posterior hyaloid, removal of vitreo-retinal adherences, cauterization of bleeding vessels, panretinal photocoagulation and sclerotomy site cryotherapy. The degree of post-operative vitreous haemorrhage was scaled according to the Diabetic Retinopathy Vitrectomy Study (DRVS) grading system[12](Table-I).

Ocular examination included visual acuity by Early Treatment Diabetic Retinopathy Study chart and intraocular pressure (IOP) by Goldmann applanation tonometer. Slit lamp examination of anterior and posterior segments and indirect ophthalmoscopy was performed. B-scan was performed to rule out retinal detachment. All treatment options and the off-label use of intravitreal bevacizumab were discussed with the patient; all patients provided written consent.

Table-I: Vitreous Hemorrhage Scaling (DRVS).

Grade	*Description*
0	No VH.
1	Mild VH with visible fundus details.
2	Moderate VH with no visible fundus details but with orange fundus reflex.
3	Severe VH with no retinal details and no orange fundus reflex.

vH=Vitreous Hemorrhage

Intravitreal bevacizumab was injected, in accordance with the standard protocol for an intravitreal injection. Response to treatment was monitored on day 1, weeks 1, 2, and 4, and monthly thereafter. At each visit, detailed evaluation was carried out, including visual acuity, fundoscopy and B-scan, and possible side-effects i.e. rise in IOP, uveitis and endophthalmitis were looked for. Systemically, the patients were monitored for blood pressure rise, chest pain and thromboembolic events.

Main outcome measures were vitreous clear-up time and change in vitreous haemorrhage scale from the baseline. Vitreous clear-up time was defined as the interval between intravitreal bevacizumab and the time when retinal details were visualized (grade 0 or 1 in DRVS). Change in vitreous haemorrhage scale was recorded at 4 weeks and 3 months after intravitreal bevacizumab.

RESULTS

Sixteen eyes of 16 patients were evaluated. Baseline characteristics of the patients' are described in Table-II. Table-III describes vitreous clear-uptime and changes in vitreous haemorrhage scale and visual acuity.

At baseline, 8 eyes had grade 3 vitreous haemorrhage, while 8 eyes had grade 2 vitreous haemorrhage(mean=2.5$\pm$0.52). After intravitreal bevacizumab, vitreous haemorrhage cleared in 13(81%) eyes within 4 weeks. Mean vitreous clear-uptime was 2.9 weeks. At 4 weeks, retina was clearly visible in these 13 eyes, with no haemorrhage in 8 eyes and grade 1 haemorrhage in 5 eyes. Mean vitreous haemorrhage scale at 4 weeks was 0.81$\pm$1.0, which was significantly better than the baseline(p=<0.001). After clearance

Table-II: Baseline characteristics of study eyes.n = 16

Variables	
Gender(no.):	
Male	10(62%)
Female	06(38%)
Age(yrs), mean ±SDRange=38–70yrs	57.2±9.2
Mean follow-up period(months), mean±SD Range =3–9months.	5.56+2.16
Interval b/w VH and IVB(weeks), mean±SD Range=2–10weeks.	4.12±2.1

VH=Vitreous Hemorrhage
IVB=Intravitreal Bevacizumab

Table-III: Summary of VCT and changes in VH scale and Visual Acuity

No.	*Change in VH Scale*			*Change in Visual Acuity*			*VCT (wks)*	*Additional Treatment*
	Baseline	*4weeks*	*3mths*	*Baseline*	*4weeks*	*3mths*		
01	3	1	0	HM	20/200	20/125	3	PRP
02	2	0	0	20/400	20/80	20/80	2	PRP
03	3	0	2	HM	20/125	20/200	3	Recurred VH VL, PRP
04	3	0	0	CF	20/160	20/40	2	PRP
05	2	0	0	CF	20/125	20/50	3	Macular Laser
06	3	3	0	LP	HM	20/160		Non-clearing VH VL, AFx, PRP
07	2	0	0	20/400	20/100	20/63	1	PRP
08	2	1	0	20/400	20/200	20/32	4	PRP
09	3	2	0	HM	CF	20/125		Non-clearing VH VL, AFx
10	2	0	0	CF	20/125	20/80	3	PRP
11	2	3	0	CF	HM	20/80		Non-clearing VH VL, AFx
12	3	1	0	HM	20/160	20/50	4	PRP
13	2	0	0	CF	20/80	20/40	2	PRP
14	3	1	2	HM	20/400	20/100	4	Recurred VH VL, PRP
15	2	1	0	20/400	20/160	20/63	3	PRP
16	3	0	3	HM	20/125	20/100	4	Recurred VH

VH=Vitreous Hemorrhage
CF=Counting Fingers
LP=Light Perception
PRP= Panretinal Photocoagulation
VCT=Vitreous clear-up time
HM=Hand Motion
VL=Vitroeus Lavage
AFx=Air-Fluid exchange

of haemorrhage, persistent noevascularization was found to be the cause in 9 eyes, so additional laser was performed. Vitreous haemorrhage did not clear in 3(19%) eyes, and vitreous lavage was performed, with supplemental laser, sclerotomy site cryotherapy and air-fluid exchange.

At 3 months, 10(77%) of the 13 eyes had clear vitreous, while 3(23%) developed recurrent vitreous haemorrhage. Mean vitreous haemorrhage scale at 3 months, in these 13 eyes, was 0.53±0.45, which was significantly better than the baseline (p=<0.001).The 3 eyes with recurrent haemorrhage underwent vitreous lavage, additional laser, cryotherapy and air-fluid exchange. Overall, additional vitreous surgery was required in 6(38%) eyes.

The visual acuity at baseline ranged from 20/400 to Light Perception. All the 13 eyes with cleared vitreous haemorrhage had visual improvement, with a mean visual acuity of 20/160(range=20/400-20/80) at 4 weeks. At 3 months, mean visual acuity in these 13 eyes improved to 20/63(range=20/125-20/32). No ocular or systemic adverse events were reported in any of our patients, till the latest follow-up.

DISCUSSION

Many cases of postoperative vitreous haemorrhage have been attributed to the persistent noevascularization. Intravitreal bevacizumab induces temporary regression of retinal noevascularization, with subsequent cessation of bleeding, which allows re-absorption of vitreous haemorrhage. The off-label use of intravitreal bevacizumab is based on the results of clinical reports indicating resolution of vitreous haemorrhage due to proliferative diabetic retinopathy[11]; intravitrealbevacizumab has also been used pre-operatively[13] and intra-operatively[14] to prevent post-vitrectomy vitreous haemorrhage.

Table-IV: Comparison of Vitreous hemorrhage scale between baseline and post intravitrealbevacizumab

VH Scale	*Mean±SD*	*Comparison*	*p –Value*
Base line(A)	2.50±0.52		
4 weeks(B)	0.81±1.05	AVsB	<0.001
3 months(C)	0.53±0.45	AVsC	<0.001

VH=Vitreous Hemorrhage

Bevacizumab is preferred to other anti-VEGF agents because of its much lower cost.

Standard treatment options for post-vitrectomy vitreous haemorrhage are air-fluid exchange or vitreous lavage. Air-fluid exchange is a less invasive procedure, but the patient has to maintain a face-down position. In vitreous lavage, the vitreous cavity is irrigated to clear the blood; it is a more invasive procedure that can lead to retinal breaks, retinal detachment and endophthalmitis.[1] Intravitreal triamcinolone injection is also being used for this purpose[8]; it may be associated with its well-known complications i.e. raised IOP, cataract and endophthalmitis.[15] Intravitreal bevacizumab is a less invasive option that may delay or even avoid further vitreous surgery. Injection related complications have been reported following intravitreal use of anti-VEGF drugs and the possibility of cerebrovascular and cardiovascular thromboembolic events after Intravitreal bevacizumab should also be kept in mind.[16]

With lack of large number of patients, longer follow-up and control group, it is hard to say that intravitreal bevacizumab is superior to the standard treatment. However, in our study, vitreous haemorrhage cleared in most eyes (81%) along with improvement in vision within 4 weeks. Thus possibly more rapid clearance of vitreous haemorrhage by intravitreal bevacizumab enabled faster visual rehabilitation. It also allowed fundus visualization for the detection of persistent noevascularization, so that additional laser was possible in 9 eyes, which may have prevented recurrent haemorrhage. Additionally, in terms of less invasiveness and avoiding face-down posture, intravitreal bevacizumab is more convenient.

In this study, additional vitreous surgery was required in 6(38%) eyes and possibly avoided in 10(62%) eyes. Recurrent vitreous haemorrhage in 3 of our patients suggests the presence of protracted neovascularization or sustained release of angiogenic factors.Because bevacizumab has only temporal effects, the possibility of recurrent haemorrhage raises the question of whether intravitreal bevacizumab should be repeatedly used in such cases.

The pharmacokinetic data of bevacizumab in vitrectomized eyes is still lacking, but it is thought that bevacizumab may have a shorter half life in a vitrectomized eye than a nonvitrectomized eye[17]; this is based on results from intravitreal antibiotic studies, which show that the clearance of drugs in vitrectomized eyes is 2 or 3 times faster.[18]

We could not find any local study conducted in Pakistan to evaluate the efficacy of intravitreal bevacizumab injection in treating vitreous haemorrhage after diabetic vitrectomy. A study conducted by Yeh PT etal[17]compared vitreous clear-uptime, need for vitreous surgeries, vitreous re-bleeding rates, and visual acuity changes between bevacizumab group and a control group; they concluded that intravitreal bevacizumab may be effective in facilitating re-absorption of vitreous haemorrhage and may reduce additional vitreous surgeries. Jose M[19] reported complete clearance of grade 3 post-vitrectomy vitreous haemorrhage and improvement in vision in all eyes without any adverse effects with intravitreal bevacizumab. Liu L[20] reported clearance of post-vitrectomy haemorrhage in 4 of their 8 patients, but 3 patients developed ghost cell glaucoma. It has been suggested that VEGF plays a role in maintaining the normal platelet function.[21] Anti-VEGF agents may disrupt blood clot formation and cause release of degenerated red blood cells(ghost cells) in a vitrectomized eye which may induce ghost cell glaucoma.[22] We did not experience any such side effect in our series, but this emphasizes the need for repeated IOP measurements after intravitreal bevacizumab.

Our results suggest that intravitreal bevacizumab is quite effective in clearing post-operative vitreous haemorrhage after diabetic vitrectomy. We recognize that the limitations of our work include a small sample size; use of an off-label drug; no comparison with natural course of post-vitrectomy haemorrhage; and relatively short follow-up time. Despite these limitations, intravitrealbevacizumab is an optional treatment of post-vitrectomy vitreous haemorrhage as a less invasive procedure that possibly provides quicker visual recovery and early fundus visualization, while possibly obviating the need for further vitreous surgery. Randomized, controlled prospective studies with larger sample size, including other possible therapeutic possibilities, will confirm the efficacy of this treatment.

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