



Original Article

Effect of Preoperative Intravitreal Bevacizumab Injection on Visual Outcome in Vitrectomy for Diabetic Vitreous Haemorrhage.

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Objective: To evaluate the effect and safety of bevacizumab pretreatment on visual acuity after pars plan vitrectomy for diabetic vitreous Haemorrhage.

Study Design: Quasi-experimental study.

Setting: Ophthalmology unit III, Mayo Hospital, King Edward Medical University Lahore Pakistan.

Duration: The study was carried out in one year, from 01, January 2013 to 31, December 2013.

Materials and Methods: A total of sixty patients diagnosed with dense non clearing diabetic vitreous haemorrhage fulfilling inclusion and exclusion criteria were identified and registered. In group A, thirty (30) eyes were treated preoperatively with Bevacizumab and in group B thirty (30) eyes were not treated with Bevacizumab before vitrectomy for diabetic vitreous haemorrhage. All patients were followed for post operative outcome measures including best corrected visual acuity (BCVA), post operative vitreous haemorrhage, and other complications for three to six months.

Results: At six (06) months follow up best corrected visual acuity improved significantly in 70 % patients, more than 6/60 in group A versus 46.66 % in group B. Post operative recurrent vitreous haemorrhage occurred significantly less frequently in group A (12 %) than in group B (50 %). The incidence of other post operative complications did not differ significantly between two groups. No significant systemic or ocular side effect encountered.

Conclusion: Pretreatment with intravitreal Bevacizumab improved visual outcome in patients undergoing vitrectomy for diabetic vitreous haemorrhage and reduced incidence of recurrent vitreous haemorrhage.



Introduction:

The incidence of diabetic vitreous haemorrhage is increasing due to increased number of diabetic patients worldwide and it is a grave complication of advanced diabetic eye disease. Non resolving diabetic vitreous haemorrhage is usually treated by pars plana vitrectomy with endolaser panretinal photocoagulation.¹ Many studies have proved anatomical and clinical benefits of using intravitreal bevacizumab preoperatively as adjunct in vitrectomy for management of complications of proliferative diabetic retinopathy. Being anti-vascular endothelial growth factor, bevacizumab, regresses neovessels in proliferative diabetic retinopathy. So, it was assumed that intravitreal injection of bevacizumab used preoperatively can decrease intra-operative bleeding during pars plana vitrectomy in treatment of complications of diabetic eye disease. Chen first reported that pretreatment with intravitreal bevacizumab was helpful in facilitating vitrectomy in severe proliferative diabetic retinopathy.^{2,3}

Bevacizumab was previously used in oncology for treatment of colon cancer. It is effective against vascular endothelial growth factor (VEGF). Currently, bevacizumab is being used in treating many inflammatory and retino-vascular disorders. There is release of vascular endothelial growth factor (VEGF) due to ischemia in retinovascular disorders, which leads to formation of neovessels in retina. Abnormal neovessels create many troubles like macular edema, fibrovascular proliferation and dreadful vitreous haemorrhage. It was thought that if we block VEGF by using anti-VEGF like bevacizumab, could affect visual acuity drastically, by causing damage to retinal neurons. But it is now proved by Electroretinogram (ERG) and Visual field analysis (VF) that anti-VEGF is not harmful to retinal neurons, and causes no risk to visual acuity. It was found to be safer to wash out anti-VEGF in one week from vitreous cavity. Recent trials have proved that efficacy and safety of bevacizumab to other anti-VEGF drugs is also comparable.⁴

A few retina surgeons believe that presurgical intravitreal administration of bevacizumab for vitrectomy in diabetic vitreous haemorrhage has no beneficial effect on recurrent vitreous haemorrhage and final visual acuity. Moreover, tractional retinal detachment may be a serious complication of bevacizumab therapy due to its tendency to increase traction element during fibrovascular proliferations. So bevacizumab after intravitreal injection should be closely monitored because it can lead to poor visual outcome due to tractional retinal detachment.⁵

Despite this, many retina surgeons are convinced that using intravitreal bevacizumab injection before vitrectomy in diabetic vitreous haemorrhage is significantly helpful, by decreasing retinal edema and reducing incidence

of recurrent post operative vitreous haemorrhage.⁶ Bevacizumab can be helpful to get better visual outcome due to decrease in surgical time due to less aggressive neovessels and recurrent vitreous haemorrhage.⁷ A study conducted by Jirawison revealed that postoperative use of intravitreal bevacizumab as adjunct to vitrectomy, had better anatomical and visual outcome in diabetic patients. Usually dose, used postoperatively for intravitreal injection of bevacizumab was 1.25 mg/ 0.05 ml, and it leads to reduced incidence of recurrent vitreous cavity bleed.⁸

Ophthalmic surgeons are always in search of better technique for management of diabetic vitreous haemorrhage for a successful surgery and better visual outcome. Although intravitreal bevacizumab is being used in management of proliferative diabetic retinopathy but it remains controversial that either it is beneficial or detrimental. This study will evaluate and compare the efficacy and safety of intravitreal injection of bevacizumab pretreatment versus no treatment in vitrectomy for diabetic vitreous haemorrhage, with final best-corrected visual acuity (BCVA) as primary outcome measure and recurrent vitreous haemorrhage and other complications like tractional retinal detachment as secondary measures.

Material and Methods:

It was a Quasi-experimental study conducted at Ophthalmology unit III, Mayo Hospital, King Edward Medical University Lahore. The duration of study was one year from January 01, 2013 to December 31, 2013. The study was carried out with sixty cases of non clearing diabetic vitreous haemorrhage undergoing pars plana vitrectomy. All the patients were recruited for study through outpatient retina clinic.

Both male and female patients having dense diabetic vitreous haemorrhage, with retina in situ proved by B Scan Ultrasonography were included. Control of diabetes mellitus was given priority. The patients having vitreous haemorrhage due to trauma, posterior vitreous detachment, other retinovascular disorders like branch retinal vein occlusion (BRVO) were excluded. The patients with tractional or rhegmatogenous retinal detachment were not included.

Complete history and ophthalmic examination of patients including age, sex, address, occupation, visual acuity, previous intra ocular surgery, argon laser photocoagulation (PRP), and status of iris and lens were documented. B Scan ultrasonography was performed in all patients with hazy fundus view to document status of retina. Details of pars plana vitrectomy surgical procedure, including gauge of vitrectomy ports, complications during surgery and tamponade agent if used, were recorded.

Thirty patients in bevacizumab group (group A) received an intravitreal injection of bevacizumab

1.25mg/0.05 ml on average one week before vitrectomy. All intravitreal injections were performed under aseptic conditions after getting informed consent. Topical anaesthesia and betadine 5 % drops were instilled to ocular surface followed by insertion of lid speculum. A pre-filled syringe containing 1.25mg/0.05 ml of bevacizumab, with 30 gauge needle was used. Bevacizumab was injected, in superotemporal quadrant, 04 mm distal to limbus. The patients routinely used post injection antibiotic (Moxifloxacin) eye drops for one week. No injection related complication was noted. No eye in bevacizumab group was re-injected post operatively. Group B patients received no intravitreal injection of bevacizumab prior to pars plana vitrectomy.

The surgical procedures were performed by two surgeons randomly. Standard 20 gauge pars plana vitrectomy was performed in all cases under local anaesthesia, and vitrectomy was done carefully and precisely, under wide angle viewing system. After core vitrectomy, posterior vitreous detachment was created, vitreous base was shaved meticulously, assisted with scleral indentation. It was ensured to remove the whole blood from vitreous cavity. The membranes with fibrovascular components, were removed by segmentation and if present fibrovascular tractions were relieved especially on neovascular tissue. Intra-ocular pressure was maintained to avoid oozing or bleeding from neovascular tissue. Full endolaser photocoagulation was performed to any areas of untreated retina upto ora serrata, with scleral indentation. Endodiathermy was used during vitrectomy as required to secure haemostasis, in patients with aggressive neovascular membranes. No tamponade agent was used, only air or fluid left in vitreous cavity. Absorbable sutures were applied to all three vitrectomy ports. No specific post operative prone positioning was advised. Some patients required fill in pan retinal photocoagulation (PRP) postoperatively in both groups.

Primary outcome measure of this study was visual outcome and secondary outcome measures were recurrent post operative vitreous haemorrhage and other complications like retinal detachment. All the information was recorded in proforma.

Results:

A total of sixty cases were included in this study, divided in two groups randomly. In group A, the average age was 59.78 ± 10.79 years (range 40-80 years) and in group B, the average age was 61.01 ± 11.01 years (range 40-90 years). The p value is >0.05 , statistically no difference between two groups. (Table 1)

Table 1: Age distribution of patients of both groups

Age (years)	Group A	Group B
40 - 50	08	07
51 - 60	07	11
61 - 70	11	07
71 - 80	04	05
Total	30	30

In group A there were 18 male and 12 female patients. In group B, 14 males and 16 females were included in the study (Table 2). All Group A patients received single intravitreal bevacizumab 1.25mg/0.05 ml injection one week prior to pars plana vitrectomy and group B patients received no injection.

Table 2: Sex distribution of patients in both groups

Sex	Group A	Group B	Total
Male	18	14	32 (53.33%)
Female	12	16	28(46.66%)
Total	30	30	60 (100%)

In bevacizumab group eyes showed more regression of neovessels clinically. In addition, there was less bleeding during removal of the proliferative membrane intra-operatively. The average visual acuity was improved postoperatively in bevacizumab group; it was categorized as improvement, worsening or no change. At six months follow up, the patients in bevacizumab group (group A) 70 % had their best corrected visual acuity (BCVA) 6/60 or better. While in group B, only 46.66 % patients had best corrected visual acuity 6/60 or better (Table 3).

Table 3: Best Corrected Visual Acuity (BCVA)

BCVA	Group A	Group B	Total
FC	09	16	25 (41.66%)
6/60 - 6/36	12	08	20 (33.33%)
6/24 - 6/18	06	04	10 (16.66%)
6/12 - 6/6	03	02	05 (8.33 %)
Total	30	30	60 (100 %)

p <0.05 (significant)

There were 04 (12 %) patients in group A having postoperative vitreous haemorrhage and in group B, 15 (50%) patients had vitreous haemorrhage. There was a statistically significant difference between two groups regarding incidence of recurrent vitreous haemorrhage (P value <0.05). (Table 4)

Table 4: Frequency of recurrent vitreous haemorrhage

	Group A	Group B	Total (%)
Early Vitreous Haemorrhage	02	09	11 (18.33)
Late Vitreous Haemorrhage	02	06	08 (13.33)
No Vitreous Haemorrhage	26	15	41 (68.33)
Total	30	30	60 (100)

$p < 0.05$ (Significant)

Ocular complications were insignificant, with no systemic problem encountered.

Discussion:

Visual recovery after pars plana vitrectomy for diabetic vitreous haemorrhage depends on many factors. The most significant factors to affect visual outcome are macular edema, recurrent vitreous haemorrhage, tractional/rhegmatogenous retinal detachments and surgical complications. It also depends on systemic control of diabetes, systemic vascular risk factors like hypertension and nephropathy. Visual outcome can be reduced by worsening of macular edema and by early or late vitreous cavity bleed after pars plana vitrectomy. Incidence of tractional or rhegmatogenous retinal detachments can also lead to decreased final visual outcome.^{9,10}

Although angiogenesis is vital for ocular development and its healthy maintenance but abnormal angiogenesis can lead to loss of vision and blindness. The abnormal neovessels lead to leaking, vitreous haemorrhage, scarring and photoreceptor death. Vascular endothelial growth factor plays a vital role in angiogenesis. In diabetic patients, VEGF is released due to ischemic effects on retina due to vascular compromise. This VEGF leads to formation of abnormal neovessels, which leads to leaking, retinal edema, and vitreous haemorrhage.

Bevacizumab is a recombinant, humanized, full length monoclonal antibody, which is effective against vascular endothelial growth factor (VEGF). Bevacizumab has been suggested for many neovascular ocular conditions including choroidal neovascularization (CNV) proliferative diabetic retinopathy (PDR), diabetic macular edema, rubeosis iridis, neovascular glaucoma, and corneal neovascularization. Bevacizumab blocks VEGF and also reduces its effects, inducing regression of neovessels and reduction of permeability. The fluorescein angiography proved that there

was decrease in leakage from retinal neovessels and also lead to regression of neovascular element of fibrovascular membranes in eyes with high risk diabetic retinopathy after one week of bevacizumab intravitreal injection.^{11,12} Bevacizumab pretreatment, before diabetic vitrectomy, is increasingly being used by retina surgeons with a view that it leads to decreased intra-operative bleeding and operative time. Chen first reported that pretreatment with intravitreal bevacizumab was helpful in making pars plana vitrectomy easier to some extent in diabetic eye disease.¹³

Presurgical use of bevacizumab is still not considered standard part in management of diabetic vitreous haemorrhage, rather it is considered usually a retinal surgeon's discretion whether to pretreat or not. Recently many retina surgeons are using bevacizumab as adjunct to vitrectomy in diabetic vitreous haemorrhage. Intravitreal bevacizumab is being used pre-operatively, per-operatively and also post-operatively to vitrectomy, to reduce incidence of post-operative vitreous haemorrhage and to achieve better visual outcome. However, some studies also showed that administration of bevacizumab lead to increased incidence of post-operative tractional retinal detachment leading to poor visual outcome, while others concluded that there is no beneficial effect of bevacizumab as adjunct in diabetic vitrectomy.¹⁴

Ahmadih's study showed that intravitreal bevacizumab leads to significant resolution of diabetic vitreous hemorrhage and improvement in visual acuity. Laboratory experiments proved that a lower number of erythrocytes, retrieved from vitrectomy cassette, were found in patients pretreated with intravitreal bevacizumab two weeks prior to surgery.¹⁰

Since intravitreal injection of bevacizumab can lead to regression of vascular part of fibrovascular membranes and the membranes become less adherent to underlying retina, a little bit elevated and separated from retina. So the retina surgeons are of the view, that segmentation and delamination becomes easier after intravitreal bevacizumab. The cavity bleed during vitrectomy is also decreased due to bevacizumab, leading to changes in retinal vessels like constriction and reduced flow in neovessels. The reduction of vitreous bleed provide a good view of surgical field which facilitate vitrectomy.¹⁵

Rizzo showed that for eyes treated with bevacizumab injection had more frequent direct fibrovascular membrane peeling easily. The regression and fibrosis of neovessels after bevacizumab made surgery quicker because it required less tool exchange, which also lead to decreased surgical timing.¹⁶

There was decreased incidence of iatrogenic retinal breaks in diabetic vitrectomy patients pretreated with



intravitreal bevacizumab. Because vascular leakage, retinal thickness and congestion decreased after intravitreal bevacizumab injection and retina became more resilient to tractions. Lesser bleed during vitrectomy provide good view of retina, which lead to reduce incidence of iatrogenic retinal breaks.^{17,18}

Post-operative vitreous haemorrhage is important factor affecting directly, final visual outcome. Many studies revealed that IVB pretreatment reduced the rate of recurrent post-operative vitreous haemorrhage. Previous research proved that bevacizumab can be found in retinal tissue two weeks after intravitreal injection. Although bevacizumab in vitreous cavity is removed by vitrectomy but remaining part in retinal tissue may have some effect. This remaining bevacizumab is partly considered to be helpful in post operative vitreous cavity blood resolution. Other factors involved in blood clear up of vitreous cavity after vitrectomy for diabetic vitreous haemorrhage should also be considered like left over blood after pars plana vitrectomy, iatrogenic bleeds from injured blood vessels, bleed from traction on fibrovascular tissue, inflammatory cells and fibrin within the vitreous. Intravitreal bevacizumab can reduce these factors, helping to decrease incidence of recurrent vitreous haemorrhage.¹⁹

Visual rehabilitation is the most important issue for both patients and retina surgeons. The improved visual outcome for diabetic patients, after intravitreal use of bevacizumab, is an important factor to be considered. This is attributed to diminished trauma to retina during vitrectomy surgery, a decreased extent of vitreous bleed, and posterior fibrovascular repletions, or clearance of media after surgery in patients treated with bevacizumab. The effect of reducing diabetic macular edema plays a positive role in increasing visual outcome.²⁰

The ideal timing for pretreatment with bevacizumab prior to diabetic vitrectomy is unknown. Di Lauro performed a comparative study of a 7- day with 20- day pre-vitrectomy administration of bevacizumab. Clinical outcomes revealed no statistically significant differences between two groups but intraoperative bleeding, frequency of endodiathermy, iatrogenic retinal breaks, surgical mean time and incidence of post operative vitreous haemorrhage were found more in 20-day group.^{17,21}

There is a potential harm of intravitreal bevacizumab injection, worsening vitreoretinal traction caused by rapid neovessels involution and fibrosis, which leads to contraction of fibrovascular membranes.²² Many studies have revealed aggravation of fibrosis after intravitreal bevacizumab injection for active progressive diabetic eye disease. One recent study showed that tractional retinal detachments worsened and newly formed in 11 eyes (5.2 %) of 211 intravitreal

bevacizumab injections in high-risk proliferative diabetic retinopathy. The time interval between injection and diagnosis of tractional retinal detachment was 13 days on an average. Ishikawa injected intravitreal bevacizumab in eight eyes and reported that two eyes injected one week before vitrectomy, had worsening of fibrosis, which lead to occurrence of surgical complications. There are evidences showing that the effect of intravitreal bevacizumab is rapid on regression of neovessels, often after one day. So it seems that 3 to 5 days or even less time is sufficient for bevacizumab to have its effect on retinal neovascularization.⁴ Bevacizumab is considered now safe and effective drug in the world. Its use is still off label but it is being used in many countries due to its cost-effective value. The recent comparative clinical trials now proved that no significant local and systemic complications related to intravitreal bevacizumab were found as compared to other anti-VEGF drugs. The postoperative retinal detachment and repeat surgery showed no significant differences. These can be possibly related to natural process of proliferative diabetic retinopathy.²³

Our study showed that 70% of the patients had improved best corrected visual acuity, with bevacizumab pretreatment in diabetic vitrectomy and there were insignificant ocular and no systemic side effects. There was a statistically significant difference in final visual outcome in with- and without- bevacizumab groups. Only one drawback in our study was that we did not have data for macular status of patients. It was not possible due to preoperative dense vitreous haemorrhage but it was our special consideration to see status of macula postoperatively. Whenever needed, we also performed fundus fluorescein angiography of our patients. Our findings were relevant to other studies done previously, with statistically significant benefit of using intravitreal bevacizumab in diabetic vitrectomy.^{22,23}

Conclusion:

Pretreatment with intravitreal bevacizumab injection as adjunct to pars plana vitrectomy is effective to have better visual outcome in management of diabetic vitreous haemorrhage.

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