

ROLE OF AVASTIN ON THE INCIDENCE OF POST OPERATIVE VITREOUS HEMORRHAGE AFTER VITRECTOMY IN DIABETIC VITREOUS HEMORRHAGE

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Abstract

Diabetic retinopathy is one of the most common cause of legal blindness. Five to 10% of diabetic patients suffer from the proliferative diabetic retinopathy which includes the formation of new vessels on the retina

and optic disc which can be complicated as vitreous hemorrhage and tractional retinal detachment. Pars plana vitrectomy along with laser photocoagulation is being used for the management of vitreous hemorrhage. In our study we used injection avastin one week before surgery to see its role on the incidence of re-bleed after vitrectomy in diabetic vitreous hemorrhage.

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Materials and Methods: Fifty patients were divided into 2 equal groups on the basis of simple random sampling. 25 patients in Group I were operated with routine pars plana vitrectomy with endolaser photocoagulation while in Group II all the 25 patients were given injection avastin intra-vitreally one week before surgery. Evaluation was done on the first post operative day, first follow up visit (one week) and after one month to see the incidence of re-bleed. Chi-square test was used for statistical analysis.

Results: Fifty patients divided into two groups. In Group I, 3 patients had recurrent vitreous hemorrhage on first post-operative day, 3 patients had re-bleed on first follow up visit, and only 2 patients had re-bleed after one month. In Group II, none of the patients had recurrent vitreous hemorrhage on first post-operative day and on first follow-up visit (one week) while 2 patients had re-bleed after one month.

Conclusion: Injection intravitreal Avastin (Bevacizumab) one week before surgery significantly reduces the risk of vitreous hemorrhage after vitrectomy in diabetic patients.

Keywords: Avastin, bevacizumab, re-bleed, recurrent vitreous hemorrhage, diabetes, proliferative diabetic retinopathy.

Introduction

Diabetes mellitus is an endocrine disorder characterized by elevated levels of glucose due to either decreased production or response of insulin. Type I diabetic patients are affected more (40%) with proliferative diabetic retinopathy than type two diabetics (20%). One of the most important indicator contributing towards diabetic retinopathy is the duration of diabetes. 50% of patients with diabetes develop proliferative eye disease after 10 years and 90% after 30 years.¹

The hallmark of proliferative diabetic retinopathy is the growth of new blood vessels in response to ischemia. These blood vessels can grow anywhere on the retina or the optic disc. The angiogenic factors play a vital role in the sprouting of these new vessels, Out of them vascular endothelial growth factor is the most important. The end products of glucose metabolism lead to the development of vitreous abnormalities found in the proliferative diabetic retinopathy. The newly formed blood vessels are firmly adherent to the posterior vitreous facing the retina, thus when the posterior hyaloid contracts it pulls the new blood vessels forcing them to rupture leading to vitreous hemorrhage. As a result of this pull tractional or rehgmatogenous retinal detachment can occur. As concluded by the diabetic retinopathy study, pan retinal photocoagulation leads to a decrease in visual loss by more than 50% in diabetic patients with high risk factors.

The severe non proliferative diabetic retinopathy is defined as hemorrhages in all the four retinal quadrants, beading together of veins in two retinal quadrants or the presence of intra retinal microvascular abnormalities in on retinal quadrant, The Early Treatment Diabetic Retinopathy Study concluded that pan retinal photocoagulation was beneficial in diabetic patients with severe non proliferative stage and older than 40 years. The diabetic retinopathy vitrectomy study recommended that pars plana vitrectomy done within 6 months of onset of vitreous hemorrhage was associated with better prognosis in diabetic patients irrespective of the stage and type of diabetes.¹ The aim of pars plana vitrectomy is to remove the vitreous affected by hemorrhage along with the posterior hyaloid facing towards the retina so as to relive the traction.

Various methods have been purposed to excise the traction between retina and vitreous. Of them delamination and segmentation techniques are the most commonly used ones in the excision of fibro-vascular growth on the internal limiting membrane and extending into the vitreous. Anti-vascular endothelial growth factors are being used in addition to laser as an adjunct to reduce the risk of neovascularization.² Vitrectomy surgery may have intra-operative and post-operative complications such as cataract, anterior hyaloid fibrovascular proliferation, fibro-vascular ingrowth, retinal detachment and recurrence of vitreous hemorrhage.

Bevacizumab (Avastin) is the most commonly used anti VEGF. It is an antibody which is monoclonal in structural composition. It targets the inactive forms of vascular endothelial growth factor and inhibits them thus preventing them from conversion into active forms.

It is this ability of Bevacizumab which stops the sprouting of new blood vessels diabetic retinopathy³. The purpose of my study is to investigate the role of avastin on the incidence of rebleed after vitrectomy in patients with diabetic vitreous hemorrhage.

Materials and Methods

This was a randomized controlled trial study conducted at Institute of Ophthalmology Unit – III, Mayo Hospital Lahore over a duration of two years from February 2012 to February 2014. 50 patients with type II diabetic vitreous hemorrhage were included. Patients were divided into two groups of equal size on the basis of simple random sampling. Group I included 25 patients which were operated with routine pars plana vitrectomy with endolaser photocoagulation. Group II included 25 patients which were given injection avastin 125 mg / 0.05 ml one week before surgery. All the patients with type II diabetic vitreous hemorrhage were included while patients with combined retinal detachment/tractional retinal detachment and rubeosis iridis were excluded. Informed consent was taken from patients. After history detailed anterior and posterior segment examination was performed with the help of slit lamp and indirect ophthalmoscope. B – Scan was performed in cases where fundus was not visible. Evaluation was done on first post-operative day, on first follow-up visit after one week and then second follow-up visit after one month. Statistical analysis was done with the help of Chi-square test.

Results

Fifty patients with type – II diabetes of age between 30 – 60 years were divided into two groups containing 25 each. In Group I, 17 male (68%) and 8 female (32%) while in Group II there were 15 male (60%) and 10 female patients (40%).

Table 1:

	Group 1		Group 2	
Males	17	68%	15	60%
Females	8	32%	10	40%
Total Patients	25	50%	25	50%

On evaluation at first post-operative day 3 patients (12%) had re-bleed while 22 patients (88%) had no recurrent bleed in Group I while in Group II none of the patients (0%) had re-bleed at first post-operative day. On evaluation at the first follow-up visit 3 more patients (24%) in Group I had re-bleed while 19 patients (76%) had no re-bleed and in Group II no patients (0%) had re-bleed. Regarding the evaluation after one month, 2 more patients (32%) in Group I had re-bleed and there was no re-bleed in other 17 patients (68%) while in Group II, 2 patients (8%) presented with recurrent vitreous hemorrhage. So as a whole comparing

Group I and II, 8 patients (32%) had re-bleed in Group I and 2 patients (8%) had re-bleed in Group II. Chi-square Test was used for statistical analysis for the comparisons between the two groups with a p-value = 0.03 (statistically significant). Regarding the complications among all the patients, in one patient there was post operative anterior uveitis, one had cataract formation and in one patient there was rise in Intraocular pressure.

Discussion

Treatment of the proliferative diabetic retinopathy has always been a challenge because the repeated bleeding during the procedure makes the procedure lengthy and difficult and is frequently associated with recurrent vitreous hemorrhage. The recurrence of vitreous hemorrhage is multifocal. It could be localized, re-proliferation into the hyaloid face or ingrowth of vessels from the sclerostomy sites after pars plana vitrectomy.⁴ The recurrence of vitreous hemorrhage immediately after pars plana vitrectomy is not due to re-proliferation⁵ unless these have been incompletely removed during surgery. Major causes for the recurrence of vitreous hemorrhage are aggressive intraoperative surgical maneuvers, inappropriate homeostasis, persistent retinal neovascularization and from surgically injured retinal vessels.

Table 2: 1st Post Operative Day.

	Group 1		Group 2	
	Number of Patients	%	Number of Patients	%
Patients without re-bleed	22	88%	25	100%
Patients with re-bleed	3	12%	0	0%

Table 3: 1st Follow-up after 1 Week.

	Group 1		Group 2	
	Number of Patients	%	Number of Patients	%
Patients without re-bleed	19	76%	25	100%
Patients with re-bleed	6	24%	0	0%

Table 4: 2nd Follow-up after 1 Month.

	Group 1		Group 2	
	Number of Patients	%	Number of Patients	%
Patients without re-bleed	17	68%	23	92%
Patients with re-bleed	8	32%	2	8%

Hypoxia induced by capillary loss in diabetic retinopathy warrants the need for increased blood supply by inducing a feedback response. As a result vascular endothelial derived growth factor is produced which leads to the growth of new blood vessels and it is a key mediator for angiogenesis.⁶ Thus, in the prevention of diabetic retinopathy suppression of vascular endothelial growth factor is important.⁷

The caliber of blood vessel plays an important role in preventing the recurrence of vitreous hemorrhage after intravitreal bevacizumab (avastin) has been administered. The vascular endothelium is responsible for a number of haemostatic functions, one of which is maintaining the vascular tone which in turn is modulated by vascular endothelial derived growth factor.⁸ Thus, blockage of vascular endothelial derived growth factor by bevacizumab will result in vasoconstriction ultimately leading to vascular regression.

The effect of anti vascular endothelial growth factor only lasts for days and after that it reverses. Thus in order to obtain the maximum benefit from pars plana vitrectomy it is advised that it must be done during this window period to reduce the trauma related hemorrhage into the vitreous cavity.

Yang et al concluded in their study that recurrence of vitreous hemorrhage was drastically reduced with the use of a surgical adjuvant 10% C₃F₈ tamponade (1 out of 31, 3.2%).⁹ They also concluded that administering Bevacizumab after vitrectomy with tamponade (10% C₃F₈) increases the clearance of early postoperative vitreous hemorrhage (7.2 ± 5.6 days vs. 15.2 ± 11.4 days in no pretreatment group).¹⁰

Ishikawa et al reported minimum bleeding during surgical dissection of fibro-vascular membranes in patients who received Intravitreal bevacizumab 3 to 30 days before vitrectomy.¹¹ Romano et al performed a non-controlled prospective study on 32 eyes with persistent vitreous hemorrhage resulting from active Proliferative diabetic retinopathy, in which 2.5 mg Intravitreal bevacizumab was injected within 1 week before pars plana vitrectomy.¹² The percentage of severe recurrent vitreous hemorrhage (grade 3) was 3% at the 1 – week and 1 – month follow-ups, and mean best corrected visual acuity significantly improved from 1.6 to 0.40 log MAR units. Intraoperative bleeding was also minimized when cutting the fibro-vascular tissues. The authors suggested that intravitreal bevacizumab injection a few days before planned surgery could be efficacious in decreasing the possibility of significant early postoperative vitreous hemorrhage. They performed fluid – air exchange at the end of the procedure,

whereas this study excluded eyes in which internal tamponade was used because of the controversial effect of air, long – acting gas, or silicone oil on the rate and distribution of postoperative hemorrhage.¹³

Rizzo et al conducted a clinical trial and showed decreased surgical time, less need for intraoperative tool exchange, less intraoperative bleeding, reduced need for endo-diathermy, and better 6-month visual results in patients who received Intravitreal bevacizumab 5 to 7 days before vitrectomy.¹⁴ Although this study showed no statistically significant difference between the 2 groups regarding the number of endo-diathermy applications during vitrectomy, intraoperative bleeding was significantly less common in the intravitreal bevacizumab group. Early postoperative vitreous hemorrhage was not evaluated in the study by Rizzo et al, whereas it was the primary outcome measure in the present clinical trial.

Preliminary evidence suggests that intravitreal bevacizumab may be effective in decreasing vitreous hemorrhage secondary to proliferative diabetic retinopathy. In a study by Spaide and Fisher, 2 patients with vitreous hemorrhage secondary to proliferative diabetic retinopathy were treated with 1 intravitreal injection of 1.25 mg bevacizumab.⁷ There was partial resolution of vitreous hemorrhage in each patient at 1 week followed by complete resolution at 1 month. In a recent study by Moradian et al, it was shown that 1 bevacizumab in eyes with active progressive proliferative diabetic retinopathy resulted in significant resolution of vitreous hemorrhage.¹⁵ Intravitreal bevacizumab results in regression of new blood vessels leading to the cessation of bleeding while resorption of hemorrhage continues. This results in clearing of the vitreous hemorrhage and improvement of vision. Resolution of vitreous hemorrhage after intravitreal bevacizumab was noteworthy in this study. In 9 patients who were scheduled for vitrectomy for non-clearing vitreous hemorrhage, decreased vitreous hemorrhage and significant improvement of vision occurred after bevacizumab injection, obviating the need for surgical intervention.

In our series, 50 patients were divided into two equal groups. All the patients were operated for Pars Plana Vitrectomy. 25 patients in group I were operated with routine pars plana vitrectomy while the other 25 patients in group II were given injection intravitreal Avastin 1.25mg/.05ml one week prior to surgery.

On evaluation at first post-operative day 3 patients (12%) had rebleed while 22 patients (88%) had no recurrent bleed in group I while in Group II none of the patients (0%) had recurrent vitreous hemorrhage.

On evaluation at the first follow-up visit 3 more patients in group I (24%) had post operative vitreous hemorrhage while 19 patients (76%) had no re-bleed as compared to these statistics in Group II no patient (0%) had re-bleed. Regarding the evaluation after one month, 2 more patient (32%) in group I had re-bleed and there was no recurrent hemorrhage in other 17 patients (68%). In group II, 2 patients (8%) had a recurrent vitreous hemorrhage and 23 patients (92%) had no re-bleed. So as a whole comparing Group I and II, 8 patients (32%) had re-bleed in Group I and 2 patients (8%) had re-bleed in Group II.

Chi-square test was used for statistical analysis for the comparisons between the two groups with a p-value = 0.03 (statistically significant). So the intravitreal Injection avastin can be good adjuvant to avoid the re-bleed in patients undergoing vitrectomy presenting with diabetic vitreous hemorrhage. We also found that the preoperative bevacizumab injection minimize the intraoperative bleeding during the delamination / de-segmentation in the patients with advanced diabetic eye disease also associated with reduced surgical time, less endo-diathermy application and reduced chances of retinal damage like iatrogenic retinal breaks.

We conclude that preoperative intravitreal injection bevacizumab is beneficial for the management of proliferative diabetic retinopathy/vitreous hemorrhage as it makes the procedure safe and easy.¹⁶

In summary, intravitreal injection of bevacizumab 1 week before pars plana vitrectomy for proliferative diabetic retinopathy decreases the incidence of early post-vitrectomy hemorrhage.

Conclusions

Intravitreal injection of bevacizumab 1 week before vitrectomy is statistically significant in reducing the incidence of early post-vitrectomy hemorrhage in diabetic patients.

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