

Efficacy of Preoperative Bevacizumab Injection for Vitrectomy in Diabetic Tractional Retinal Detachment

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ABSTRACT

Purpose: To evaluate the efficacy of preoperative intravitreal bevacizumab (IVB) in patients undergoing pars plana vitrectomy for diabetic tractional retinal detachment (TRD).

Methods: In this prospective clinical trial 130 eyes of 116 diabetic patients who were candidates for vitrectomy were randomly assigned to receive 1.25 mg intravitreal bevacizumab 3 to 5 days before operation (injection group I = 64) or no injection before operation (noninjection group II = 66). Amount of intraoperative bleeding, number of endodiathermy applications, total time of raised intraocular pressure, postoperative visual acuity and vitreous hemorrhage (VH) were recorded. Minimum follow-up was of 6 months.

Results: The injected group I had less intraoperative bleeding ($p = 0.003$), better visual acuities ($p = 0.003$), less number of endodiathermy applications (1 vs 3), required reduced time of raised IOP (1.5 vs 4 min) to control the intraoperative bleed. In injected group I, one patient developed significant postoperative VH obscuring the fundus and one had minimal bleed at 1 month follow-up as against 6 and 4 eyes in group II respectively ($p = 0.03$).

Conclusions: Preoperative intravitreal bevacizumab injection for Diabetic TRD facilitates the surgery, decrease the amount of intraoperative bleeding, decrease the rate of postoperative VH and improves visual acuity.

Keywords: Diabetic retinopathy, TRD, Bevacizumab, Vitreous hemorrhage, Bleeding.

INTRODUCTION

Surgical management of diabetic tractional retinal detachment (TRD) is among the most challenging vitreoretinal techniques. These eyes often have multiple or thick layers of neovascular proliferative tissue, resulting in significant intra- and postoperative bleeding. Intraoperative bleeding often occurs while removing fibrovascular tissue and this can hinder successful completion of the surgery. The incidence of postoperative vitreous hemorrhage in patients undergoing pars plana vitrectomy (PPV) for vitreous hemorrhage in proliferative diabetic retinopathy (PDR) is around 29 to 75%.¹⁻⁴ It has also been shown that an intraocular bleed is associated with increased risk of vitreous hemorrhage (VH) in the early postoperative period.⁵ This interferes with fundus examination, detection of iatrogenic retinal breaks and performing a laser therapy, if required. It also delays visual recovery and can necessitate an additional surgery. Thus, there is a need for regression of neovascularization prior to vitrectomy for PDR.

Use of intravitreal bevacizumab (Avastin, Genentech, South San Francisco, CA) being given prior to surgery for the purpose of regressing neovascularization has been reported by Chen and Park.¹⁷ Yeoh J et al⁶ and Ishikawa et al⁷ reported

improvement in surgical ease and decrease in surgical bleed in small series of patients. However, these reports were not substantiated in a randomized controlled fashion. Rizzo et al⁸ randomized 22 patients into two arms, one of which received intravitreal bevacizumab 5 to 7 days before vitrectomy, while the other underwent direct PPV. Preoperative intravitreal bevacizumab was associated with reduction in operative times, tool exchanges during surgery, number of endodiathermy applications, intraoperative bleeding and significantly better visual acuity at 6 months compared with direct PPV. However, they did not study the incidence of postoperative hemorrhage. Another study by Yeung L et al⁹ looked at the incidence of early vitreous hemorrhage after vitrectomy, but they do not include factors related to intraoperative bleeding.

Further, there is no mention in literature regarding an objective, clinical grading of intraocular hemorrhage, particularly from the perspective of the operating surgeon. Since this is one of the most important factors in the context of vitrectomy for PDR, we have devised a scheme to quantify intraocular bleeding during surgery and the use of hemostatic procedures (see 'methods' section below).

In order to overcome the limitations of the published studies and to obtain a composite picture of both, intra- and

postoperative results following intravitreal bevacizumab prior to vitrectomy for PDR, we carried out this randomized controlled trial.

PATIENTS AND METHODS

Following approval of Institutional Ethics Committee (IEC), we undertook this prospective, double blind, randomized clinical trial, comparing the effect of preoperative intravitreal bevacizumab injection with subjects undergoing direct PPV, enrolling patients from January 2009 to December 2009.

Participants: The study population consisted of 143 eyes of 129 patients scheduled to undergo vitrectomy for TRD involving the macula due to PDR, who agreed to participate in the study and signed an informed consent form after an explanation of the study was given to them. They were randomized to preoperative intravitreal bevacizumab (Group I) or no injection (Group II). We excluded subjects with history of previous vitreoretinal surgery and previous intravitreal anti-VEGF injection/s in the past 3 months. Presence of coincidental ocular pathology/ies (e.g. glaucoma, uveitis, retinal vascular occlusions, retinal degenerations and dystrophies, etc.) was considered as an exclusion criteria. Patients with history of thromboembolic accidents, such as myocardial infarction, stroke, etc. were not considered for the study. Subjects that underwent silicone oil injection or simultaneous vitrectomy with any other surgery were also not included in the study. Patients with redetachment following surgery were not considered for final statistical analysis. On basis of these criteria, 13 eyes had to be further excluded and 130 eyes of 116 patients were finally considered for statistical evaluation.

Preoperative examinations: Following enrolment patients underwent complete ophthalmic examination including BCVA (Snellen) and IOP (noncontact tonometry) measurements, slit lamp examination for anterior segment and detailed funduscopy with 90 diopter lens and indirect ophthalmoscopy. Further investigations such as optical coherence tomography, B-scan and fluorescein angiography were performed as indicated. Detailed history of coincidental and past systemic and ocular pathologies and procedures were elucidated.

Preoperative preparations: All subjects underwent either intravitreal or sham injection procedure 3 to 5 days before vitrectomy. Subjects of group I received 1.25 mg (0.05 ml) bevacizumab (Avastin, Genentech incorporate) intravitreal injection, under complete sterile preparations (application of povidone iodine ophthalmic solution on the conjunctival surface, eyelashes, eyelid margins and periocular skin, use of sterile drape and speculum) in the operating theater, under topical anesthesia (proparacaine-0.5%). Following the injection, all subjects received topical antibiotic (moxifloxacin) eyedrops for 3 days. All injections were given by a single surgeon (NSC). Patients of group II received sham injections by pressing the hub of the tuberculin syringe against the subject's sclera, preceded by similar sterile preparations and followed by the same post-injection routine as in group I. In this way we insured

that both the patient and the operating surgeon (MN) were kept blinded about the preparatory intravitreal injection, only the injector was unblinded to this information.

Surgery details: Pars plana vitrectomies were performed within 3 to 5 days of the injection. After core vitrectomy, posterior vitreous face was pierced and delamination and segmentation was carried out from center toward periphery. The areas of active neovascularization were recognized and cauterized before dissection. In order to tackle the intraocular bleeding, IOP was raised with the foot pedal to instantly control intraocular bleeding instead of raising bottle height pressure. Digital control eliminates manual raising and lowering of the IV pole, which is required with traditional gravity infusion method. The Alcon Accurus machine beeps every minute and helps to monitor the total time of raised IOP required during the procedure. If required meticulous endodiathermy was carried out using the unipolar cautery. Once again the assistant kept a record of the total number of endodiathermy applications during a case. Retinotomy was employed whenever the retina could not be reattached despite removal of epiretinal membranes. Endolaser panretinal photocoagulation was applied to previously untreated retinal areas. Fluid was replaced by air, silicone oil, or sometimes no tamponade was used. Silicon oil was used in complicated detachment cases or to control bleeding. Eyes, in which oil was used, were not considered for statistical analysis.

Outcome measures: Our main outcome measures were comparison of intra and postoperative bleeding and visual acuity. We devised a grading scale to comment on the severity of intraocular bleeding from the perspective of the operating surgeon. It enabled us to study objectively (as the operating surgeon was blinded) the efficacy of preoperative IVB in inducing regression of retinal neovascularization and its implications on the surgery. To the best of our knowledge, such a scale does not exist in literature. It is as follows:

- *Grade 0:* indicating no or self limited bleeding without hemostatic procedures
- *Grade 1:* indicating hemostasis achieved with elevated IOP
- *Grade 2:* indicating hemostasis achieved with elevated IOP and endodiathermy of the bleeding point
- *Grade 3:* despite adequate attempt to achieve hemostasis (with elevated IOP and/or endodiathermy), thick clot formation or uncontrolled bleeding interfering with the surgical plane.

Postoperative examination: Each patient was seen on day 1, month 1, 3 and 6 months following the surgery. During each visit complete ophthalmic examination as detailed above was carried out. We looked for presence and severity of postoperative VH at 4 weeks after surgery, grading it according to a system reported by Kuppermann et al.¹⁰

- *Grade 0:* defined as no VH (a clear view throughout)
- *Grade 1:* mild to moderate VH, where a good view of the optic disk and macular details was maintained
- *Grade 2:* dense VH, with significant obscuration of the disk and macular details.

All patients were first examined 1 month following the surgery. Patients with grades 1 or 2 vitreous hemorrhage underwent ultrasound examination to assess retinal status. Patients with grade 2 vitreous hemorrhage were reviewed again after one month. Those with persistent vitreous hemorrhage underwent resurgery. The 4 weeks time interval was chosen to allow for complete resorption of intravitreal gas (if used) and to avoid cases of immediate postoperative VH that could have been caused by resuspension of residual blood in the vitreous base.

Statistical methods: Statistical analysis was performed with SPSS software. Qualitative variables were expressed using percentages, whereas quantitative data were defined using mean, standard deviation, confidence interval, or a combination thereof. The t-test, Chi-square test, and Mann-Whitney U-test were used for inferential statistics. The level of significance was set at 0.05.

RESULTS

Baseline data: 143 eyes of 129 patients were enrolled in the study. Out of these 143 eyes, nine eyes were injected with silicon oil at the time of surgery, two had developed rhegmatogenous detachments and two did not complete the minimum follow-up. Of the 13 excluded eyes 9 were in groups 2 and four belonged to Group 1. Thus, totally 13 eyes were excluded and the final analysis was done for 130 eyes of which 64 eyes were in group I and 66 eyes in group II. Their demographic data can be studied in Table 1. The two groups were well matched for age, gender, number of cases with systemic hypertension and history of panretinal photocoagulation. There was no statistically

significant difference in baseline BCVA between the two groups ($p = 0.219$) (Table 1).

Intraoperative bleeding: Group I required significantly reduced total time of raised IOP (1.5 vs 4 min, $p < 0.001$) and less number of endodiathermy (average 1 vs 3) applications ($p = 0.01$, not significant) to control the intraoperative bleed as compared to group II. Grade 0 bleeding occurred in 36 patients in group I and 12 patients in group II, difference being statistically significant ($p = 0.003$). Intraoperative bleeding requiring some hemostatic procedure (grades 1, 2 and 3) occurred in 28 patients in group I compared to 54 patients in group 2 and this difference was also statistically significant ($p = 0.003$) (Table 2).

Postoperative course and reoperation rates: In the postoperative period, vitreous hemorrhage (Grade 1, 2) developed in 4 patients in group I as against 20 patients in group II and this difference was found to be statistically significant ($p = 0.03$).

In group I, 2 patients developed Grade 2 postoperative VH obscuring the fundus and 2 had grade 1 bleeding at one month follow-up, while in the group II, 12 patients developed grade 2 postoperative VH obscuring the fundus and 8 developed grade 1 bleed.

Reoperation (vitrectomy) was performed in eight patients in the group II due to rebleed while two patients in group I required resurgery to clear the VH, after which no eyes had recurrent postoperative VH (Table 3).

Visual recovery: At final follow-up the mean logmar visual acuity in group I (1.02) was statistically better than mean visual acuity in group II (1.72), this difference being statistically significant ($p = 0.003$) (Table 4).

Table 1: Baseline patient characteristics in study groups

Characteristics	Group 1 with preoperative avastin	Group 2 without preoperative avastin	p-value
No. of eyes	64	66	
Age (years) mean (range)	51.21(28-65)	51.81(25-68)	0.798
Sex			
Male	36	34	0.89
Female	28	32	0.89
Systemic hypertension (n)	18	32	0.15
Prior PRP (n)	38	42	0.92
LOGMAR			
BCVA (standard deviation)	1.79 (0.75)	2.06 (0.81)	0.219

Table 2: Comparison of intraoperative procedures in study groups

Characteristics	Group 1	Group 2	p-value
No. of eyes	64	66	
No. of endodiathermies mean (range)	1 (0-4)	3 (0-8)	0.01
Cumulative time of raised IOP mean (range)	1.5 minutes (0-8)	4 minutes (1-7)	< 0.001
Intraocular bleeding			
Grade 0	36	12	0.003
Grade 1	14	18	
Grade 2	10	22	0.003
Grade 3	4	14	

Table 3: Comparison of incidence of postoperative vitreous hemorrhage in study groups

Characteristics	Group 1 with avastin	Group 2 without avastin	p-value
No. of eyes	64	66	
Postoperative vitreous hemorrhage (4-6 weeks)			
Grade 0	60	46	
Grade 1	2	8	
Grade 2	2	12	0.03
Repeat surgeries to clear vitreous hemorrhage	2	8	0.36

Table 4: Postoperative visual acuity in study groups

Characteristics	Group 1 with avastin	Group 2 without avastin	p-value
No. of eyes	64	66	
Mean range postoperative visual acuity (LOGMAR)	1.02	1.72	0.003

DISCUSSION

Use of antiangiogenic agents prior to diabetic vitrectomies in order to decrease pre- and postoperative bleeding through regression of neovascularization has been common. The aim of this study was a systematic elucidation of the effect of this manoeuvre on facilitation of the surgery and postoperative course, especially to describe these factors from the perspective of the operating surgeon.

Following bevacizumab injection, new vessel constriction has been noted within 1 day after treatment. In addition, the caliber of the normal retinal vessels also becomes smaller in the major and secondary branches.¹¹ Decrease in retinal circulation, greatly reduce the likelihood of intraoperative bleeding. As the surgical field and surgical plane are not obscured by a fresh blood clot, retinal vessels are less likely to be damaged during delamination, further reducing the possibility of intraoperative bleeding.¹²⁻¹⁴

The optimal time interval between IVB and vitrectomy is still unclear. In a rabbit study by Bakri et al²⁰ peak vitreous concentration reached 1 day following intravitreal injection of 1.25 mg bevacizumab. The half life of the drug was 4.32 days. Most reports show significant resolution of neovascularization within the first week of IVB.^{12,15,16} It is feasible to perform vitrectomy 1 to 30 days after IVB. However, hypothetically, vitrectomy is best performed after most neovascularization has regressed and before the progression of TRD by fibrovascular complex contraction. In previous studies, IVB was performed safely 3 to 33 days before vitrectomy.^{7,13,17} However, Ishikawa et al (2007) reported that two patients who received bevacizumab 7 days before surgery showed strong fibrosis and adhesion of the fibrovascular membrane, which caused some surgical complications.

We studied the beneficial effect of intravitreal bevacizumab injection in terms of objective measurement of hemostatic procedures, namely the total time for which the IOP was kept high and the number of cautery applications. We devised the grading system to comment on the severity of intraocular

bleeding from the perspective of the operating surgeon. It helped us to objectively (as the operating surgeon was blinded) assess the efficacy of preoperative intravitreal bevacizumab in inducing regression of retinal neovascularization and its implications on the surgery. Extensive cautery causes necrosis and shrinkage of retinal tissue and may incite postoperative inflammation. Prolonged elevation of IOP causes corneal edema impairing surgical visualization and also IOP fluctuations cause damage to the optic nerve. Group I required less number of total endodiathermy applied and reduced total time for which the IOP was kept high suggesting facilitation of the surgery, on the other hand, higher range of these factors in group II suggests greater intraocular bleeding, which was more difficult to control.

No patient in our series developed a progression of TRD following intravitreal bevacizumab, although in the presence of marked glial proliferation it has been shown to result in rapid shrinkage of fibrovascular tissue and development of diabetic TRD.^{7,13} The reported time interval between injection and diagnosis of retinal detachment has been as short as 3 days, and on the average 13 days.¹⁸ Moradian et al¹⁹ also reported exacerbation and subsequent contracture of fibrous tissue leading to TRD in two patients who received intravitreal bevacizumab for active progressive TRD. We feel that the relatively short (3-5 days) interval between the injection and vitrectomy in our series, provided the beneficial antiangiogenic effect, and at the same time did not lead to this devastating complication.

The inhibitory effect of bevacizumab on fibrovascular activity may persist even if the vitreous is removed. Incidence of postoperative vitreous hemorrhage following preoperative intravitreal bevacizumab varies from 13 to 25% in different studies.^{21,22} In our study, the incidence of postoperative vitreous hemorrhage was 6.25% in group I and 30.3% in group II. Lower incidence in group I suggests that preoperative injection of avastin is helpful in decreasing the early postoperative VH as well. Our results also showed that bevacizumab pretreatment results in better visual recovery, postoperatively. This possible

difference may be due to decrease in injury and insult to retinal tissue/s during surgery (in terms of endodiathermy, raised IOP) or decreased incidence and extent of hemorrhage after surgery in bevacizumab treated cases.

Rizzo et al⁸ reported their results in 22 patients divided into two groups in one of which 1.25 mg bevacizumab was intravitreally injected 5 to 7 days before vitrectomy. They observed a significant reduction of operative time, mean tool exchange, intraoperative bleeding and number of endodiathermy applications in the bevacizumab treated group. The mean 6 month postoperative visual acuity was significantly better than preoperative values in the group with intravitreal bevacizumab injection but not in the control group. The sample size was small and they did not comment on incidence of postoperative vitreous hemorrhage after preoperative bevacizumab.

Randomized clinical trial by Ahmadih et al²² demonstrated the efficacy of intravitreal bevacizumab in reducing the overall rate of early postvitrectomy hemorrhage and that of more severe grades of vitreous hemorrhage. However, the number of cases were limited to draw any definite conclusion regarding safety of the procedure.

Intraoperative bleeding was assessed by D da R Lucena et al²³ where they observed lower number of erythrocytes recovered from the cassette fluid in patients treated with intravitreal bevacizumab 2 weeks before surgery as compared to them who did not receive the preoperative injection. It has also not addressed regarding postoperative vitreous hemorrhage.

In a report by Wayne Lo et al²¹ bevacizumab pretreatment did not influence rates of postoperative vitreous hemorrhage or final visual acuity. These conflicting results may be due to the retrospective nature and possibility of treated group at much higher risk of postoperative vitreous hemorrhage than untreated group in their study.

Intravenous bevacizumab administration has been known to be associated with systemic hypertension and thromboembolic events.^{9,24} Intravitreal injections involve a 400-fold less dosage of drug and a more targeted delivery. We identified no cases of uveitis, endophthalmitis, ocular toxicity, hypertension, or thromboembolic events after injection in any of our patients.

Our study does have some limitations. We have enrolled all patients with TRD requiring vitrectomy which does not provide an exact measure of severity of fibrovascular proliferation. It is a fact that TRDs can exist from a simple case to a complex inoperable situation. Unfortunately, there is no better classification available at present. In fact, lack of a satisfactory classification system for PDR, limits the accurate matching of control and intervention groups necessary for any controlled clinical trial. Moreover, the fact that we excluded eyes in those which we injected silicon oil or those that developed rhegmatogenous retinal detachment following surgery can be looked as a limitation. The main outcome measures of our study are to mainly look at the role that

preparatory avastin plays in relation to pre and postoperative bleeding. Injection of silicon oil and rhegmatogenous RD development create new variables which possibly could have a bearing on the results but to analyze these small numbers in relation to the whole study would not give correct correlation. Hence we choose to exclude those eyes. These factors would complicate the analysis and with these small numbers it would be difficult to come to any statistical conclusion. One would require a much larger study to look at these variables in relation to bleeding.

CONCLUSION

This study provides objective proof that the intravitreal injection of bevacizumab before vitrectomy for TRD, facilitates the surgery, decreases the surgical bleeding and need for hemostatic measures, decrease the rate of postoperative VH and improves the visual acuity results. Therefore, we recommend this procedure especially in patients with TRD having active neovascularization and/or extensive or multiple layers of fibrovascular proliferation.

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