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Visual Outcomes and Incidence of Recurrent Vitreous Hemorrhage after Vitrectomy in Diabetic Eyes Pretreated with Bevacizumab (Avastin)

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Abstract

Purpose—To evaluate the safety and effect of bevacizumab pretreatment on incidence of recurrent vitreous hemorrhage and visual acuity after vitrectomy for proliferative diabetic retinopathy (PDR).

Study Design—Consecutive, retrospective, comparative cohort study

Methods—Patients undergoing vitrectomy from September 2006 through November 2007 at the Emory Eye Center for complications of PDR were identified and reviewed. A total of 33 eyes pretreated with bevacizumab and 104 eyes untreated were followed for postoperative vitreous hemorrhage and final visual acuity.

Results—Patients in the bevacizumab group were significantly younger than the untreated group (average age 46.4 vs. 58.4) and were more likely to have 20 ga instrumentation (58% vs. 36%). An average of 9.6 days passed between injection and surgery. Early (4–6 weeks) rebleed rates were 15% vs. 13% in the bevacizumab and untreated groups, respectively, and not statistically different. Preoperative (7/200 vs. CF 4'), 1 month postoperative (20/200⁻³ vs. 20/150), and 3 month postoperative visual acuity (20/100⁻³ vs. 20/100⁺²) were not statistically different between groups. No statistical difference was found in rebleed rates with regard to gauge of vitrectomy.

Conclusions—Bevacizumab pretreatment for diabetic vitrectomy was not associated with any observed complications, but may not influence rates of postoperative vitreous hemorrhage or final visual acuity. The overall incidence of postoperative early vitreous hemorrhage in this series was 13% and appears lower than historically reported rates.

Keywords

Avastin; bevacizumab; diabetes; proliferative diabetic retinopathy; vitrectomy; vitreous hemorrhage

Introduction

Postoperative vitreous hemorrhage (VH) following pars plana vitrectomy (PPV) for proliferative diabetic retinopathy (PDR) is a common event with a reported incidence of

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29% to 75%.¹⁻⁴ This complication delays visual recovery and can necessitate additional surgery. Though the source is often not identifiable, etiologies of early hemorrhage include dispersion of residual blood from the peripheral vitreous skirt or retinal surface into the vitreous cavity and from dissected fibrovascular tissue. Sources of later VH include fibrovascular proliferation from sclerotomy sites and neovascularization of residual fibrovascular tissue, the vitreous base, and the iris or angle. Intraoperative techniques such as peripheral retinal cryotherapy,⁵ sclerotomy cryotherapy,⁶ or intravitreal gas⁷ have been suggested to help reduce these hemorrhages. In addition to vitrectomy, intra-office techniques such as fluid-air or fluid-gas exchange have been utilized to clear the blood.^{3, 8, 9}

Recently, an adjunctive treatment for diabetic vitrectomy has been advocated in the form of intravitreal bevacizumab (Avastin®; Genentech Inc., San Francisco, CA).^{10, 11} Typically administered days to weeks prior to surgery, this VEGF-inhibitor subjectively reduces the amount of intraoperative hemorrhage and facilitates fibrovascular membrane dissection. It also has been utilized in patients with non-clearing VH to expedite resolution.¹² However, the effect of bevacizumab pretreatment on final visual acuity and recurrent vitreous hemorrhage remains unknown. The intent of this study was to directly compare the incidence of rebleed and final visual acuity among a consecutive cohort of diabetic eyes with and without bevacizumab pretreatment undergoing vitrectomy for PDR and to monitor for any complications.

Methods

This was a retrospective, comparative, consecutive cohort study which was approved by the Emory University Institutional Review Board, Atlanta, GA.

The charts of all diabetic patients with PDR undergoing PPV between September 2006 and November 2007 at the Emory Eye Center were identified and reviewed. Diabetic eyes undergoing surgery for nonclearing VH or tractional retinal detachment (TRD) with or without a rhegmatogenous component were included for analysis. Eyes undergoing PPV for reasons unrelated to complications from PDR including chronic macular edema, epiretinal membrane, or vitreomacular traction (VMT) were excluded. Additional exclusion criteria included intraocular surgery of any type within the prior 3 months, treatment with bevacizumab or other anti-VEGF agents greater than 1 month before surgery, use of silicone oil (SO), re-operations on eyes with prior diabetic vitrectomy, fellow eyes of the same patient, history of filtering surgery for neovascular glaucoma, and less than 6 weeks of follow-up.

Subject characteristics including age, visual acuity, prior intraocular surgery, history of panretinal photocoagulation (PRP), and lens status were documented from review of the patient's chart. Surgical characteristics including gauge of instruments, intraoperative complications, and use of gas tamponade were recorded from the operative note.

Eyes in the bevacizumab group received an injection less than 1 month (average 9.6 days) before surgery. All intravitreal injections were performed in standard fashion after obtaining informed consent. Briefly, a subconjunctival injection of 2% lidocaine was administered inferior-temporally and topical antibiotic and 5% betadine were applied to the ocular surface. After insertion of a lid speculum, 0.05 ml of bevacizumab (1.25 mg) in a pre-filled syringe was injected using a 30 gauge needle 3.5 mm distal to the limbus. Patients were routinely placed on post-injection antibiotics and no injection related complications were observed. The untreated group consisted of all remaining eyes which were not pretreated with bevacizumab. No eye in the bevacizumab group was re-injected post-operatively.

The surgical procedure consisted of a standard 20, 23, or 25 gauge three-port PPV depending on the individual preference of the surgeon. In each case meticulous shaving of the vitreous base under a wide-angle viewing system with assisted sclera depression was performed with careful attention to remove as much residual blood as possible. Fibrovascular tissue and tractional membranes were removed using a combination of segmentation and delamination, primarily with intraocular scissors or the microvitrektor tip. Full attention was directed at relieving all traction on neovascular fronds. Hemostasis was maintained by raising intraocular pressure or endodiathermy. Thorough PRP was administered to any areas of previously untreated retina out to the level of the ora under sclera depression. No eyes received treatment with cryotherapy, and no eyes received supplemental PRP in the post-operative period.

Primary outcomes of this study were incidence and severity of VH at 4-6 weeks after surgery and final visual acuity. The time point of 4-6 weeks was chosen to allow for complete resorption of intravitreal gas and to avoid cases of immediate postoperative VH which can be caused by factors not necessarily affected by bevacizumab (i.e. resuspension of residual blood in the vitreous base). As VH grading is subjective and examiner dependent, we adopted a grading scale similar to the classification used in the Vitrase® for Vitreous Hemorrhage study.¹³ Grade 0 is defined as no VH (a clear view throughout). Grade 1 was a mild to moderate VH where a good view of the optic disc and macular details was maintained. Grade 2 was dense VH with significant obscuration of the disc and macular details.

Descriptive statistics including mean and standard deviation were calculated for case characteristics. Age and visual acuity comparisons were performed with the Mann-Whitney-Wilcoxon test; group comparisons were performed using the Fisher's exact test and Chi-square test. A *P* value < 0.05 was considered significant. Snellen visual acuity was converted to logMAR units (logarithm of minimum angle of resolution) for analysis purposes.

Results

A total of 214 diabetic vitrectomy surgeries were performed during the study period. Of these, 24 required SO infusion (6 pretreated with bevacizumab, 18 untreated), 16 had insufficient follow-up, 11 underwent PPV for macular edema, epiretinal membrane, or VMT, and 3 had a history of neovascular glaucoma. Nine received bevacizumab too far in advance of their surgery to meet inclusion criteria. Two received bevacizumab at surgery end. Ten eyes were fellow operative eyes, and two eyes were re-operations. Thus, a total of 137 surgeries were analyzed.

Of these surgeries, 33 eyes (24% of total) received preoperative bevacizumab; 5 had predominantly VH and 28 had TRD. During the same time period, 104 eyes (76% of total) underwent vitrectomy without pretreatment. Fifty eyes had predominately VH and 54 had TRD. Characteristics of the two groups are compared in Table 1. Thirteen of the 33 bevacizumab treated eyes (39%) and 23 of the 104 untreated eyes (22%) received intraocular gas tamponade of either 20% SF₆ or 14% C₃F₈. This difference between groups was not statistically different.

Statistical differences were identified in age, gauge of surgical instrumentation, and lens status between groups. The interval between pretreatment and surgery ranged between 1 – 27 days with an average of 9.6. There was no significant difference in the percentage of patients who had received preoperative PRP. The percentage of patients who received SO intraoperatively (and excluded from further study) was not statistically different.

Table 2 summarizes the incidence of early postoperative rebleed or persistent VH and retinal detachment. In the bevacizumab group, 5 patients had VH at the 4-6 week visit (15%). One of these required repeat vitrectomy. In the untreated group, 13 patients had repeat vitreous hemorrhage (13%); four required repeat surgery. There was no statistical significance in the incidence or severity of hemorrhage between groups. Three patients in the bevacizumab group and two in the untreated group had postoperative retinal detachment.

Results of late postoperative hemorrhage are detailed in Table 3. No additional VH occurred in patients in either group between 1-3 months. Only 1 eye of 19 with sufficient follow-up in the bevacizumab group experienced a rebleed (at 5.3 months). Only 5 eyes in the untreated group experienced late postoperative VH (3.1 -7.7 range, average 5.0 months).

The visual acuity of the two groups preoperatively and at 1 and 3 months postoperatively are compared in Table 4. Patients with postoperative retinal detachment were excluded from the latter calculations. There was no statistical difference between groups at any time point.

All previous studies examining rebleed rates were conducted before the advent of sutureless 25 and 23 gauge vitrectomy.^{1, 2, 4} Therefore, early postoperative VH in the untreated group was reanalyzed in relation to instrument gauge (Table 5). No difference in rebleed rates was identified between gauge instrumentation and 20 gauge surgery was not significantly associated with a higher retinal detachment rate.

Discussion

Early or persistent rebleed after vitrectomy not only hinders visual recovery, but also prevents timely and thorough evaluation of eyes which are at particular risk of postoperative complications after complex vitrectomy. Bevacizumab has been advocated for a wide variety of ocular neovascular conditions including PDR, rubeosis iridis, neovascular glaucoma, and corneal neovascularization.¹³⁻¹⁵ In particular, injection of bevacizumab before diabetic vitrectomy is increasingly practiced among retina specialists with anecdotal impressions of reduced intraoperative bleeding and operative time. However, the safety of its use for this indication and its effect on postoperative VH have not been investigated in detail. Therefore, we focused primarily on these endpoints and observed no difference in visual acuity or rates of recurrent VH with its preoperative use or any overt side effects.

Pretreatment with bevacizumab is not considered standard of care, and thus, it was left to the surgeon's discretion whether to pretreat. No surgeon in the study routinely pretreated all diabetic vitrectomy cases. As a result, the treated group in this study clearly clustered toward younger, more poorly managed diabetic patients who were more likely to be phakic, have Type I diabetes, and have greater severity of retinopathy. Hence, the expectation of more severe intraoperative bleeding and need for extensive membrane dissection in this group explains its preferential treatment with bevacizumab. Twenty gauge vitrectomy was also more frequently used, likely in anticipation of greater surgical manipulation and need for the widest array of available instrumentation. Despite this obvious selection bias against bevacizumab treated eyes, no significant difference in visual acuity was observed at any time point. Thus, our results suggest that pretreatment with bevacizumab has no detrimental effect on visual acuity (out to 3 months).

The ideal timing for pretreatment is unknown. One recent study found TRDs were worsened or newly created in 11 of 211 injected eyes (5.2%), leading to significant vision loss.¹⁶ The patients in our study spanned the course of 15 months; as knowledge of this possible association came to light, the preoperative window for bevacizumab injections became shorter. The average time between injection and vitrectomy in our series was 9.6 days, and

our current practice is to administer bevacizumab less than one week before surgery. If there is any possibility of postponement of surgery, injections are withheld.

Our study revealed no statistical significance in the incidence of VH in the treated group (15%) compared to the untreated group (13%) at the 4-6 week visit. It is possible a beneficial effect of bevacizumab may have been masked by the greater severity of disease in the treated group. Likewise, no difference was found in the incidence of later vitreous hemorrhage up to 6 months. The lack of effect on late VH with bevacizumab was not unexpected given its relatively short half-life and the universal application of thorough endolaser panretinal photocoagulation in this series. Furthermore, almost all residual bevacizumab in the vitreous would be removed at the time of surgery and thus unavailable to inhibit remaining or future fibrovascular growth. Consequently, further studies evaluating the safety and efficacy of re-injection of bevacizumab at the conclusion of surgery, a practice some surgeons anecdotally describe, on postoperative VH would be informative. Randomized, prospective studies are needed to better define the benefits and long-term safety of bevacizumab pretreatment for diabetic vitreous hemorrhage, but the results of this study and others¹⁷ provide useful reference for future trials.

There are conflicting reports in the literature on the benefit of air or gas tamponade on reducing early recurrent VH.¹⁷⁻¹⁹ The percentage of patients receiving gas tamponade in the treated vs. untreated groups in this series was not statistically different. Analysis of our untreated group comparing use of gas tamponade (SF₆ or C₃F₈) vs. air or no tamponade and also comparing specific types (SF₆ vs. C₃F₈) of gas did not reveal a statistical effect on VH (data not shown). However, our study was not appropriately designed to evaluate these endpoints and thus our conclusions are limited.

To our knowledge, only one other study to date has compared the effect of bevacizumab pretreatment on postoperative rebleed rates after diabetic vitrectomy. This report observed a beneficial effect of bevacizumab in hastening clearance of VH.¹⁷ However, that study was limited by its small sample size and all eyes were concurrently treated with peripheral retinal cryotherapy, sclerotomy cryotherapy, and 10% C₃F₈ gas tamponade. Thus, the study's conclusions can neither be directly compared to our results nor extrapolated to situations where such techniques are not employed.

Incidence rates of postoperative VH after diabetic vitrectomy of PDR vary substantially in the literature.^{1-4, 20, 21} Schachat et al and Novak et al reported incidence rates of immediate postoperative VH of 75% and 63%, respectively and recurrent VH of 29% and 23%, respectively.^{1, 2} However, both these reports were published more than 20 years ago and predate modern vitrectomy instrumentation and techniques. Although direct comparison of incidence rates among different studies is difficult due to differences in defining and grading VH, we observed an overall incidence rate of 13% (18 out 137 eyes). Our lower incidence rate may reflect intervening advances in modern vitrectomy and changing indications for earlier surgical intervention.

As with all retrospective studies, our results should be interpreted with caution. In particular, we cannot rule out the possibility of selection bias and in fact, feel that our treated group was at higher risk of postoperative VH and complications. Despite this, our results do not show poorer outcomes in the treated group and the severity of disease in this group may in fact mask a positive effect of pretreatment. Our limited follow-up time, use of Snellen visual acuity, and dependence on 5 different surgeons may have influenced our findings. Patient lens status was not controlled for; however, as there were significantly more phakic patients in the pretreated group, we would expect any visual acuity changes due to worsening cataract to skew the pretreated group towards worse visual outcome, which we did not

observe. Patients receiving SO were excluded from our analysis. This may result in some selection bias towards lower rates of hemorrhage and detachment compared to studies conducted before SO usage. Finally as this was a teaching institute, vitreoretinal fellows but not residents were involved in all cases and their degree of involvement varied. On the other hand, we would like to point out several strengths of our study which include comparisons made between groups adjusted for length of follow-up, the relatively large number of eyes, and the consecutive nature of our data. Finally, the results of our study, and in particular the apparent lack of overt complications of bevacizumab pretreatment, provide some reference for future prospective, randomized trials.

In conclusion, postoperative VH after diabetic vitrectomy remains a major cause of morbidity, but advances in modern vitrectomy and adjunctive treatments seem to be having a positive effect on its incidence. The adoption of bevacizumab pretreatment will continue to gain widespread popularity and in this series appeared to be safe. However, future randomized prospective studies are necessary to fully evaluate the effects of bevacizumab pretreatment on postoperative VH and visual recovery and its long-term safety.

Summary Statement

A consecutive, retrospective, comparative cohort study was performed on patients undergoing vitrectomy for complications from proliferative diabetic retinopathy. Bevacizumab pretreatment for diabetic vitrectomy did not appear to affect rates of postoperative vitreous hemorrhage or final visual acuity and was not associated with any observed complications. The overall incidence of postoperative vitreous hemorrhage in this series was 13%.

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Table 1
Patient and Surgical Characteristics

	Bevacizumab Group	Untreated Group	P
N (eyes)	33	104	
<u>Age</u>			
Average age $\pm$ SD	46.4 $\pm$ 11	58.4 $\pm$ 12	<0.001 [*]
Median	44.7	58.8	
<u>Lens status</u>			
Phakic	27 (82%)	55 (53%)	0.004 [†]
Pseudophakic / Aphakic	6 (18%)	49 (46%)	
Prior panretinal photocoagulation	23 (70%)	81 (78%)	0.356 [†]
Days between injection and surgery	9.6 $\pm$ 6.4	N/A	
<u>Gauge surgery</u>			
20 ga	19 (58%)	37 (36%)	0.041 [†]
25 ga / 23 ga	14 (42%)	67 (64%)	

* Mann-Whitney-Wilcoxon test

[†] Fisher's exact test

Table 2
Early Postoperative Outcome (4-6 Weeks) by Treatment Group

	Bevacizumab Group	Untreated Group
N (eyes)	33	104
Vitreous Hemorrhage [*]		
None (Grade 0)	25 (75%)	89 (86%)
Grade 1	1 (3%)	4 (4%)
Grade 2	4 (12%)	9 (9%)
Required repeat surgery [†]	1/5 (20%)	4/13 (31%)
Retinal Detachment [‡]	3 (9%)	2 (2%)

^{*} Chi-square test, P=0.76

[†] Fisher's exact, P=1.00

[‡] Fisher's exact, P=0.09

Table 3
Late Postoperative Vitreous Hemorrhage in Patients with Adequate Follow-Up

	Bevacizumab Group	Untreated Group
1-3 Months Post-Op (N)	29	80
Vitreous Hemorrhage	0	0
Required Repeat Surgery	0	0
3-6 Months Post-Op (N)	19	60
Vitreous Hemorrhage*	1 (5%)	5 (8%)
Required Repeat Surgery	0	1/5 (20%)

* Fisher's exact test, P=1.00

Table 4
LogMAR Visual Acuity at Select Time Points (Excludes Patients with Postoperative RD)

	Bevacizumab Group	Untreated Group	P*
Preoperative (Approximate Snellen)	1.47 ± 0.8 (7/200)	1.72 ± 0.9 (CF 4')	0.128
1 Month Postoperative	1.07 ± 0.9 (20/200 ⁻³)	0.87 ± 0.9 (20/150)	0.230
3 Month Postoperative	0.76 ± 0.8 (20/100 ⁻³)	0.65 ± 0.6 (20/100 ⁺²)	0.993

* Mann-Whitney-Wilcoxon test

Table 5
Postoperative Hemorrhage and Detachment by Surgical Gauge in Untreated Group

	20 g	25/23 g	P
N	37	67	
Vitreous Hemorrhage			
None (Grade 0)	30 (81%)	59 (88%)	0.797*
Grade 1	2 (5%)	2 (3%)	
Grade 2	3 (8%)	6 (9%)	
Retinal Detachment	2 (5%)	0	0.124 [†]

* Chi-square test

[†] Fisher's exact test