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The Role of Perioperative Anti-VEGF During Vitrectomy for Vitreous Hemorrhage in Relation to Postoperative Nonclearing Vitreous Hemorrhage and Cystoid Macular Edema

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Abstract

Purpose: To assess the role of perioperative anti–vascular endothelial growth factor (anti-VEGF) on the incidence of rebleed and foveal thickness in patients undergoing pars plana vitrectomy (PPV) for nonclearing vitreous hemorrhage due to retinal vascular disorders. **Design:** Retrospective, randomized, comparative interventional study. **Methods:** Three hundred twelve eyes were assigned to group A (eyes undergoing PPV without anti-VEGF, n = 165) and group B (eyes undergoing PPV with anti-VEGF, n = 147) and were followed up for a minimum of 6 months. The incidence of rebleed and 1 month postoperative central foveal thickness (CFT) was recorded and analyzed. **Results:** The incidence of postoperative vitreous hemorrhage (POVH) in group A was 21.81%, which was significantly ($P = .025$) higher than in group B (12.24%). Mean CFT in group A (289.24 $\pm$ 49.47 μm) was higher as compared to group B (263.42 $\pm$ 94.42), but the difference was not statistically significant. **Conclusion:** Perioperative intravitreal anti-VEGF given at the end of the surgery significantly reduces the incidence of POVH and helps in achieving better CFT postoperatively.

Keywords

nonclearing vitreous hemorrhage, postoperative vitreous hemorrhage, perioperative anti-VEGF, vitrectomy for nonclearing vitreous hemorrhage, vitreous hemorrhage, POVH, anti-VEGF.

Introduction

Vitreous hemorrhage (VH) is a common complication of retinal vascular disorders and can lead to severe vision loss.[1] It can be managed through panretinal photocoagulation (PRP), cryopexy, anti–vascular endothelial growth factor (VEGF), and vitrectomy.[2] The choice of treatment depends upon the patient's visual and systemic status. Vitrectomy is advised usually in cases of nonclearing VH and early in cases associated with secondary complications such as neovascularization of iris or neovascular glaucoma, retinal detachment (RD), or in 1-eyed patients. With the introduction of anti-VEGF, its use in treating VH as a monotherapy[3] or in combination with laser photocoagulation (PHC) or vitrectomy has been tried with variable success.

Every eye with VH due to vascular disorder has a high incidence of developing macular edema (ME) due to disruption of the inner blood–retinal barrier by VEGF released from the ischemic retina.[4] Also, it has been well-documented that in diabetic eyes, any intraocular surgical intervention (including pars plana vitrectomy [PPV]) results in the rise of angiogenic factors such as VEGF in response to surgical trauma and inflammation.[5-9] Vitrectomy in cases of VH clears the visual axis and allows the endolaser PHC for ischemia and bleeders.

Preoperative anti-VEGF has been proven to be effective in reducing neovascularization and improving ease of surgery by decreasing surgical time along with reducing the incidence of postoperative vitreous hemorrhage (POVH),[10-15] but it gets washed out during PPV. Anti-VEGF given at the end of the surgery may help in the further regression of neovascularization and reduce ME postoperatively.

In the past, few researchers have tried to evaluate this, but the results are variable.[16-21] These studies were limited to proliferative diabetic retinopathy as the cause of VH. We have also

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evaluated the effect of perioperative anti-VEGF in eyes with VH due to other etiologies.

Patients and Methods

We did a retrospective, comparative, randomized study on a consecutive series of 312 eyes of 224 patients who underwent PPV for nonresolving VH due to vascular disorders between the period of January 2013 to June 2016.

The exclusion criteria were (1) use of anti-VEGF within 3 months of the date of surgery, (2) history of any surgical intervention for posterior segment, (3) eyes that required internal tamponade, (4) history of trauma, and (5) postoperative follow-up of fewer than 6 months. Three hundred twelve eyes were studied and divided into 2 groups: group A with 165 eyes and group B with 147 eyes. Group A was the control group with eyes, which did not receive intravitreal anti-VEGF, whereas, eyes in group B received intravitreal anti-VEGF at the end of surgery. The choice of receiving anti-VEGF at the end of surgery was made solely by the patient based on their affordability. Two experienced vitreoretinal surgeons (M.N. and N.M.) performed all surgeries. Institutional review board of the hospital approved the study. The functional results of surgery in diabetic eyes depend on the number of preoperative and intraoperative characteristics. Eyes with tractional retinal detachment requiring tamponade were excluded. Eyes with and without preoperative laser PHC were separately assessed.

The patients underwent standard 3-port PPVs under local or general anesthesia. A 23- or 25-gauge vitrectomy (Constellation Vision System; Alcon Laboratories, Inc, Fort Worth, TX) was used for surgery in all the eyes. First, a core vitrectomy was done, then the posterior hyaloid was separated using suction of the vitreous cutter. Clots adherent to the vitreous skirt were removed as safely as possible to the vitreous base. Hemostasis was obtained by raising the intraocular pressure to 60 mm Hg and then treating the bleeders with either internal diathermy or endolaser PHC, as and when required. In all cases, endolaser PRP was performed. At the end of surgery, patients of group B received an intravitreal injection of 1.25 mg/0.05 mL bevacizumab or 0.05 mg/0.05 mL ranibizumab (as chosen by the patient), through the port. Planned to follow-up visits were done at months 1, 3, and 6. Those patients who experienced any ocular discomfort were examined additionally. At each postoperative follow-up visit, each patient's complete ocular examination including visual acuity, intraocular pressure, and the detailed retinal examination was recorded.

We defined POVH as a new episode of VH occurring anytime between 4 weeks and 6 months of surgery during the follow-up period. All patients with POVH, except 1-eyed, were observed for another period of 1 month, at 1-month follow-up, before any intervention was advised. In cases, with nonresolving hemorrhage, air–blood exchange or revitrectomy was done. The available 1-month postoperative optical coherence tomographies (OCTs) were collected and analyzed. The primary outcomes studied were the incidence of rebleed and the 1-month postoperative mean central foveal thickness (CFT).

Table 1. Baseline Patient Demographic Data.

	Total	Group A	Group B
Total eyes	313 eyes	165 eyes	147 eyes
Mean age, y		50.8 ± 13.28	52.79 ± 11. 74
Gender			
Male	240	129	111
Female	72	36	36
Lens status			
Clear lens	116	68	48
Cataract	128	71	57
Pseudophakia	67	25	42
Aphakia	1	1	0
Etiology of VH			
PDR	235	110	125
Vasculitis	45	32	13
BRVO	26	19	7
CRVO	7	4	3

Abbreviations: BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; PDR, proliferative diabetic retinopathy; VH, vitreous hemorrhage.

Secondary outcomes were the incidence of rebleed associated with various retinal vascular disorders and whether the prior lasered status of eyes affected the incidence of rebleed.

Statistical Analysis

The statistical analysis was performed by a statistician with SSPS version 21 and applying the χ^2 test. The significance of CFT was calculated by using independent test. A "*P* value" of less than or equal to .05 was considered significant.

Results

The study included 312 eyes of 296 patients. The male preponderance was seen with a number of 224 eyes as compared to 72 eyes of female patients. Group A included 165 eyes with a mean age of 50.8 ± 13.28 years, and group B included 147 eyes with a mean age of 52.79 ± 11.74 years. Etiological subgrouping of VH in both the groups was done to assess the outcomes of the study in the matched group. Proliferative diabetic retinopathy (PDR) in both the groups was the most common cause. The incidence of PDR in groups A and B was 66.66% and 85.03%, respectively (Table 1).

Analysis of postoperative complications occurring between 1 and 6 months from the date of surgery revealed that the incidence of POVH was significantly more in group A (21.81%) than in group B (12.24%; $P = .02$).

PDR was the most common cause of POVH in both the groups, with its incidence in groups A and B as 18.78% and 8.84%, respectively. The difference was statistically significant ($P = .01$; Table 2). Preoperative subgrouping on the basis of lasered status of the eyes was done to evaluate the effect of the laser (Table 3).

The incidence of rebleed was more in nonlasered eyes as compared to lasered eyes. In all the etiologies, group A showed more incidence of POVH irrespective of the prior lasered status

Table 2. Postoperative Complications.

Etiology	POVH			RD		
PDR	31 (18.78%)	13 (8.84%)	0.01	2 (1.21%)	1 (0.68%)	0.63
Vasculitis	2 (1.21%)	1 (0.68%)	0.63	1 (0.60%)	1 (0.68%)	0.93
Venous occlusion	3 (1.81%)	0	0.10	0	0	0.29
Total	36 (21.81%)	14 (9.52%)	0.02	3 (1.81%)	2 (1.36%)	0.74

Abbreviations: PDR, proliferative diabetic retinopathy; POVH, postoperative vitreous hemorrhage; RD, retinal detachment.

Table 3. Preoperative Laser Status in Various Etiologies.

	Nonlasered Eyes		Lasered Eyes	
Cause of VH	Group A, 93 (56.36%)	Group B, 82 (55.78%)	Group A, 72 (43.63%)	Group B, 65 (44.21%)
PDR	43	64	68	60
Vasculitis	28	11	3	2
BRVO	18	4	1	3
CRVO	4	3	0	0

Abbreviations: BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; PDR, proliferative diabetic retinopathy; VH, vitreous hemorrhage.

Table 4. Analysis of Complications Based on the Lasered Status of the Eye.

	Nonlasered Eyes			Lasered Eyes		
Etiology	Group A, n = 93	Group B, n = 82	*P* Value	Group A, n = 72	Group B, n = 65	*P* Value
PDR						
POVH	19 (20.43%)	8 (5.44%)	.03	12 (16.66%)	5 (7.69%)	.11
RD	1 (1.07%)	1 (1.21%)	.92	1 (1.38%)	0	.34
Vasculitis						
POVH	1 (1.07%)	1 (1.21%)	.63	1 (1.38%)	0	.17
RD	1 (1.07%)	1 (1.21%)	.92	0	0	
BRVO						
POVH	3 (3.22%)	0	.10	0	0	
RD	0	0		0	0	
CRVO	0	0		0	0	

Abbreviations: BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; PDR, proliferative diabetic retinopathy; POVH, postoperative vitreous hemorrhage; RD, retinal detachment.

of the eye, but the results were statistically significant in nonlasered PDR cases only ($P = .03$; Table 4).

The incidence of POVH was slightly more in the first 3 months (Table 5). Table 6 showed the time of presentation of RD.

Best-corrected visual acuity improvement was seen in both the groups following surgery. But the mean change was more in group B (1.05 ± 0.63) than in group A (0.85 ± 0.58; Table 7).

Postoperative CFT recorded at 1-month follow-up was available in 48 eyes of group A and 94 eyes of group B. No statistical difference was found in both the groups, but the overall macular anatomy was better maintained in the eyes that received peroperative anti-VEGF (Table 8). Figure 1A and B shows postoperative images of group A patient, and Figure 2A and B shows postoperative images of group B.

Table 5. Time of Presentation of POVH.

	POVH in Group A			POVH in Group B		
Etiology	<1 month	1 to 3 months	4 to 6 months	<1 month	1 to 3 months	4 to 6 month
PDR	4	18	13	3	8	5
BRVO	0	3	0	0	1	0
Vasculitis	0	1	1	0	0	0

Abbreviations: BRVO, branch retinal vein occlusion; PDR, proliferative diabetic retinopathy; POVH, postoperative vitreous hemorrhage.

Table 6. Time of Presentation of RD.

	RD in Group A			RD in Group B		
Etiology	<1 month	1 to 3 months	4 to 6 months	<1 month	1 to 3 months	4 to 6 months
PDR	0	0	2	0	0	1
BRVO	0	0	0	0	1	0
Vasculitis	0	0	1	0	0	1

Abbreviations: BRVO, branch retinal vein occlusion; PDR, proliferative diabetic retinopathy; RD, retinal detachment.

Table 7. Mean Change in BCVA.

	Mean BCVA of Both the Groups (logMAR)		
Groups	Preoperative	Postoperative	Mean change
Group A	3.37 ± 0.70	0.84 ± 0.58	0.85 ± 0.58
Group B	1.5 ± 0.61	0.45 ± 0.40	1.05 ± 0.63

Abbreviations: BCVA, best-corrected visual acuity; logMAR, logarithm of the minimal angle of resolution.

Table 8. Postoperative Central Foveal Thickness.

	Mean CFT (μ)		
Etiology	Group A, n = 48	Group B, n = 94	*P* Value
PDR	291.14 ± 60.41	261.91 ± 99.66	.15
Vasculitis	293 ± 33.52	276 ± 90.45	.58
Venous occlusion	241 ± 24.93	258.5 ± 40.90	.15
Total	289.24 ± 49.47	263.42 ± 94.42	.07

Abbreviations: CFT, central foveal thickness; PDR, proliferative diabetic retinopathy.

Discussion

This retro-prospective study was done to analyze the effect of peroperative intravitreal anti-VEGF in reducing the incidence

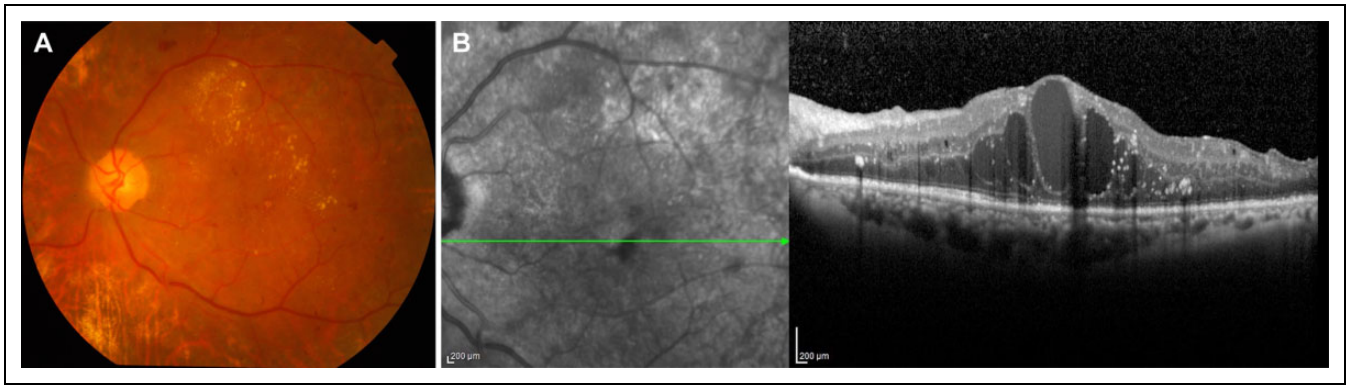

Figure 1. (A) Fundus image of a patient undergoing pars plana vitrectomy (PPV) for nonclearing vitreous hemorrhage without anti-vascular endothelial growth factor (VEGF). (B) Infrared and optical coherence tomography of a patient undergoing PPV for nonclearing vitreous hemorrhage without anti-VEGF.

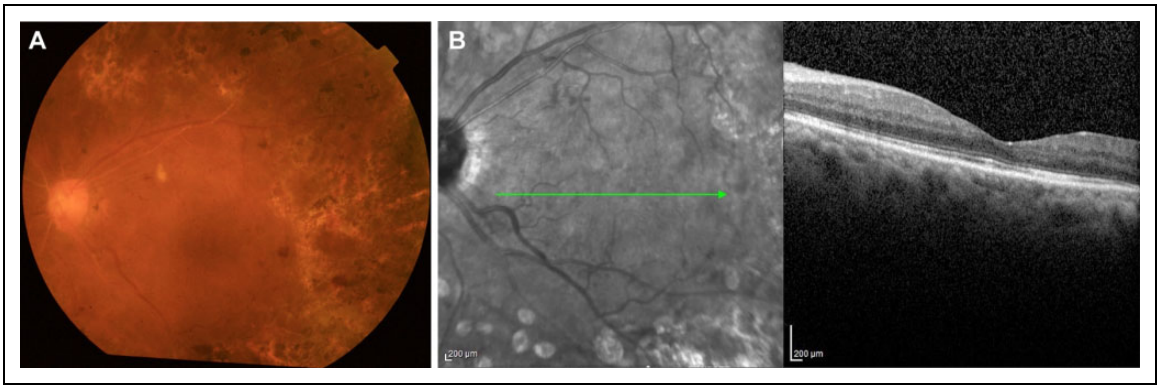

Figure 2. (A) Fundus image of a patient undergoing pars plana vitrectomy (PPV) for nonclearing vitreous hemorrhage with anti-vascular endothelial growth factor (VEGF). (B) Infrared and optical coherence tomography of a patient undergoing PPV for nonclearing vitreous hemorrhage with anti-VEGF.

of POVH and achieving a better anatomical outcome in patients undergoing vitrectomy for nonresolving VH due to vascular disorders.

Early POVH can occur due to oozing of the remnant neovascularization, from sclerotomy site or from clot lysis. Late hemorrhage can result from persistent or recurrent traction or new vessels, which either persisted after surgery or developed later.

Funatsu et al[21] in their study showed that eyes with a high level of VEGF in vitreous fluid had a significantly greater risk of PDR progression after vitreous surgery than eyes with low VEGF. Later in 2007, he and his associates also identified high vitreous levels of VEGF[22] as a significant risk factor for the outcome of vitreous surgery in patients with PDR. Pars plana vitrectomy and laser PHC have been found to improve oxygenation[23] in the long term, but the VEGF surge induced by surgical trauma can enhance the neovascularization of iris[7] and fibrovascular proliferation that may lead to VH in the postoperative period.

Intravitreal anti-VEGF injection antagonizes the VEGF secreted irrespective of the status of the vitreous humor (ie, clear, hemorrhagic, or vitrectomized eye). Di Lauro et al showed that preoperative intravitreal bevacizumab eases surgery in eyes with severe PDR by reducing iris and retinal neovascularization.[24] Meta-analysis by Zhang et al showed that adjuvant intravitreal bevacizumab prior to vitrectomy in patients with PDR significantly eased the procedure, diminished intraoperative complications, and reduced early postoperative hemorrhage without increasing the risk of vision-threatening complications. It also shortens the surgical time by facilitating fibrovascular membrane dissection, reducing bleeding, and favoring visual recovery.[25]

With vitrectomy, there is a complete washout of any anti-VEGF injected before surgery in the vitreous cavity, which leaves the postsurgical VEGF unimpeded and allows it to produce postoperative complications. It is also a well-known fact that after vitrectomy as the vitreous gel is replaced by a less viscous contents such as air, balanced salt solution, or normal saline and eventually the aqueous humor, the transport of all the molecules is improved, including that of oxygen and cytokines.[26]

All the vascular etiologies included in this study (PDR, vasculitis, and venous occlusion) are known to present with ME as one of the commonest causes of visual deterioration. Vitrectomy for VH in all these cases may help with clearing the

media and by decreasing the VEGF load, but it does not add any benefit to the resolution of ME. Thus, peroperative anti-VEGF might be able to reduce the edema and achieve a faster and better visual recovery.[27,28]

All these theoretical explanations go in favor of the use of anti-VEGF at the end of surgery, but the evidence from previous studies showed anti-VEGF is both significant and nonsignificant in reducing the incidence of POVH.[16-20] Also, all the studies included only PDR in their etiology. Ours is the first study that compared the anatomical outcome of anti-VEGF.

The incidence of POVH seen in patients who received peroperative intravitreal anti-VEGF was 12.24%, which was significantly less than the incidence of POVH in patients who did not receive anti-VEGF (21.81%; $P = .0256$). Both the lasered and nonlasered eye had a higher incidence of POVH in eyes that were refrained from receiving anti-VEGF along with PPV. The difference was seen statistically significant in nonlasered eyes.

Group A showed the incidence of POVH in cases of PDR to be 18.78%. This was in close comparison with that seen by Park et al[17] and Ahn et al,[18] who had an incidence of 21.1% and 14.7%, respectively. Cheema et al[20] reported an incidence of 42%, which was the highest among all.

Group B PDR eyes showed an incidence of 8.84% in our study, which was second to the incidence found in a study by Cheema et al[20] (4%). Park et al,[17] Ahn et al,[18] and Romano et al[16] had an incidence of 16.7%, 16.2%, and 30%, respectively. In eyes that received peroperative intravitreal anti-VEGF, both the study of Cheema et al[20] and our study showed a significant difference among both the groups.

Ours was the first study that analyzed the anatomical benefit of anti-VEGF by comparing the CFT. The mean CFT in all the etiologies of groups A and B did not show a significant difference at the 1-month postoperative period, but the eyes of group B showed a better anatomy.

All the other studies done to evaluate peroperative anti-VEGF included only PDR cases and had less number of patients as compared to our study. We included other major vascular etiologies of VH and also increased the sample size as compared to other studies so that it can represent the population more effectively. The major limitation of our study was its retrospective nature. Although due to the natural incidence of disease occurrence, the sample size of VH in venous occlusion and vascuitic VH was less as compared to the eyes with VH due to PDR. Thus, a need for further study with a higher number of patients in every etiology and a regular postoperative OCT can be planned to assess the effect of peroperative anti-VEGF in cases of nonresolving VH.

By this study, we conclude that peroperative anti-VEGF is significantly effective in decreasing the incidence of POVH and achieving a better macular anatomy in cases of nonresolving VH with vascular etiology.

Ethical Approval

Ethical approval for this study was obtained from the Retina Foundation Institutional Ethics Committee (ECR/366/inst/Gj/2013D).

Statement of Informed Consent

Not applicable.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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References

1. Spraul CW, Grossniklaus HE. Vitreous hemorrhage. *Surv Ophthamol*. 1997;42(1):3-39.
2. Saxena S, Jalali S, Verma L, Pathengay A. Management of vitreous hemorrhage. *Indian J Ophthalmol*. 2003;51(2):189-196.
3. Spaide RF, Fisher Y. Intravitreal bevacizumab (Avastin) treatment of proliferative diabetic retinopathy complicated by vitreous hemorrhage. *Retina*. 2006;26(3):275-278.
4. Joussen AM, Wolfensberger TJ. *Mechanisms of macular edema and therapeutic approaches*. In: Ryan SJ, ed. *Retina* 5th ed. Philadelphia, PA: Elsevier; 2013:593.
5. Patel JI, Hykin PG, Cree IA. Diabetic cataract removal: postoperative progression of maculopathy-growth factor and clinical analysis. *Br J Ophthalmol*. 2006;90(6):697-701.
6. Sadiq SA, Chatterjee A, Vernon SA. Progression of diabetic retinopathy and rubeotic glaucoma following cataract surgery. *Eye (Lond)*. 1995;9(pt 6):728-738.
7. Stefansson E. Physiology of vitreous surgery. *GraefesArch Clin Exp Ophthalmol*. 2009;247(2):147-163.
8. Simo R, Carrasco E, Garcia-Ramirez M, Hernandez C. Angiogenic and antiangiogenic factors in proliferative diabetic retinopathy. *Curr Diabetes Rev*. 2006;2:71-98.
9. Funatsu H, Yamashita H, Ikeda T, Mimura T, Eguchi S, Hori S. Vitreous levels of interleukin-6 and vascular endothelial growth factor are related to diabetic macular edema. *Ophthalmology*. 2003;110(9):1690-1696.
10. Yeung L, Liu L, Wu WC, et al. Reducing the incidence of early postoperative vitreous hemorrhage by preoperative intravitreal bevacizumab in vitrectomy for diabetic tractional retinal detachment. *Acta Ophthalmol*. 2010;88(6):635-640.
11. Ahmadieh H, Shoeibi N, Entezari M, Monshizadeh R. Intravitreal bevacizumab for prevention of early postvitrectomy hemorrhage in diabetic patients: a randomized clinical trial. *Ophthalmology*. 2009;116(10):1943-1948.
12. Rizzo S, Genovesi-Ebert F, Di Bartolo E, Vento A, Miniaci S, Williams G. Injection of intravitreal bevacizumab (Avastin) as a preoperative adjunct before vitrectomy surgery in the treatment of severe proliferative diabetic retinopathy (PDR). *Graefes Arch Clin Exp Ophthalmol*. 2008;246(6):837-842.
13. Modarres M, Nazari H, Falavarjani KG, Naseripour M, Hashemi M, Parvaresh MM. Intravitreal injection of bevacizumab before vitrectomy for proliferative diabetic retinopathy. *Eur J Ophthalmol*. 2009;19(5):848-852.

14. El-Batarny AM. Intravitreal bevacizumab as an adjunctive therapy before diabetic vitrectomy. *Clin Ophthalmol*. 2008;2(4): 709-716.
15. Romano MR, Gibran SK, Marticorena J, Wong D, Heimann H. Can a preoperative bevacizumab injection prevent recurrent postvitrectomy diabetic vitreous haemorrhage? *Eye (Lond)*. 2009; 23(8):1698-1701. doi:10.1038/eye.2008.354.
16. Romano MR, Gibran SK, Marticorena J, Wong D, Heimann H. Can an intraoperative bevacizumab injection prevent recurrent postvitrectomy diabetic vitreous hemorrhage? *Eur J Ophthalmol*. 2009;19(4):618-621.
17. Park DH, Shin JP, Kim SY. Intravitreal injection of bevacizumab and triamcinolone acetonide at the end of vitrectomy for diabetic vitreous hemorrhage: a comparative study. *Graefes Arch Clin Exp Ophthalmol*. 2010;248(5):641-650.
18. Ahn J, Woo S J, Chung H, Park KH. The effect of adjunctive intravitreal bevacizumab for preventing postvitrectomy hemorrhage in proliferative diabetic retinopathy. *Ophthalmology*. 2011;118(11):2218-2226.
19. Smith JM, Steel DH. Anti-vascular endothelial growth factor for prevention of postoperative vitreous cavity haemorrhage after vitrectomy for proliferative diabetic retinopathy. *Cochrane Database Syst Rev*. 2011;(5):CD008214.
20. Cheema RA, Mushtaq J, Al Khars W, et al. Role of intravitreal bevacizumab (Avastin) injected at the end of diabetic vitrectomy in preventing postoperative recurrent vitreous hemorrhage. *Retina*. 2010;30(10):1646-1650.
21. Funatsu H, Yamashita H, Noma H, et al. Outcome of vitreous surgery and the balance between vascular endothelial growth factor and endostatin. *Invest Ophthalmol Vis Sci*. 2003;44(3): 1042-1047.
22. Funatsu H, Yamashita H, Mimura T, Noma H, Nakamura S, Hori S. Risk evaluation of outcome of vitreous surgery based on vitreous levels of cytokines. *Eye (Lond)*. 2007;21(3):377-382.
23. Stefansson E.The therapeutic effects of retinal laser treatment and vitrectomy. A theory based on oxygen and vascular physiology. *Acta Ophthalmol Scand*. 2001;79(5):435-440.
24. Di Lauro R, De Ruggiero P, di Lauro R, di Lauro MT, Romano MR. Intravitreal bevacizumab for surgical treatment of severe proliferative diabetic retinopathy. *Graefes Arch Clin Exp Ophthalmol*. 2010;248(6):785-791. doi:10.1007/s00417-010-1303-3.
25. Zhang ZH, Liu HY, Hernandez-Da Mota SE, et al. Vitrectomy with or without preoperative intravitreal bevacizumab for proliferative diabetic retinopathy: a meta-analysis of randomized controlled trials. *Am J Ophthalmol*. 2013;156(1):106-115.e2. doi:10.1016/j.ajo.2013.02.008.
26. Sawada O, Kawamura H, Kakinoki M, Sawada T, Ohji M. Vascular endothelial in aqueous humor before and after intravitreal injection of bevacizumab in eyes with diabetic retinopathy. *Arch Ophthalmol*. 2007;125(10):1363-1366.
27. Oshima Y, Shima C, Wakabayashi T, et al. Microincision vitrectomy surgery and intravitreal bevacizumab as a surgical adjunct to treat diabetic traction retinal detachment. *Ophthalmology*. 2009; l16(5):927-938.
28. da R Lucena D, Ribeiro JA, Costa RA, et al. Intraoperative bleeding during vitrectomy for diabetic fractional retinal detachment with versus without preoperative intravitreal bevacizumab (IBeTra study). *Br J Ophthalmol*. 2009;93(5):688-691.