Preoperative Effectiveness of Bevacizumab in Patients Undergoing Vitrectomy Due to Diabetic Vitreous Hemorrhage

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ABSTRACT

Purpose: To analyze the effect of preoperative intravitreal bevacizumab on final visual acuity and developing re-hemorrhage in cases undergoing pars plana vitrectomy (PPV) due to diabetic vitreous hemorrhage.

Material and Methods: In our clinic between 2014 and 2018, patients who underwent PPV with the diagnosis of diabetic vitreous hemorrhage (VH) and regularly followed for at least six months postoperatively were included in the study. Preoperative bevacizumab administered eyes were classified as group 1 and those not administered as group 2. The patients' demographic characteristics, preoperative bevacizumab administration time (1.25mg 0.05ml), patients' preoperative and postoperative follow-up periods, complications during and after surgery, and surgeries and treatment approaches due to complications were recorded.

Results: 68 eyes of 60 patients were included in the study. Preoperative mean BCVA logMAR was 2±0,9 in group 1 vs. 2,1±0,9 in group 2, with no showing a statistically significant difference (p=0,398). In the postoperative follow-up, the mean BCVA logMAR increased significantly in both groups (p <0.005 in each group), and the mean BCVA did not differ significantly between the groups (p>0.05). Intravitreal bevacizumab (1.25 mg/0.05ml) was administered to 29 of 68 eyes with diabetic VH (group1) (%42,64), a mean of 7.9 ± 9 days before the operation. It was also found that the incidence of postoperative early (≤4 weeks) (p = 0.736) and late (> 4 weeks) (p = 0.556) vitreous hemorrhages did not make a significant difference between groups.

Conclusion: In diabetic vitreous hemorrhage, the effect of preoperatively applied bevacizumab on final visual acuity and developing re-hemorrhage is limited.

Keywords: Vitreous Hemorrhage, Diabetic Vitreous Hemorrhage, Bevacizumab, Vitrectomy

INTRODUCTION

Vitreous hemorrhage (VH) is the clinical manifestation of a primary disease that occurs spontaneously or as a result of trauma and prevents vision by disrupting the transparency of optical media.

The leading cause of spontaneous VH is often diabetic retinopathy (DRP). [1] Apart from DRP, retinal vein occlusions, hypertension, choroidal neovascular membrane are among the most common etiologies for VH. [1,2]

The most common causes of vision loss in patients with DRP are complications such as macular edema, proliferative diabetic retinopathy (PDR), extensive fibrovascular proliferation, preretinal fibrosis ± tractional retinal detachment (TRD), and VH. As a result of retinal ischemia associated with DRP, angiogenesis expression stimulates VEGF and insulin-like growth factor-1, and fibrovascular structures with neovascularization develop.[3,4] Vitreous hemorrhage may develop due to these fibrovascular membranes. In diabetic vitreous hemorrhages, by performing PPV, very high anatomical and functional success could be achieved. However, re-hemorrhages after vitrectomy can lead to prolonged and severe vision loss, and some of them require re-surgery. In recent years, intravitreal anti-VEGF drugs have been widely used to treat macular edema due to DRP.[5-7] Moreover, intravitreal anti-VEGF drugs, which are also claimed to reduce the risk

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of re-hemorrhage, have generally been recommended to be used as pre-surgical adjuvant therapy in DRP-associated VH's treatment.[8-13] However, many literature data do not support this view too.[14-18]

This study aimed to reveal preoperatively administered bevacizumab's effectiveness on visual acuity and developing re-hemorrhage in PDR and VH cases. For this reason, the study parameters were statistically analyzed and compared between the study groups.

MATERIAL AND METHODS

Files of patients who have undergone PPV as the cause of diabetic VH were retrospectively scanned at the University of Health Sciences Istanbul Training and Research Hospital, Department of Ophthalmology Clinic between January 2014 and January 2018. The local ethics committee at the University of Health Sciences Istanbul Training and Research Hospital approved this study. The operation's possible risks and benefits were explained fully to the study participants, with the obtainment of informed consent in accordance with the Helsinki Declaration in advance of surgery.

Patients who developed VH due to PDR and underwent PPV were included in the study. Dialysis patients, subjects with a follow-up period of fewer than six months, patients with diabetic foot problems, a corneal pathology, and history of trauma, complicated cataract surgery, previous PPV, uncontrolled hypertension, cardiovascular disease, blood clotting disorder, cerebrovascular disease (CVD), and chronic obstructive pulmonary disease (COPD) were excluded.

Demographic information, best-corrected visual acuity (BCVA) before and after surgery, intraocular pressure (IOP), history of systemic disease, eye disease, and surgery, lens condition, preoperative and postoperative follow-up time, and panretinal photocoagulation (PRP) information were recorded by scanning patients' files. The time of bevacizumab administration, complications during and after surgery, treatment of complications, and surgical techniques used were also noted in subjects with intravitreal bevacizumab administration before PPV. Snellen visual acuities at preoperative and control examinations were converted to logMAR (logarithm of the minimum angle of resolution) equivalent for statistical analysis. Visual acuity changes of less than 0.20 logMAR were accepted to be the preservation of visual acuity. A 0.20 logMAR decrease was considered an increase in visual acuity, with a 0.20 logMAR increase was evaluated as a decrease in visual acuity.

As a result of the ophthalmoscopic examination in diabetic cases, if large retinal vessels and the optic disc could be selected even if it was blurry, incomplete laser treatment had been attempted to be completed. If the laser could not be completed due to bleeding, surgical preparation was made. If lasers could be completed, it was waited for two months, considering the possibility of resorption of vitreous hemorrhage afterward. In cases where no details of the retina could be seen, we waited for one month if intensive pan-retinal photocoagulation was performed. At the end of one month, surgery was decided if the fundus reflex could not be detected. In the presence of no pan-retinal laser history, surgical treatment was recommended without waiting. If findings were suggesting tractional retinal detachment in B-Scan USG, surgical treatment was recommended urgently.

Eyes preoperatively bevacizumab administered were included in group 1, and those not administered in group 2. Intravitreal injections were done to aphakic and pseudophakic patients from 3 mm behind the limbus in the inferotemporal quadrant and to aphakic patients from 3 mm behind the limbus. Bevacizumab was planned to be administered 3-5 days preoperatively. In some instances, it was administered a minimum of 1, a maximum of 20 days in advance due to patient personal reasons.

The patients' postoperative visual acuity and visual acuity gains were compared statistically between groups 1 and 2. Postoperative rehemorrhage was divided into two subgroups as early VH (≤4 weeks) and late VH (>4 weeks), in which measurement parameters were statistically analyzed. The detectable causes of postoperative rehemorrhage were discussed.

Surgical Technique

PPV was performed under general or local anesthesia according to the patient's general condition and surgical requirement. If cataract operation would be undertaken in phakic patients, a foldable one-piece hydrophobic acrylic lens was implanted in the capsular bag following phacoemulsification. 3-port 23 gauge PPV was performed in all eyes using a non-contact wide-angle imaging system (SDI BIOM 3, OculusInc, Germany) to visualize the posterior segment during surgery. Core vitrectomy was done first; then, intravitreally injected half-diluted triamcinolone acetonide was given. The remaining vitreous base and vitreous hemorrhage were cleaned by 360 degrees scleral indentation. In the presence of a membrane in the optic nerve head or retina, it was lifted and stripped with micro forceps' help. The membrane was peeled off by air-fluid change after applying dual membrane paint

trypanblue+brilliant blue, MembraneBlue® Dual Syringe) under air, where necessary. Air, long-acting gas or silicone oil (1000 cSt, 5000 cSt) were used as endotamponade in required cases. Intravitreal triamcinolone acetonide of 0.2 ml was administered before endotamponade. After the retinal examination for a retinal tear at the end of the operation, panretinal laser photocoagulation (also including the equator's anterior) was completed using scatter laser photocoagulation on cases with an incomplete laser with an endolaser. The sclerotomy areas were closed with 8-0 Vicryl; the operation was terminated by subconjunctival antibiotic injection. All operations were performed by the same surgeon (HG).

While the patients were discharged, topical steroids (Predforte, Allergan, France), antibiotic drops (one drop per hour) (Vigamox, Alcon, USA), and oral moxifloxacin (once a day) (Avelox, Bayer, Turkey) were prescribed until the first postoperative visit. Oral moxifloxacin was discontinued at the end of the first week. After three days, antibiotic drops were reduced to one drop four times a day and stopped on day 15. Steroid drops were tapered for up to 30 days. The patients were called for controls at the 1st week, the second month, third month, and sixth months.

Statistical analysis

We used SPSS 22.0 package program for all statistical analyses. Descriptive statistics (mean, standard deviation, median, minimum, maximum, frequency, and ratio values) were conducted on the data obtained and are presented on tables. The normality of distributions of the variables was tested with the Kolmogorov-Smirnov test. Mann-Whitney U test was used to analyze independent quantitative data, whereas the Wilcoxon test analyzed dependent quantitative data. A Chi-square test was applied for analyzing independent qualitative data.

RESULTS

The demographic findings and main characteristics of the groups are summarized in table 1. The two groups were similar in terms of demographic characteristics (Table 1). 68 eyes of 60 patients (40 women, 20 men) eligible for inclusion were included. Eyes were divided into two groups as those administered preoperative intravitreal bevacizumab (group 1, n = 29) and those that were not administered (group 2, n = 39). It was observed that intravitreal bevacizumab was administered to 29 eyes in group 1 preoperatively 7.9 ± 4.9 (minimum 1, maximum 20) days before (Table 1).

There was no difference between the groups in preoperative mean BCVA. In the postoperative follow-up, while mean BCVA analyzes did not differ between groups, significant improvement in mean BCVA was observed in both groups

Table 1. *Demographic findings and main features.*

Parameters	Group 1(n:29)	Group 2 (n:39)	P
Mean(age)+SD	61,06+8,78	62,84+10,88	0,958*
Female/Male	18/11	26/13	0,695**
Preoperative Follow-Up Time (days)	25+14,21	28,48+14,92	0,582*
Postoperative Follow-up Time (months)	22,24+15,07	19,74+17,05	1,051*
Phacic/Pseudophacic	19/10	24/15	0,736**
Preoperative PRP +/-	6/23	4/35	0,431**

SD: Standart Deviation PRP:Panretinal photocoagulation *independent samples t-test **chi-square test

Table 2: *Comparison of the best corrected visual acuity between the groups.*

BVCA LogMAR	Group 1(n:29)	Group 2(n:39)	P*
Preoperative	2,0090±0,94454	2,1999±0,89363	0,398
3. month	1,3602±0,74851 p**=0,001	0,8627±0,73222 p**=0,000	0,171
6. month	1,1549±0,64870 p**=0,000	0,9932±0,65175 p**=0,000	0,314
Last Visit	0,9142±0,52245 p**=0,000	1,1095±0,68520 p**=0,000	0,736

BVCA: Best Corrected Visual Acuity, * independent samples t-test ** paired samples t test

(p = 0,000) (Table 2). In group 1, two eyes (%6,8) showed decreased postoperative 6th-month BCVA, two eyes (%6,8) showed no change. In group 2, this BCVA decreased in one eye (%2,5) but did not change in four eyes (%7,6). There was no statistically significant difference in postoperative 6th-month BCVA between the groups (p=0,652 Chi-square test). Similarly, there was no difference in the groups' 6th-month visual acuity gains (p=0,091 Independent Samples Test) (Table 2).

While there were 12 eyes in group 1 accompanied by tractional retinal detachment (TRD) secondary to DRP, group 2 had no eyes with TRD. There was a statistically significant difference between the groups in this respect (p <0.05). These 12 eyes received bevacizumab approximately 6 ± 3.5 (minimum 1, maximum 10) days before the operation.

According to the groups, analysis of the patients' intraoperative and postoperative features and complications is shown in Table 3.

The incidence of intraoperative iatrogenic tears was 2 (%6,8) in group 1 and 1 (%2,5) in group 2, and there was no significant difference between the groups (p=0,3) (Table 3). Tamponades used showed no significant difference between groups 1 and 2 (p=0,17) (Table 3).

Postoperative rehemorrhage was detected in 7 (%24,1) eyes in group 1 and 11 (%28,2) eyes in group 2 (p=0,462) (Table 3). It was also divided into two groups as early VH (≤4 weeks) and late VH (>4 weeks), and no significant differences were found between the groups (p>0,05).

Pars plana vitrectomy (PPV) was repeated in 8 (%27,5) eyes in group 1 and 8 (%20,5) eyes in group 2. There was no statistically significant difference between the groups in this respect (p=0.346) (Table 3). PPV was performed in group 1, all 7 eyes due to rehemorrhage, and group 2, 7 of 11 eyes due to rehemorrhage. This application did not differ significantly between the groups (p=0,226).

DISCUSSION

As a result of retinal ischemia associated with DRP, VEGF release increases and angiogenesis is stimulated, and fibrovascular structures with neovascularization develop.[4] Bevacizumab is the recombinant human monoclonal antivascular endothelial growth factor antibody and thus prevents neovascularization. It has been a common practice to use intravitreal bevacizumab preoperatively in severe cases of PDR.[19-21]

In VH caused by DRP, rehemorrhage after PPV is common and prevents visual rehabilitation significantly.[22-26] Mahalingam et al. reported that the most important risk factor for recurrent VH was preoperative panretinal laser photocoagulation (PRP) deficiency. [26] In our study, preoperative PRP did not differ significantly between the groups. While some authors in the literature reported similar results with our study[14,18,27], some others reported different results.[11,12,15,17]

Khuthaila et al.[27] found no statistically significant relationship between postoperative rehemorrhage and preoperatively administered bevacizumab. The study performed by Sato et al.[18] in diabetic VH patients compared the groups in terms of preoperative bevacizumab administration by dividing rehemorrhages postoperatively into two groups as early VH (≤4 weeks) and late VH (>4 weeks). In the bevacizumab group, early VH incidence

Table 3: *Comparison of intraoperative and postoperative features and complications.*

Parametreler	Group 1(n:29)	Group 2(n:39)	P
PPV/Phaco+PPV	17(%58,7)/12(%41,3	27(%69,2)/12(%30,8)	0,365*
Gas / Silicon / Air / Liquid	8/12/8/1	13/8/17/1	0,179*
Intraoperative Complication Iatrogenic Tear	2(%6,8)	1(%2,5)	0,307*
Postoperative Rehemorrhage	7(%24,1)	11(%28,2)	0,462*
Postoperative Rehemorrhage Early	2(%6,9)	2(%5,1	0,739*
Postoperative Rehemorrhage Late	5(%17,2)	9(%23,1)	0,556*
RE-PPV **-Rehemorrhage** **-RD**	8(%27,5) 7 1	8(%20,5) 7 1(TRD)	0,346* 0,226* 0,675*

*Chi-square test RD: Traction retinal detachment Phaco:Phacoemulsification PPV:Pars plana vitrectomy RE-PPV: Recurrent Pars Plana Vitrectomy RD:Retinal Detachment TRD: Tractional retinal detachment Rehemorrhage: Recurrent hemorrhage

was significantly higher than the other group (p=0.027), but in contrast, late VH incidence showed no significant difference. Contrary to data emerging from the studies mentioned above, Modarres et al.'s prospective study revealed lower postoperative vitreous hemorrhage in the preoperative bevacizumab applied group (3-5 days before PPV) compared to the non-applied group.[11] Gupta et al.[15] found a significant reduction in rehemorrhage rates in the preoperative bevacizumab group similarly. Data derived from all these published studies were similar to the results obtained from Lauro et al.'s study highlighting the decrease in the incidence of rehemorrhage in the same group.[12] In our study, we found that preoperatively administered bevacizumab did not make a significant difference in the rehemorrhage ($p > 0.05$) rates. When eyes with postoperative rehemorrhage divided into two groups, as early VH (≤4 weeks) and late VH (>4 weeks), no significant difference was found again ($p > 0.05$).

Whether preoperative bevacizumab treatment contributes to visual improvement is a controversial issue. In our study, although we determined that postoperative 6th-month mean BCVA logMAR increased significantly in both groups, we observed no significant difference between the groups in this respect ($p>0.05$). Ergun et al.[14] stated that, in diabetic VH eyes, bevacizumab before PPV did not show a statistically significant difference in increasing visual acuity. Additionally, Gupta et al.[15] emphasized that preoperative bevacizumab did not make a statistically significant difference in 6th-month BCVA. Several studies have been conducted to date in the literature to reveal the curious unknowns about this subject. As one of them, again, results from a meta-analysis indicated that intravitreal anti-VEGF use had no significant effect on 6th-month BCVA.[28]

The intraoperative iatrogenic tear is one of the significant complications of PPV. Based on recently published literature data, different results regarding the effect of preoperative bevacizumab administration on intraoperative iatrogenic tear have been obtained, and they should be interpreted with caution. For instance, Farahvash et al.[29] said that iatrogenic retinal tears' incidence was not statistically significant among groups. Conversely, several clinical trials suggest that preoperative bevacizumab administration can significantly reduce intraoperative iatrogenic tear incidence.[11,30,31] It appears that the incidence of intraoperative iatrogenic tears was similar in both groups in our study.

Some studies in the literature have hypothesized that preoperative bevacizumab injection can induce TRD.[32,33] Most importantly, these studies have also emphasized that TRD develops primarily in the absence of preoperative PRP.[32,33] Opposite to these findings, for complicated PDR, some researchers have stated that preoperative anti-VEGF therapy is relatively safe; moreover, it may not trigger the development or progression of TRD.[19,34] In the present study, there was no difference between groups 1 and 2 in terms of PRP. 12 eyes in Group 1 had TRD, and all these patients had a history of PRP. While no new TRD development was observed in group 1 during follow-up, new developing TRD was seen in only 1 case in group 2 (Table 3); moreover, PRP was enhanced with PPV in this patient. Considering all these findings, we suggested that preoperative anti-VEGF injection was relatively safe for a complicated PDR, and it might not trigger TRD development or progression; besides, we thought that preoperative PRP history could prevent TRD from progressing.

We are aware of the limitation of the current study due to its retrospective nature. In addition, the lack of sham injection and non-homogeneous distribution of TRDs in the control group is one of the other limitation reasons.

It is interesting to note that although preoperative intravitreal bevacizumab is used to reduce postoperative rehemorrhage and achieve better final visual acuity, the incidence of postoperative rehemorrhage did not differ significantly in the early and late periods in our study. The final visual acuity was also strikingly not better in the preoperatively bevacizumab administered group than the control group. We hope that our comments raised herein shed light on further and more comprehensive studies.

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Conflict of Interest

The authors do not declare a conflict of interest.

REFERENCES

1. Butner, R. W., & McPherson, A. R. (1982). Spontaneous vitreous hemorrhage. Annals of ophthalmology, 14, 268-70.
2. Smiddy, W. E., Isernhagen, R. D., Michels, R. G., & Glaser, B. M. (1988). Vitrectomy for nondiabetic vitreous hemorrhage. Retinal and choroidal vascular disorders. Retina (Philadelphia, Pa.), 8, 88-95.
3. Meyer-Schwickerath, R., Pfeiffer, A., Blum, W. F., Freyberger, H., Klein, M., Lösche, C., & Schatz, H. (1993). Vitreous levels of the insulin-like growth factors I and II, and the insulin-like growth factor binding proteins 2 and 3, increase in neovascular eye disease. Studies in nondiabetic and diabetic subjects. The Journal of clinical investigation, 92, 2620-5.

4. Aiello, L. P., Avery, R. L., Arrigg, P. G., Keyt, B. A., Jampel, H. D., Shah, S. T., & Nguyen, H. V. (1994). Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders. New England Journal of Medicine, 331, 1480-7.

5. Blinder, K. J., Dugel, P. U., Chen, S., Jumper, J. M., Walt, J. G., Hollander, D. A., & Scott, L. C. (2017). Anti-VEGF treatment of diabetic macular edema in clinical practice: effectiveness and patterns of use (ECHO Study Report 1). Clinical ophthalmology (Auckland, NZ), 11, 393.

6. Lazic, R., Lukic, M., Boras, I., Draca, N., Vlasic, M., Gabric, N., & Tomic, Z. (2014). Treatment of Anti-Vascular Endothelial Growth Factor-Resistant Diabetic Macular Edema With Dexamethasone Intravitreal Implant. Retina, 34, 719-24.

7. Ünsal, E., & Çubuk, M. Ö. (2019). The Results of Aflibercept Treatment in Patients With Naive Diabetic Macular Edema: A Real World Study. Retina-Vitreus/Journal of Retina-Vitreous, 28.

8. Ishikawa K, Honda S, Tsukahara Y, Negi A. Preferable use of intravitreal bevacizumab as a pretreatment of vitrectomy for severe proliferative diabetic retinopathy. Eye (Lond). 2009;23:108-11.

9. Zhao, L. Q., Zhu, H., Zhao, P. Q., & Hu, Y. Q. (2011). A systematic review and meta-analysis of clinical outcomes of vitrectomy with or without intravitreal bevacizumab pretreatment for severe diabetic retinopathy. British journal of ophthalmology, 95, 1216-22.

10. Arevalo, J. F. (2013). Intravitreal bevacizumab as anti-vascular endothelial growth factor in the management of complications of proliferative diabetic retinopathy. Medical hypothesis, discovery and innovation in ophthalmology, 2, 20.

11. Modarres, M., Nazari, H., Ghasemi Falavarjani, K., Naseripour, M., Hashemi, M., & Mehdi Parvaresh, M. (2009). Intravitreal injection of bevacizumab before vitrectomy for proliferative diabetic retinopathy. European journal of ophthalmology, 19, 848-52.

12. Di Lauro, R., De Ruggiero, P., Di Lauro, R., Di Lauro, M. T., & Romano, M. R. (2010). Intravitreal bevacizumab for surgical treatment of severe proliferative diabetic retinopathy. Graefe's Archive for Clinical and Experimental Ophthalmology, 248, 785-91.

13. Ünsal, E., Çubuk, M. Ö., Filik, A., & Çiftçi, F. (2019). The Outcomes of Pars Plana Vitrectomy For Diabetic Vitreous Hemorrhage: The Effect of Preoperative Intravitreal Anti Vascular Endothelial Growth Factor Agents. Retina-Vitreus/ Journal of Retina-Vitreous, 28.

14. Berk Ergun, S., Toklu, Y., Cakmak, H. B., Raza, S., & Simsek, S. (2015, May). The effect of intravitreal bevacizumab as a pretreatment of vitrectomy for diabetic vitreous hemorrhage on recurrent hemorrhage. In Seminars in ophthalmology, 30, 3, 177-80. Informa Healthcare.

15. Gupta, A., Bansal, R., Gupta, V., & Dogra, M. R. (2012). Six-month visual outcome after pars plana vitrectomy in proliferative diabetic retinopathy with or without a single preoperative injection of intravitreal bevacizumab. International ophthalmology, 32, 135-44.

16. Farahvash, M. S., Majidi, A. R., Roohipoor, R., & Ghassemi, F. (2011). Preoperative injection of intravitreal bevacizumab in dense diabetic vitreous hemorrhage. Retina, 31, 1254-60.

17. Lo, W. R., Kim, S. J., Aaberg Sr, T. M., Bergstrom, C., Srivastava, S., Yan, J.,& Hubbard III, G. B. (2009). Visual outcomes and incidence of recurrent vitreous hemorrhage after vitrectomy in diabetic eyes pretreated with bevacizumab (avastin). Retina (Philadelphia, Pa.), 29, 926.

18. Sato T, Morita S, Bando H. Early vitreous hemorrhage after vitrectomy with preoperative intravitreal bevacizumab for proliferative diabetic retinopathy. Middle East Afr J Ophthalmol. 2013;20:51-5.

19. ZhaoXY, XiaS, ChenYX.Antivascular endothelial growth factor agents pretreatment before vitrectomy for complicatedproliferative diabetic retinopathy:a metaanalysis of randomised controlled trials. Br J Ophthalmol. 2018 Aug;102:1077-85.

20. Blankenship GW, Machemer R. Long-term diabetic vitrectomy results. Report of 10 year follow-up. Ophthalmology 1985;92:503-6.

21. Yüksel, K., Baz, Ö., Çelik, U., Herdem, U., Alagöz, C., Özgürhan, E., & Demirok, A. (2015). Diyabetik traksiyonel retina dekolmanlı olgularda 23-gauge pars plana vitrektomi cerrahisi sonuçları. Journal of Clinical and Experimental Investigations, 6, 27-32.

22. Yang, C. M., Yeh, P. T., & Yang, C. H. (2007). Intravitreal long-acting gas in the prevention of early postoperative vitreous hemorrhage in diabetic vitrectomy. Ophthalmology, 114, 710-5.

23. West, J. F., & Gregor, Z. J. (2000). Fibrovascular ingrowth and recurrent haemorrhage following diabetic vitrectomy. British journal of ophthalmology, 84, 822-5.

24. Brown, G. C., Tasman, W. S., Benson, W. E., McNamara, J. A., & Eagle, R. C. (1992). Reoperation following diabetic vitrectomy. Archives of ophthalmology, 110, 506-10.

25. Tolentino, F. I., Cajita, V. N., Gancayco, T., & Skates, S. (1989). Vitreous hemorrhage after closed vitrectomy for proliferative diabetic retinopathy. Ophthalmology, 96, 1495-500.

26. Mahalingam, P., Topiwalla, T. T., & Ganesan, G. (2018). Vitreous rebleed following sutureless vitrectomy: incidence and risk factors. Indian journal of ophthalmology, 66, 558.

27. Khuthaila, M. K., Hsu, J., Chiang, A., DeCroos, F. C., Milder, E. A., Setlur, V., ... & Spirn, M. J. (2013). Postoperative vitreous hemorrhage after diabetic 23-gauge pars plana vitrectomy. American journal of ophthalmology, 155, 757-63.

28. Smith, J. M., & Steel, D. H. (2015). Anti-vascular endothelial growth factor for prevention of postoperative vitreous cavity haemorrhage after vitrectomy for proliferative diabetic retinopathy. Cochrane Database of Systematic Reviews, (8).

29. Farahvash, M. S., Majidi, A. R., Roohipoor, R., & Ghassemi, F. (2011). Preoperative injection of intravitreal bevacizumab in dense diabetic vitreous hemorrhage. Retina, 31, 1254-60.

30. El-Batarny, A. M. (2008). Intravitreal bevacizumab as an adjunctive therapy before diabetic vitrectomy. Clinical Ophthalmology (Auckland, NZ), 2, 709.

31. Rizzo, S., Genovesi-Ebert, F., Di Bartolo, E., Vento, A., Miniaci, S., & Williams, G. (2008). Injection of intravitreal bevacizumab (Avastin) as a preoperative adjunct before vitrectomy surgery in the treatment of severe proliferative diabetic retinopathy (PDR). Graefe's Archive for Clinical and Experimental Ophthalmology, 246, 837-42.

32. Arevalo, J. F., Maia, M., Flynn, H. W., Saravia, M., Avery, R. L., Wu, L., ... & Sanchez, J. G. (2008). Tractional retinal detachment following intravitreal bevacizumab (Avastin) in patients with severe proliferative diabetic retinopathy. British Journal of Ophthalmology, 92, 213-6.

33. Van Geest, R. J., Lesnik-Oberstein, S. Y., Tan, H. S., Mura, M., Goldschmeding, R., Van Noorden, C. J., ... & Schlingemann, R. O. (2012). A shift in the balance of vascular endothelial growth factor and connective tissue growth factor by bevacizumab causes the angiofibrotic switch in proliferative diabetic retinopathy. British journal of ophthalmology, 96, 587-90.

34. Comyn, O., Wickham, L., Charteris, D. G., Sullivan, P. M., Ezra, E., Gregor, Z., ... & Restori, M. (2017). Ranibizumab pretreatment in diabetic vitrectomy: a pilot randomised controlled trial (the RaDiVit study). Eye, 31, 1253-8.