The Effects of Re-vitrectomy and Intravitreal anti-VEGF Treatments on Visual Outcome in Diabetic Vitreous Hemorrhage After Pars Plana Vitrectomy

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ABSTRACT

Purpose: This study analyzed the effects of re-vitrectomy and intravitreal anti-VEGF treatments and other factors on visual acuity in vitreous hemorrhages (VH) in diabetic patients after vitrectomy.

Materials and Methods: VHs seen in vitrectomized diabetic patients were reviewed retrospectively. Hemorrhages in post vitrectomy diabetic vitreous hemorrhage (PDVH) were classified in three groups as moderate, marked and severe. One group of patients was treated with re-PPV, and the other had intravitreal anti-VEGF. Best-corrected visual acuity (BCVA), HbA1C levels, and anti-VEGF treatments up to the development of VH were evaluated during the one-year follow-up of the patients.

Results: A total of 16 patients with PDVH (10 females and six males) were examined. Ten (62.5%) patients were treated with anti-VEGF and 6 (37.5%) with re-PPV. The mean age of the patients was 63.5±8.9 years, and there was no difference between the two treatment groups in terms of age (p=0.087), HbA1c (p=0.609), previous anti-VEGF treatments (p=0.488), and VH severity (p=0.091). A statistically significant difference was found between the baseline visual acuity values between the groups (p=0.016). The mean of the anti-VEGF group was 0.96 logMAR, while the mean of the re-PPV group was 1.33 logMAR (worse). There was no difference between the mean visual outcomes of the two groups at the end of six months (p=0.157) and one year (p=0.309).

Conclusion: Since there was no difference between the two treatment modalities in terms of change in BCVA, minimally invasive intravitreal anti-VEGF therapy seems to be an alternative to re-vitrectomy in the treatment of PDVH.

Keywords: Anti-VEGF therapy, diabetic retinopathy, re-vitrectomy, vitreous hemorrhage, visual outcomes.

INTRODUCTION

Diabetic retinopathy (DR) is one of the important causes of visual impairment in the adult age group. Various factors such as patient age, hemoglobin A1c level, type of diabetes, hypercholesterolemia, and disease duration are important risk factors in the development of DR[1,2]. Diabetic macular edema is the most common cause of visual impairment in proliferative diabetic retinopathy (PDR), while other causes are vitreous hemorrhage and tractional retinal detachment[3].

The incidence of recurrent vitreous hemorrhage (RVH) in PDR patients has been reported to range from 11.8% to 75%[4, 5]. Post vitrectomy diabetic vitreous hemorrhage (PDVH) can be caused by retinal and surgical reasons. Insufficient pan-retinal photocoagulation, new neovascular membrane formation, or hemorrhages due to residual neovascular membrane are retinal-derived causes. Fibrovascular growth in the sclerotomy sites after PPV, ocular trauma, and postoperative low intraocular pressure are stated to be surgical-related causes[6-8].

Depending on the severity of DR, hypoxia, neuroretinal damage, and circulatory disorders increase the release of pro-angiogenic factors such as vascular endothelial growth factor (VEGF)[9]. Increased VEGF leads to neovascularization, fibrovascular membrane development, and VH in PDR[10]. Anti-VEGF therapy causes regression in neovascular vessels and increases vision by preventing new hemorhages[11,12]. In treating recurrent VH in PDR, anti-

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VEGF drugs are preferred over other treatment modalities due to these properties[13].

PDVH seen in the early period can usually resolve spontaneously within a few weeks. However, spontaneous resorption is insufficient despite anti-VEGF treatments in some recurrent VHs seen in the late period. The re-surgery is reported to be necessary for these cases[14]. Re-PPV is recommended for recurrent VH, not resorbing within six weeks after the first PPV application or for bleeding developing four weeks after the first surgery and affecting vision[15].

This study aimed to compare the effects of intravitreal anti-VEGF treatment and re-PPV treatment and previous anti-VEGF treatments on vision outcome in PDVH patients who had previously undergone PPV due to PDR.

MATERIALS AND METHODS

Study design

Patients diagnosed with VH due to DR and had PPV between January 2019 and September 2021 in Samsun Training and Research Hospital were analyzed retrospectively. Recurrent diabetic VH patients who developed after PPV were screened in medical records. For the study, approval was obtained from the local ethics committee with the decision number 2020/12/6, dated 12.08.2020, and complied with the principles of the Helsinki Declaration. Informed consent was obtained from both the re-PPV group and the anti-VEGF patients before the treatments were applied.

Patient inclusion criteria

Patient inclusion criteria were determined as recurrent hemorrhages two weeks or more after PPV surgery, moderate or severe hemorrhage, absence of retinal detachment or tractional fibrotic bands on B-MOD ocular ultrasonography (Echoscan US-4000, Nidek Co.Ltd. Japan), VH not originating from trauma, hypertensive attack or anticoagulant, and finally having a one-year regular follow-up of the patients. Although HbA1c levels were relatively high in patients in both treatment groups, according to medical records, it was found that they were under control for metabolic and hypertension with medical treatment.

Study groups and examination protocols

PDVH was examined in two groups according to treatment options as anti-VEGF and re-PPV groups. VH was classified into three groups. Moderate VH was determined as distinguishing the optic disc and retinal vascular structures blurry and marked VH as seeing the upper retinal quadrants clearly but not the fundus details and obtaining the retinal red reflex. Severe VH was determined as the inability to select retinal structures and obtain the red reflex. Patients underwent detailed ophthalmologic examinations and OCT scans at their visits after recurrent VH and until their one-year follow-up. The age and gender of the patients, the classification of VH, the best-corrected visual acuity (BCVA) in recurrent VH and after treatment, HbA1C levels, and anti-VEGF treatment status up to the development of recurrent hemorrhage were examined. For statistical analysis, patients' BCVAs in Snellen were converted to the logarithm of the minimum angle of resolution (logMAR). The patients were examined monthly for the first six months and bimonthly for the next six months in the re-PPV and anti-VEGF groups. Patients with complaints of blurred vision and decreased vision came for interim examinations. The patient's visual acuity and the condition of the other eye were taken into account when deciding on injection or re-vitrectomy in cases.

Surgical method: In patients scheduled for re-PPV, bevacizumab (1.25 mg/0.05 cc) was administered intravitreally 3-5 days ago. The patients' surgeries in the re-PPV group were performed by the same surgeon and under retrobulbar anesthesia if there was no particular condition. A conventional three-port pars plana 23G vitrectomy was performed using a non-contact wide-field imaging system with EVA (Dutch Ophthalmic Research Center, Zuidland, Netherlands) and Stellaris (PC Vision Enhancement System, Bausch + Lomb, St. Louis, MO, USA) devices. After clearing the vitreous hemorrhage, retinal traction and residual membrane were examined for the presence. Membranes caused bleeding and could not be peeled in previous surgery and left as stumps were peeled off as much as possible. Endodiathermy was performed in cases where fibrovascular bands could not be peeled off. Panretinal photocoagulation was completed by applying lasers to the areas with insufficient photocoagulation in the previous surgery. Topical antibiotic and steroid treatment were given to the cases for three weeks postoperatively. In this group of patients, anti-VEGF treatment was applied according to the indication.

Intravitreal anti-VEGF administration:

Intravitreal injections were administered in a specialized isolated injection room or positive high-pressure injection cabinet. The treatment of PDVH patients previously treated with ranibizumab or aflibercept anti-VEGF treatments was continued. Bevacizumab (Altuzan®, Roche) was administered monthly at a dose of 1.25 mg/0.05 mL

intravitreally to patients who previously did not receive anti-VEGF therapy. Injections were performed according to standard antisepsis and application rules, and all patients used 0.5% moxifloxacin drops for five days after injection.

RESULTS

PVDH was detected in 16 patients treated with PPV. 10 (62.5%) of the patients constituted the first group treated with anti-VEGF, and 6 (37.5%) formed the second group treated with the re-PPV. The mean age of the patients was 63.5±8.9 years, 10 (62.5%) were female, and 6 (37.5%) were male. The demographic and clinical characteristics of the patients included in the study are shown in Table 1. There was no statistically significant difference between the two groups regarding gender (p=1,000) and VH severity (p=0.091). No statistically significant difference was found between the distribution of anti-VEGF treatment status before and after the first PPV treatment (p values 0.488, 0.546, respectively).

The comparison of the mean age values, HbA1c levels of the patients, and the number of anti-VEGF treatments administered for one year after the PDVH development according to the groups are shown in Table 2.

There was no statistically significant difference between the groups in the mean age values of the patients (p=0.087). While the mean age of the anti-VEGF group was 65.00, the re-PPV group was 60.33. No statistically significant difference was found between the groups in the mean values of HbA1c and the number of injections (p values 0.609, 0.533, respectively). The mean values of baseline, six-month, and one-year vision outcomes are compared in Table 3.

Table 1: *Comparison of gender, VH severity, and medical treatment status according to groups.*

	Anti VEGF group	Re-PPV group	Total	Test statistic	p
	n (%)	n (%)	n (%)		
Gender					
Female	6 (60)	4 (66,7)	10 (62,5)	---	1,000[F]
Male	4 (40)	2 (33,3)	6 (37,5)		
VH severity					
Moderate	7 (70)	1 (16,7)	8 (50)	=4,800	0,091
Marked	2 (20)	2 (33,3)	4 (25)		
Severe	1 (10)	3 (50)	4 (25)		
Treatments taken before PPV					
Aflıbersept	2 (20)	1 (16,7)	3 (18,8)	=2,428	0,488
Bemacizumab	1 (10)	0 (0)	1 (6,3)		
Ranibizumab	4 (40)	1 (16,7)	5 (31,3)		
Naive	3 (30)	4 (66,7)	7 (43,8)		
Treatments received after PPV					
Aflıbersept	2 (20)	1 (16,7)	3 (18,8)	=1,209	0,546
Bemacizumab	4 (40)	4 (66,7)	8 (50)		
Ranibizumab	4 (40)	1 (16,7)	5 (31,3)		

F: Fisher's Exact testi, $\chi 2$: Chi-square test statistic

Table 2: *Comparison of the values of age, HbA1c and number of injections according to the groups.*

	Anti VEGF group		Re-PPV group		Test statistic	p
	Mean ± SD	Mean (min. - maks.)	Mean ± SD	Mean (min. - maks.)		
Age	65,00 ± 5,50	64,50 (55,00 - 72,00)	60,33 ± 3,61	59,50 (56,00 - 66,00)	t=1,841	0,087
HbA1c level	7,75 ± 0,76	7,70 (6,60 - 9,10)	7,57 ± 0,50	7,65 (6,70 - 8,10)	t=0,523	0,609
Number of injections	4,70 ± 1,16	4,50 (3,00 - 7,00)	5,17 ± 1,94	5,50 (2,00 - 7,00)	t=-0,608	0,553

standard deviation (SD), t: two independent samples t-test statistic

Table 3: *Comparison of visual acuity between and within groups.*

BCVA *	Anti VEGF group		Re-PPV group		Test statistic	p
	Mean ± SD	Mean (min. - maks.)	Mean ± SD	Mean (min. - maks.)		
Baseline	0,96 ± 0,30a	0,85 (0,70 - 1,60)	1,33 ± 0,19a	1,35 (1,00 - 1,50)	t=-2,736	**0,016**
Sixth month	0,64 ± 0,26b	0,60 (0,30 - 1,10)	0,82 ± 0,15b	0,85 (0,60 - 1,00)	t=-1,496	0,157
Final	0,49 ± 0,25c	0,45 (0,20 - 1,00)	0,62 ± 0,19b	0,65 (0,40 - 0,90)	t=-1,055	0,309
Test statistic	F=50,035		F=26,281			
p	**<0,001**		**<0,001**			

BCVA: Best corrected Visual acuity, * logMAR , F: Repeated analysis of variance test statistic , t: Two independent samples t-test statistic, a-c: There is no difference between times with the same letter.

A statistically significant difference was found between the baseline visual acuity values between the groups (p=0.016). The mean of the anti-VEGF group was 0.96 logMAR, while the mean of the re-PPV group was 1.33 logMAR (worse). A significant difference was found between the means of vision outcomes over time in the anti-VEGF group and the re-PPV group (p<0.001). While the lowest mean vision values were obtained at the baseline, the best mean vision values were obtained at the end of the year. A statistically significant difference was found between the mean vision values within the groups (p<0.001). This difference was due to the difference between the baseline and other times. The relationship between the anti-VEGF treatments received before the first PPV treatment and the severity of PDVH is shown in Table 4.There was no statistically significant difference between the distribution of VH severity status according to medical treatment status (p=0.154).

Statistical Method

Test statistic

Data were analyzed with IBM SPSS V23. The conformity to the normal distribution was evaluated using the Shapiro-Wilk test. Chi-square and Fisher's Exact tests were used to compare categorical variables according to groups. An Independent two-sample t-test was used to compare normally distributed data according to paired groups. Repeated-measures ANOVA was used to compare normally distributed data within three or more groups over time, and multiple comparisons were analyzed with the Bonferroni test. Analysis results were presented as mean ± standard deviation and median (minimum-maximum) for quantitative data and frequency (percent) for categorical data. The significance level was taken as p<0.050.

DISCUSSION

Re-PPV and anti-VEGF therapy are alternative methods in the treatment of PDVH. In our study, when the patient's baseline vision in the anti-VEGF and re-PPV groups was compared, the vision levels were found to be lower in the re-PPV group than in the anti-VEGF group. (p<0.016). However, no difference was found between the vision levels of the patients in both treatment groups at the end of six months and one year. In the light of these findings, it has been seen that minimally invasive anti-VEGF therapy is a good alternative to re-PPV in treating PDVH. VH treatment varies depending on the etiology, the fellow eye condition, the presence of neovascularization, or the duration of the hemorrhage. Demir et al. reported that 70% of patients with VH did not require surgery[16]. Similar to the above study, 62.5% of the cases did not undergo surgery in our study.

A randomized clinical trial was conducted comparing the effects of intravitreal injections of ranibizumab versus saline

Table 4: *Comparison of VH severity according to anti-VEGF treatment before the first PPV.*

	aflibersept	bemacizumab	ranibizumab	naiv	Test statistic	p
	n (%)	n (%)	n (%)	n (%)		
VH severity						
Moderate	3 (100)	0 (0)	3 (60)	2 (28,6)	9,371	0,154
Marked	0 (0)	0 (0)	2 (40)	2 (28,6)		
Severe	0 (0)	1 (100)	0 (0)	3 (42,9)		

: Chi-square test statistic

injections in patients with VH. Ranibizumab was reported to be superior to saline injections in terms of both recurrent VH rate and visual acuity in patients. In comparing PPV need, 12% of the patients in the ranibizumab group and 17% in the saline group received PPV during the 16-week follow-up. It has been reported that these rates do not make a clinically significant difference[17].

In the treatment of PDVH, different results are reported with anti-VEGF results. Ruiz-Moreno et al. reported four intravitreal bevacizumab injection cases to treat recurrent VH in vitrectomized diabetic eyes. Two of these patients received two injections and the others three, and VH was reportedly wholly cleared. Monthly injections were applied to these patients, and cleaning of hemorrhages was accepted as a criterion[18]. In another study, VH clearance times were investigated in the bevacizumab-treated and untreated control groups in PDVH. This period was 6.5 weeks in the Bevacizumab group and 6.4 weeks in the group not receiving anti-VEGF therapy. It was reported that 27% of the patients in the treatment group required additional surgery. This study found no difference between the anti-VEGF and the control group[19]. Likewise, Alagöz et al. reported no difference in the clearance time of recurrent VHs in patients receiving and not receiving anti-VEGF therapy but a decrease in the need for surgical intervention[20]. This study obtained interesting results in terms of the number of anti-VEGF applications. The patients in the anti-VEGF treatment group received an average of 4.5 injections over one year, while the re-PPV treatment group received 5.5 injections. Although there was no statistically significant difference, this result may be because 70% of patients with moderate VH were treated with anti-VEGF and required less anti-VEGF. Atchison and Maccumber reported that recurrent VH was seen an average of four times in PVDH patients, and an average of eight intravitreal anti-VEGF was administered[21]. It was observed that the number of anti-VEGF injections performed was higher than in our study.

This study did not detect any statistical difference in anti-VEGF and re-PPV groups regarding VH severity, HbA1c levels, patient ages, and previous anti-VEGF treatments. Although the mean age of the patients in the anti-VEGF group (64.5 years) was found to be higher than that of the re-PPV group (59.5 years), this difference was not significant (p=0.087). These findings show that more conservative treatment is preferred in patients as age increases. Metita et al. reported that 17.3% of vitreous hemorrhages were due to hypertension, 21.2% of diabetes and 31.5% of hypertension + diabetes[22]. Although there was no evidence in our study, it is possible that recurrent VHs are due to hypertension. The limitation of this study is that hypertension cannot be excluded as a definitive etiological cause. Another limitation of this study is that the mean durations of diabetes and hypertension between the groups were not examined.

When the patients were analyzed in terms of VH severity, there was no statistical difference between the distribution of patients in the two groups (p=0.091). However, moderate VH accounted for half of the patients, and most of these patients were treated with anti-VEGFs. Therefore, patients with marked and severe VH were mainly treated with re-PPV. The rates of patients with marked VH and severe VH in the re-PPV group were found to be 33.3% and 50%, respectively. Therefore, patients with more severe clinical manifestations were treated with re-PPV. In addition, it is thought that patients in this group needed more anti-VEGF injections due to their retinal pathologies.

A study has been published in which the positive effects of repetitive PPV surgeries on vision and anatomical results in patients with PDVH were reported. However, this study reported no relationship between the number of surgeries or demographic variables with visual acuity[23]. Khatib et al. reported that they performed additional vitrectomies for recurrent VH in 5.6% of 360 PVDH patients. Outcome visual acuities were similar in the group requiring additional re-PPV and not requiring treatment. It has been stated that HbA1c level is not a marker for re-PPV [24]. In our study, the two groups were not statistically different regarding HbA1c and outcome visual acuities, similar to the study of Khatib et al.

The important studies have been reported related to on recurrent vitreous hemorrhages after vitreoretinal surgery in patients with proliferative diabetic retinopathy[25,26]. Çıtırık et al. found that the most common etiological cause of recurrent intravitreal hemorrhage after vitreoretinal surgery in patients with PFVF is incomplete ALF and neovascularization[25]. Bleeding from fibrovascular membrane stumps, inadequate endodiathermy applications for neovascularizations, and residual split posterior vitreous that facilitates neovascular membrane development are the most common etiological causes of recurrent VH at this study. In this regard, the two studies differ from each other. Although there are studies in the literature that previous anti-VEGF treatments reduce VH, there is no study examining the effects on recurrent VH in patients with PDVH. From this point of view, it was determined that the previous anti-VEGF treatments and being naive PDVH patients did not affect the severity of VH. Photocoagulation performed in

PPV surgery and metabolic control were found to be more effective.

In conclusion, minimally invasive intravitreal anti-VEGF therapy can be an alternative to traditional PPV in treating PDVH. It was found that the two treatment modalities did not differ significantly in terms of the change in BCVA at the end of six months and one year. It seems that intravitreal anti-VEGF therapy may be preferred in diabetic patients to avoid surgery-related morbidity.

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