

# The Outcomes of Pars Plana Vitrectomy For Diabetic Vitreous Hemorrhage: The Effect of Preoperative Intravitreal Anti Vascular Endothelial Growth Factor Agents

## Preoperatif İntravitreal Anti-vasküler Endotelyal Büyüme Faktörünün Diabetik Vitreus Hemorajisi Tedavisinde Uygulanan Pars Plana Vitrektomi Üzerine Etkisi

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### ABSTRACT

**Purpose:** To analyze the effect of preoperative intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents on intraoperative and postoperative complications of pars plana vitrectomy (PPV) applying for diabetic vitreous hemorrhage treatment.

**Method:** A retrospective study was designed to evaluate the effect of preoperative anti-VEGF agents. Patients treated with PPV for proliferative diabetic retinopathy related nonclearing vitreous hemorrhage were enrolled in this study. Patients received an intravitreal anti-VEGF injection (repackaged 1.25 mg/0.05 ml bevacizumab, 0.5 mg/0.05 mL ranibizumab, 2 mg/0.05 ml aflibercept) before surgery (1 to 14 days before surgery) were included in group 1. Patients did not receive an anti-VEGF injection were included in group 2. Different groups were compared in terms of intraoperative and postoperative complications and duration of surgery.

**Results:** Fifty-nine eyes of 59 patients have fulfilled the inclusion criteria and were analyzed in this study. Thirty eyes of 30 patients were included in group 1, and 29 eyes of 29 patients were included in group 2. Final best-corrected visual acuity (BCVA) after surgery showed significant improvement compared with baseline in 2 groups ( $p=0.001$ ). Incidence of significant intraoperative bleeding and the incidence of the iatrogenic retinal tear was higher in group 2 ( $p=0.045$ ,  $p=0.049$  respectively). Incidence of early and delayed recurrent vitreous hemorrhage (VH) did not differ significantly between the 2 treatment groups ( $p=0.76$ ,  $p=0.61$  respectively). The duration of surgery in group 1 was significantly shorter than group 2, ( $p=0.001$ ).

**Conclusion:** The preoperative anti-VEGF agents applying for diabetic VH facilitate a faster the surgery and achieve better operative results.

**Key Words:** Vitreous hemorrhage, Tractional retinal detachment, Anti-vascular endothelial growth factor.

### ÖZ

**Amaç:** Bu çalışmada preoperatif intravitreal anti-vasküler endotelyal büyüme faktörünün (anti-VEGF) diabetik (DM) vitreus hemorajisi (VH) tedavisinde uygulanan pars plana vitrektomi (PPV) cerrahisi üzerine etkilerinin değerlendirilmesi amaçlandı.

**Metod:** Kliniğimizde 2014-2018 yılları arasında PPV cerrahisi ile tedavi edilen DM ilişkili vitreus hemorajisi olgularının dosyaları retrospektif şekilde tarandı. Cerrahi öncesi 1-14 gün arasında intravitreal anti-VEGF (1.25 mg/0.05 ml bevacizumab veya 0.5 mg/0.05 mL ranibizumab veya 2 mg/0.05 ml aflibercept) uygulanan olgular grup 1, cerrahi öncesi anti-VEGF uygulanmayan olgular grup 2 olarak adlandırıldı ve çalışmaya dahil edildi. Farklı gruplar intraoperatif ve postoperatif komplikasyonlar açısından karşılaştırıldı. Preoperatif anti-VEGF tedavisinin cerrahi süresi üzerine etkisi araştırıldı.

**Bulgular:** Elli dokuz hastanın 59 gözü (30 göz grup 1, 29 göz grup 2) çalışmaya dahil edildi. Sonuç en iyi düzeltilmiş görme keskinliğinin

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(EİDGK) her iki grupta da anlamlı şekilde artış gösterdiği saptandı, ( $p=0.001$ ). İntraoperatif kanama ve intraoperatif iatrojenik yırtık insidansının grup 2'de anlamlı şekilde daha yüksek olduğu görüldü, (sırasıyla,  $p=0.045$ ,  $p=0.049$ ). Cerrahi süresinin grup 2 de anlamlı şekilde daha uzun olduğu görüldü, ( $p=0.001$ ). Postoperatif erken ve geç tekrarlayan vitreus hemorajisi oranının iki grupta benzer olduğu belirlendi, (sırasıyla,  $p=0.76$ ,  $p=0.61$ ).

**Sonuç:** Bu çalışmada preoperative anti-VEGF tedavisinin DM ilişkili VH tedavisinde cerrahi süreyi kısalttığı, intraoperatif komplikasyon oranını azalttığı ve cerrahi başarıyı olumlu yönde etkilediği saptanmıştır.

**Anahtar Kelimeler:** Vitreus hemorajisi, Traksiyonel retinal dekolmanı, Anti-vasküler endotelial büyüme faktörü

## INTRODUCTION

Although, all the crucial improvement in the understanding and treatment of diabetes mellitus (DM) over the recent years, in industrialized countries proliferative diabetic retinopathy (PDR), is the leading cause of blindness<sup>1</sup>. Proliferative diabetic retinopathy (PDR) is characterized by retinal neovascularization (RNV) in the vitreous-retinal interface which leads to serum leakage, hemorrhage, and fibrovascular proliferation<sup>2</sup>. Depending on these features, the complications of macular edema, vitreous hemorrhage (VH) and tractional retinal detachment (TRD) could emerge and these complications may severely damage patient's visual acuity and need surgical treatments<sup>2</sup>.

Pars plana vitrectomy (PPV) is the most commonly used treatment option for the management of the complications such as TRD and unhealing VH<sup>2,3</sup>. Repeated bleeding from different retinal sites during the surgery makes the operation tiresome. Elevating infusion bottle and endodiathermy are the methods to solve this problem.<sup>2,3</sup> However, particularly excessive endodiathermy may cause necrosis and an increase of postoperative inflammation.<sup>2,3</sup> Additionally, prolonged elevation of intraocular pressure due to elevating infusion bottle may induce postoperative corneal edema.<sup>2,3</sup> Besides these, the uncontrolled bleeding can be the reason of complications such as iatrogenic retinal break, retinal detachment, and secondary surgery.<sup>2,4</sup> Another important complication was vitreous rebleed (VRB) after PPV. VRB is the most common in DM patients with PDR.<sup>5-11</sup> The reported incidence of VRB ranges from 12% to 63% and resurgery for nonresolving VH is reported in 4% to 38%.<sup>5-9</sup>

It was already known that angiogenesis is the major mechanism of PDR and vascular endothelial growth factor (VEGF) was the leading cause of the increase of vascular permeability that results in diabetic macular oedema, of the neovascularization that can result to VH and TRD.<sup>12-14</sup> Inhibition of VEGF could decrease the intraoperative and postoperative complications. Therefore, today intravitreal injection of anti-vascular endothelial growth factor agents (anti-VEGF) has been widely suggested before PPV for diabetic retinopathy.<sup>15-17</sup> However, some authors claimed that there is no significant effect of anti-VEGF agents on comforting of the surgery or the postoperative process.<sup>18-20</sup>

In the current study, we aimed to analyze the effect of preoperative intravitreal anti-VEGF agents on intraoperative

and postoperative complications, to discuss our results of PPV for diabetic VH.

## METHOD

A retrospective study was designed to evaluate the effect of preoperative intravitreal anti-VEGF agents on postoperative complications and to discuss the results of PPV for diabetic VH. The study protocol was approved by the local ethics committee. The study was designed in accordance with the Declaration of Helsinki. Before the surgery was performed, informed patient consent was taken from all patients about the complications of PPV and intravitreal injection of anti-VEGF.

Medical charts of patients with a diagnosis of vitreous hemorrhage due to PDR and treated with pars plana vitrectomy combined with or without preoperative intravitreal anti-VEGF injection in our Retina Unit between January 2014 and January 2018 were retrospectively reviewed in this study.

Vitreous hemorrhage that has not been cleaned for 2 months and causes significant visual loss defined as nonclearing vitreous hemorrhage. Patients treated with PPV for PDR related nonclearing vitreous hemorrhage were enrolled in this study. Only 1 eye of each patient was included in the study. Exclusion criteria were a follow-up period of fewer than 6 months, repeat vitrectomy after the first vitrectomy for retinal diseases other than VH, previous history of vitrectomy, uncontrolled hypertension, medical history of blood coagulopathy, recent history (within 3 months) of intravitreal anti-VEGF treatment.

All surgeries were performed by the same surgeon (E.U) under retrobulbar local anesthesia. Before PPV, phacoemulsification was done if a cataract was present in cases of combined surgery. A three-port 23-gauge PPV was performed on all eyes. After applying core vitrectomy via triamcinolone acetate (10 mg/ml), the posterior vitreous detachment was induced with a vitrectomy probe around the optic disc. Procedures such as fibrovascular membrane dissection, endodiathermy, or endolaser photocoagulation were applied with 23-gauge instruments as required. Intraoperative bleeding was controlled by either endodiathermy or elevation of the irrigation bottle height. If the patient was taking any anticoagulant for underlying systemic diseases, surgery was performed after 10 day of anticoagulant discontinuation after consultation with

the related departments. Gas (14% C3F8 or 20% SF6) or 1000 cst silicone oil was used as an intraocular tamponade according to the situation of the patient.

Patients received an intravitreal anti-VEGF injection (repackaged 1.25 mg/0.05 ml bevacizumab- 0.5 mg/0.05 mL ranibizumab- 2 mg/0.05 ml aflibercept) before surgery (3 to 15 days before surgery) were included in group 1. Patients did not receive an anti-VEGF injection were included in group 2. All intravitreal injections were applied in an operating room under topical anesthesia obtained by 0,5% proparacaine hydrochloride (Alcaine; Alcon). After povidone-iodine solution (5 %) was used for irrigation of conjunctiva, anti-VEGF agent (repackaged 1.25 mg/0.05 ml bevacizumab- 0.5 mg/0.05 mL ranibizumab- 2 mg/0.05 ml aflibercept) injection was performed via the pars plana, 3,5-4 mm posterior to limbus via a syringe with 30 gauge needle.

Postoperatively topical steroids and antibiotics were prescribed and gradually tapered. Patients were examined on day 1, at 1 week, 4 weeks, 3 months and then at 6 months postoperatively.

Demographic data including age and gender, additionally the history of panretinal photocoagulation (PRP) eye were evaluated for each patient. Preoperative BCVA was tested in logMAR (Logarithm of the minimum angle of resolution or recognition) units using Early Treatment Diabetic Retinopathy Study (ETDRS) chart, slit lamp examination of the anterior segment, IOP measurement, and a dilated fundus examination was performed. Postoperative complications were documented when present.

Different groups were compared in terms of intraoperative and postoperative complications. The intraoperative complications analyzed in this study were significant intraoperative bleeding and iatrogenic tear. Intraoperative bleeding that did not decrease after the elevation of infusion bottle was defined as significant intraoperative bleeding. The postoperative complications analyzed in this study were recurrent VH, epiretinal membrane (ERM), retinal detachment and cataract. The recurrent VH occurred in two weeks was defined as early VH. The recurrent VH occurred after two weeks was defined as delayed VH.

Statistical Package for the Social Sciences (SPSS) version 20.0 software was used for all statistical analyses. Descriptive statistics are presented as minimum, maximum and mean  $\pm$  standard deviation. The normality was checked using the Kolmogorov-Smirnov test. Independent samples t test and Mann-Whitney U test were used for unpaired samples.

## RESULTS

Two hundred forty three the medical charts of the patients who were diagnosed vitreous hemorrhage due to PDR were reviewed. Fifty-nine eyes of 59 patients were fulfilled the inclusion criteria and were analyzed in this study. Thirty eyes of 30 patients were included in group 1, and 29 eyes of 29 patients were included in group 2.

The demographic characteristics of the different groups are shown in Table 1. The different groups were comparable except for the follow-up period.

Parameters	Group 1(n:30)	Group 2(n:29)	p
Mean Age(y), SD	60.9 $\pm$ 6.8	64.1 $\pm$ 11.5	0.15*
DM Type ½	0/30	0/29	
Patients/eye	30/30	29/29	
Female/male	14/16	7/22	0.06**
Mean Follow-up Time(m), SD	11.9 $\pm$ 9.1	19.3 $\pm$ 10.9	0.003*
Preoperative anti-VEGF (d), SD	9.8 $\pm$ 5.2 (3-15)		
Beva/Rani/Afli	12/4/14		
PPV/Phaco + PPV	12/18	17/12	0.1**
Preop TRD present/absent	7/23	5/24	0.1**
Air/C3F8/SF6/Silicon Oil	3/6/11/10	9/1/14/5	
History of glaucoma	2/30	2/29	0.45**
History of hypertension	21/30	19/29	0.53**
Use of anticoagulant therapy	1/30	2/29	0.09**
Previous history of PRP	19/30	14/29	0.24**
HbA1c (Mean $\pm$ SD)	8.1 $\pm$ 0.9	8.0 $\pm$ 1.0	0.82*

DM: diabetes mellitus; m: months; d: day; VEGF: vascular endothelial growth factor; Beva: bevacizumab; Rani: ranibizumab; Afli: aflibercept; PPV: Pars plana vitrectomy; TRD: tractional retinal detachment; PRP: panretinal photocoagulation; HbA1c = hemoglobin A1c; \*independent samples t test; \*\*Chi-square

Although the preoperative mean logMAR BCVA values were better in group 1, analysis of the postoperative mean logMAR BCVA after surgery showed no difference between the groups. Final BCVA after surgery showed significant improvement compared with baseline in all 2 groups, ( $p=0.001$ ), (Table 2).

Parameters	Group 1(n:30)	Group 2 (n:29)	p*
Preoperative VA	2.0 ± 0.69	2.6 ± 0.76	0.005*
Postoperative VA	1.3 ± 1.0	1.1 ± 0.83	0.44*
p**	0.001	0.001	

VA: visual acuity; p\*: independent samples t test; p\*\*: paired samples t test

Analysis of intraoperative complications was also performed. The incidence of intraoperative complications was summarized in Table 3. The incidence of significant intraoperative bleeding was higher in group 2, ( $p=0.045$ ). Additionally, the incidence of iatrogenic retinal tear was higher in group 2, ( $p=0.049$ ). Besides, it was shown that the duration of surgery in group 1 was significantly shorter than group 2, ( $p=0.001$ ).

Results of the postoperative VH incidence analysis between the 2 treatment groups were summarized in Table 4. The incidence of early and delayed recurrent VH did not differ significantly between the 2 treatment groups, ( $p=0.76$ ,  $p=0.61$  respectively), (Table 4). The other postoperative complications were also shown in Table 4. Two patients with postoperative tractional+rhegmatogenous retinal detachment, two patients in group 1 with recurrent VH and two patients in group 2 with recurrent VH need reoperation. The other patients with recurrent VH were healed without an additional intervention. Additionally, one patient in group 2 had transient choroidal effusion, healed with topical intensive steroid therapy. One patient from both groups had postoperative optic atrophy.

Parameters	Group 1(n:30)	Group 2(n:29)	p
Sig.Intraoperative bleeding	3/30	9/29	0.045*
Iatrogenic tear	1/30	5/29	0.049*
DOS (PPV) ±SD (min-max), m	49.4±8.7 (36-68)	58±8.2(45-71)	0.001**
DOS (Phaco + PPV) ±SD (min-max), m	54.4±9.1(44-73)	62.6±8.4(45-74)	0.001**
PRP rates in patients with sig. intraoperative bleeding	2/3	5/9	0.38*

VH: vitreous hemorrhage; RD: retinal detachment; ERM: epiretinal membrane; Sig: Significant; DOS: duration of surgery m: minute PRP: panretinal photocoagulation \*Chi-square test \*\*independent samples t test

**Table 4. Intergroup Comparison of Postoperative Complication Rates.**

Parameters	Group 1 (n:30)	Group 2 (n:29)	p*
Recurrent VH (Early)	3/30	3/29	0.76
Recurrent VH (Delayed)	1/30	2/29	0.61
Postoperative Cataract	5/30	3/29	0.72
Postoperative RD	1/30	1/29	0.83
Postoperative ERM	0/30	3/29	0.06

VH: vitreous hemorrhage; RD: Tractional+Rhegmatogenous retinal detachment; ERM: epiretinal membrane; \*Chi-square test

There were no occurrences of systemic adverse events such as myocardial infarction or cerebrovascular accidents. Additionally, there was no case of endophthalmitis and development of new TRD after intravitreal anti-VEGF injection.

## DISCUSSION

This study is a retrospective designed study to compare the effects of preoperative intravitreal anti-VEGF injection on the incidence of intraoperative and postoperative complications.

The VEGF was one of the major cytokines causing retinal neovascularization observed in PDR, therefore there was an intense curiosity about the effect of anti-VEGF on neovascular retinal diseases<sup>21,22</sup>. Previously, intravitreal injection of an anti-VEGF antibody, in patients with PDR was found to improve retinal and iris neovascularization and even vitreous hemorrhage<sup>23</sup> however, pars plana vitrectomy is still the most common procedure for the management of the PDR complications such as TRD and unhealing VH<sup>2,3</sup>. Studies evaluating the intraoperative and postoperative complications of PPV after preoperative intravitreal anti-VEGF administration generally found less intraoperative bleeding and surgical complications with shorter surgical duration, improved postoperative best-corrected visual acuity (BCVA), less postoperative VH and secondary surgery.<sup>2, 15-17, 24-27</sup>

Intraoperative bleeding is a condition that prolongs the surgical period and complicates surgery. The perfect visualization during surgery may be disturbed, and an iatrogenic retinal break may occur during the intraoperative clot removal. The amount of intraoperative bleeding differs among studies. The IBeTra study measures the erythrocyte count in the fluid retrieved from the vitrectomy cassette using a Neubauer counting chamber.<sup>24</sup> They found that the preoperative intravitreal bevacizumab injection was associated with reduced intraocular bleeding during PPV for diabetic macula-involving TRD.<sup>24</sup> El-Batarny<sup>25</sup> defined intraoperative bleeding as the number of bleeding attacks per case and they presented that the frequency of bleeding attacks was significantly higher in patients without preoperative injection of bevacizumab. Similarly, Yolar et al.<sup>27</sup> reported that preoperative intravitreal injection of bevacizumab increased the success rate of PPV in severe PDR patients. Additionally Rizzo et al.<sup>28</sup> divide the intraoperative bleeding into mild (controlled by elevation of infusion bottle) and severe (controlled by cautery); they showed that both types were more frequent in the noninjected group. In the present study, intraoperative bleeding that could not be controlled by elevation of infusion bottle was defined as significant intraoperative bleeding. Similar to literature, we found that the incidence of significant intraoperative bleeding was higher in the noninjected group. In contrast to this data Farahvash et al.<sup>19</sup> argued that preoperative intravitreal bevacizumab has no significant effect on intraoperative bleeding.

Intraoperative iatrogenic retinal breaks is another crucial complication of PPV. The results of different literature suggested that anti-VEGF pretreatment could significantly reduce the incidence of intraoperative iatrogenic breaks.<sup>18,25-28</sup> Similarly, we showed that intraoperative iatrogenic tear was frequent in the noninjected group. Conversely, Farahvash et al.<sup>19</sup> showed that the incidence of iatrogenic retinal breaks between groups was not statistically significant.

The affect of preoperative anti-VEGF agents on the duration of surgery appeared heterogeneous, however it was suggested that, bevacizumab and conbercept could significantly reduce the duration of surgery<sup>2,18,25,28,29</sup>. Similarly, we found that the duration of surgery in a patient treated with preoperative anti-VEGF agents was significantly shorter in group 1, ( $p=0.001$ ).

One possible disadvantage of preoperative anti-VEGF injection is the progression of fibrosis and membrane contraction that can induce TRD.<sup>30,31</sup> Van Geest et al.<sup>31</sup> claimed that preoperative anti-VEGF injections for patients without a history of complete PRP might induce intraocular fibrosis, the difficulty of the membrane dissection and increases the risk of intraoperative complications. Conversely, Zhao et al.<sup>2</sup> suggest that anti-VEGF pretreatment before vitrectomy for complicated PDR is relatively safe and may not induce

development or progression of TRD. In the current study, 7 patients in group 1 and 5 patients in group 2 had TRD, and all of these patients had a previous history of PRP. We did not observe any progress of TRD in treated with previous anti-VEGF. We thought that the preoperative history of PRP may prevent from the progression of TRD.

It was well known that recurrent VH is a frequent postoperative complication of diabetic PPV.<sup>5-9</sup> Mahalingam et al.<sup>32</sup> reported that the major risk factor for early recurrent VH was lack of preoperative PRP, they also claimed that inadequate blood sugar control and high blood pressure level are major risk factors for delayed VRB. In the current study, the rates of preoperative PRP, history of hypertension, and HbA1c values were similar in the two groups. The outcomes of our study indicate that the incidence of early and delayed recurrent VH was not affected by the preoperative intravitreal anti-VEGF injection. While some authors reported comparable results with our study, the others did not.<sup>15-20,33</sup> Farahvash et al.<sup>19</sup> suggested that due to the short half-life of bevacizumab preoperative injection of bevacizumab could not affect the frequency of postoperative recurrent VH in diabetic vitrectomy. Additionally, Ahn et al.<sup>20</sup> found that the preoperative injection of bevacizumab did not have a significant effect on postoperative recurrence of VH in vitrectomy for PDR. Conversely, Zhao et al.<sup>2</sup> reported that preoperative application of anti-VEGF agents could significantly decrease the incidence of early recurrent, while there was no effect on late recurrent VH. Similarly, Doganay et al.<sup>33</sup> reported that intravitreal bevacizumab could decrease the incidence of recurrent VH. We thought that the timing of preoperative application of intravitreal anti-VEGF injection could cause different results in the literature.

The limitations of the current study include retrospective design, the small sample size, the lack of sham injection in the control group, a variable period in which preoperative anti-VEGF injection was performed, and the lack of double-masking. Additionally, the use of three different anti-VEGF agents could affect our results.

In conclusion, we recommended the preoperative anti-VEGF agents for diabetic VH to facilitate much easier the surgery and achieve better operative results. However, according to our results, the postoperative recurrence of VH could not be reduced.

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