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ARTICLE

Efficacy of bevacizumab for vitreous haemorrhage in proliferative diabetic retinopathy with prior complete panretinal photocoagulation

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Abstract

Purpose To investigate the efficacy of intravitreal bevacizumab injections (IVBs) for vitreous haemorrhage (VH) in proliferative diabetic retinopathy (PDR) with prior complete panretinal photocoagulation (PRP).

Methods A multicentre cohort study of eyes with new VH in PDR after documented previous complete PRP was performed. Eyes were grouped according to IVB treatment at baseline, and cumulative rate of vitrectomy and spontaneous clear-up rate were compared as the main outcome. Eyes requiring vitrectomy within 1 month, or with tractional retinal detachment (TRD), or with spontaneous clear-up within 1 month, were excluded.

Results In total, 44 eyes with IVB and 92 control eyes without IVB were followed up to 20.1 months. Cumulative probability of vitrectomy was lower in the IVB group at 12 months (0.16 vs 0.42, IVB vs controls), and throughout the follow-up period ($p = 0.005$). Cumulative probability of spontaneous clear-up was higher in the IVB group at 12 months (0.81 vs 0.68, IVB vs controls), and throughout the follow-up period ($p = 0.013$). Best-corrected visual acuity (BCVA) at 1 month after onset of VH was significantly better in the IVB group (0.513 vs 0.942 logarithm of the minimal angle of resolution, $p = 0.002$); however, the difference of BCVA lost significance with further follow-up. IVB treatment was the only factor significantly associated with vitrectomy risk on multivariate analysis ($p = 0.047$, hazard ratio 0.506).

Conclusion In VH after prior complete PRP, IVB was effective in decreasing vitrectomy requirement, although overall visual benefit was short-term. IVB can be considered to defer vitrectomy in PDR VH eyes with prior complete PRP and no TRD.

Introduction

Vitreous haemorrhage (VH) is a common complication of proliferative diabetic retinopathy (PDR) causing visual loss, sometimes bringing devastating results by masking tractional retinal detachment (TRD) by precluding the fundus visualization. VH may interfere with treatment of PDR with panretinal photocoagulation (PRP), and vitrectomy may be required in dense, non-clearing cases or cases with higher-possibility TRD.

With a wide range of indications against neovascularization in various diseases such as diabetic retinopathy, retinal vein occlusion, exudative age-related macular degeneration and retinopathy of prematurity, anti-vascular endothelial growth factor (VEGF) injection may be considered as a possible choice as adjunctive therapy for VH in PDR. Intravitreal bevacizumab (Avastin, Genentech Inc., San Francisco, CA), a full-length humanized monoclonal antibody to VEGF, which can inhibit both types of VEGF receptors, VEGFR-1 and VEGFR-2 [1], has been used off-label in PDR, and has been reported to enhance the clearance of VH in PDR with no reported complications in some

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case series [2, 3]. However, in a well-designed randomized clinical study by the Diabetic Retinopathy Clinical Research Network [4], ranibizumab (Lucentis, Genentech Inc., San Francisco, CA), another anti-VEGF agent, showed no significant benefit in decreasing vitrectomy rate or visual improvement in VH due to PDR. Another smaller randomized clinical study by another group also showed similar results [5]. However, these studies included patients with variable degree of prior PRP, with up to 50% with no prior PRP at all. The advantages of intravitreal bevacizumab injection (IVB) on VH in PDR eyes with prior complete PRP are not fully elucidated in these studies.

Eyes that received prior complete PRP may show more favourable results in the response to anti-VEGF injection. Therefore, in this study, we investigated if IVB may be of benefit in eyes with documented prior complete PRP presenting with VH due to PDR, in terms of deferring vitrectomy and inducing spontaneous clear-up.

Materials and methods

The institutional review board of SMG-SNU Boramae Medical Centre (No. 30-2019-133/113) and Seoul National University Bundang Hospital (No. B-2001-588-403) approved this retrospective study, which adhered to the tenets of the Declaration of Helsinki. Informed consent was waived due to the retrospective nature of the study. Patients with PDR who presented with new VH between June 2006 and June 2019 after previous full PRP were recruited. Inclusion criteria were as follows: (1) total dense VH presenting as an obscured fundus or invisible retinal details in 1–3 quadrants indicating partial dense VH [6], (2) previous complete PRP treatment according to the Diabetic Retinopathy Study Research Group Guidelines [7], defined as at least 1800–2400 shots of laser with a spot size of 200 μm and duration of 0.02 s, (3) at least 18 years of age with type 2 diabetes and (4) follow-up for more than 1 month after the onset of VH. Exclusion criteria were as follows: (1) VH with spontaneous clear-up within 1 month, (2) vision of no light perception, (3) advanced glaucoma or TRD at the onset of VH, (4) previous vitrectomy or vitrectomy conducted within 1 month after the onset of VH for any reason such as personal demand of early visual recovery, combined tractional detachment threatening central vision or poor vision in the contralateral eye, (5) any macular oedema with central foveal thickness > 300 μm, (5) VH within 1 month after PRP and (6) intravitreal anti-VEGF treatment for another indication (including macular oedema) within 6 months of the onset of VH or throughout the follow-up.

As baseline clinical information, the patients' medical history, including symptom onset, and diagnosis of diabetes mellitus or hypertension were also collected. At baseline and every following visit, a complete ophthalmological examination was performed, including best-corrected visual acuity (BCVA) using a Snellen chart, applanation tonometry, slit-lamp examination of the anterior segment and dilated fundus examination. Imaging studies—fundus photography (VX-10, Kowa OptiMed, Tokyo, Japan) or ultra-wide-field fundus photography (Optos plc., Dunfermline, Scotland), spectral-domain optical coherence tomography (SD-OCT, Spectralis OCT, Heidelberg Engineering Inc, Heidelberg, Germany)—were performed at the treating physicians' discretion. In patients for whom fundus examination was not adequate due to dense VH, a B-scan ultrasonography was performed to rule out any retinal detachment.

Patients were divided into two groups according to whether intravitreal injection of bevacizumab 1.25 mg/0.05 ml was done or the patients were observed without injection at the time of the first visit after VH onset at the treating physicians' discretion. During follow-up, clinical information, including BCVA, slit-lamp examination findings of the anterior segment and dilated fundus examination findings were collected, along with information on whether additional treatments such as additional PRP, additional IVB or vitrectomy were performed. Vitrectomy was performed at the treating physicians' discretion in cases with severe neovascularization and fibrous proliferation, TRD and dense VH for long durations severely limiting the patients' daily activities.

Outcome measurement

Vitrectomy rates at follow-up visits were calculated and compared among the two groups as the primary outcome measure. Cumulative probability of vitrectomy and spontaneous clear-up without vitrectomy were compared between the two groups as secondary outcome measures, along with improvement in BCVA at follow-up visits. BCVA measurements were converted to the logarithm of the minimal angle of resolution (logMAR).

Statistical analysis

The number of cases and percentage were used to describe the qualitative data and mean ± standard deviation to describe the quantitative data. Univariate analyses were performed using Pearson's chi-square test and Fisher's exact test for categorical variables, and the independent *t*-test for continuous variables. Gehan–Breslow–Wilcoxon test was used to compare the survival curves of the two groups. Cox regression analysis was applied for the survival analyses for predictive factors for vitrectomy-requiring cases, then predictive factors with a p value < 0.10 were entered into a backwards stepwise model selection process for multivariate analysis. All p values < 0.05 were considered statistically significant. All statistical analyses were

Table 1 Clinical characteristics of the participants.

	Treated with IVB	Observation	*p* value
Total number	44 eyes of 40 patients	92 eyes of 89 patients[a]	
Age at the onset of VH (year)	53.1 ± 9.1 (24–76)	59.2 ± 10.0 (33–84)	**<0.001**[c]
Sex (male, *n*)	25 eyes (56.8%)	64 eyes (69.6%)	0.144[b]
Follow-up duration (month)	18.1 ± 15.7 (1.7–60.2)	21.1 ± 26.9 (1.1–110.8)	0.486[c]
HbA1c (%)	7.2 ± 1.1 (26 eyes)	7.8 ± 1.9 (73 eyes)	0.070[c]
Pseudophakia	8 eyes (18.2%)	26 eyes (28.3%)	0.204[b]
High-risk PDR at the time of PRP[d]	10 eyes (23%)	20 eyes (22%)	0.897[b]
Time from completion of PRP to VH onset (month)	15.8 ± 12.2 (2.2–54.4)	33.1 ± 31.5 (1.12–168.0)	**0.001**[c]
BCVA before onset of VH (logMAR)	0.192 ± 0.191 ($n = 44$)	0.211 ± 0.215 ($n = 92$)	0.587[c]
BCVA immediately after onset of VH (logMAR)	0.919 ± 0.730 ($n = 44$)	1.128 ± 0.755 ($n = 92$)	0.126[c]
VH severity (BCVA difference before and after onset of VH, logMAR)	0.728 ± 0.725 ($n = 44$)	0.917 ± 0.753 ($n = 92$)	0.163[c]
Number of IVB for VH	1.25 (9.1%)	0	
Fill-in PRP after the onset of VH	22 eyes (50.0%)	38 eyes (41.3%)	0.339[b]

Statistically significant *p* values (<0.05) are in bold face.

BCVA best-corrected visual acuity, *IVB* intravitreal bevacizumab injection, *PRP* panretinal photocoagulation, *VH* vitreous haemorrhage.

[a]Two patients had one eye treated with IVB, and the other eye observed without IVB.

[b]Pearson's chi-square test was used.

[c]Independent Student's *t* test was used.

[d]As the DR grading used by Early Treatment Diabetic Retinopathy Study Research Group.

performed using the SPSS 20 statistical software (IBM Inc., Chicago, IL, USA).

Results

A total of 44 eyes of 40 patients with IVB treatment and 92 eyes of 89 patients without IVB were included in the study. Clinical characteristics of the participants are described in Table 1. Mean age was younger in the IVB group than the observation group (53.1 vs 59.2 years, $p < 0.001$). Follow-up duration were 18.1 and 21.1 months in the IVB and observation groups, respectively ($p = 0.486$). BCVAs before VH, BCVAs immediately after the onset of VH and VH severity (which was evaluated as BCVA difference before and after the onset of VH) were similar in both groups. Mean number of IVB was 1.25 times in the IVB group, with 33 eyes (75.0%) receiving one injection, 9 eyes (20.5%) with two injections and 2 eyes (4.5%) with three injections. Additional PRP after the onset of VH was done in 22 eyes (50%) in the IVB group, 38 eyes (41.3%) in the observation group ($p = 0.339$).

Vitrectomy rate, presented in Table 2, was significantly lower in the IVB group than the observation group (25% (11 eyes) vs 42% (39 eyes), $p = 0.049$), with also a significantly longer time till vitrectomy in the IVB group ($p = 0.003$). Cumulative probability for vitrectomy was lower in the IVB group than the observation group throughout the follow-up period. Kaplan–Meier survival curve for vitrectomy, presented in Fig. 1, showed a significant difference among the IVB and observation groups (Gehan–Breslow–Wilcoxon test, $p = 0.005$).

For analysis of spontaneous clear-up of VH, vitrectomy-requiring cases were excluded to minimize selection bias. Spontaneous clear-up rate of VH was significantly higher in the IVB group than the observation group (88% (29 eyes) vs 80% (43 eyes), $p = 0.024$) with earlier clear-up of VH in the IVB group (6.5 vs 13.1 months, $p = 0.008$). Cumulative probability for spontaneous clear-up of VH was also higher in the IVB group than the observation group throughout the follow-up period. Kaplan–Meier survival curve for spontaneous clear-up of VH (Fig. 2) also showed significant difference among the two groups (Gehan–Breslow–Wilcoxon test, $p = 0.013$).

BCVA changes during the follow-up period are described in detail in Table 2. BCVA at 1 month after the onset of VH was significantly better in the IVB group than in the observation group (0.513 logMAR vs 0.942 logMAR, $p = 0.002$), but the significance was lost with further follow-up at 6, 12, 24 months and at the last visit.

Table 2 Treatment outcome of vitreous haemorrhage in proliferative diabetic retinopathy.

	Treated with IVB ($n = 44$)	Observation ($n = 92$)	p value
Vitrectomy (total n)	11 eyes (25%)	39 eyes (42%)	**0.049**[b]
Onset to vitrectomy (month)	11.3 ± 6.5 (2.7–19.2)	5.1 ± 5.5 (1.1–25.5)	**0.003**[c]
Cumulative probability for vitrectomy			
6 months	0.10 ($n = 35$)	0.42 ($n = 51$)	
12 months	0.16 ($n = 29$)	0.42 ($n = 37$)	
24 months	0.40 ($n = 11$)	0.46 ($n = 31$)	
Cleared-up before vitrectomy[a]	29 eyes (88%)	43 eyes (80%)	**0.024**[b]
Clear-up time (month)[a]	6.5 ± 4.5 (1.8–19.6)	13.1 ± 12.3 (1.8–54.7)	**0.008**[c]
Cumulative probability for spontaneous clear-up[a]			
6 months	0.57 ($n = 28$)	0.34 ($n = 40$)	
12 months	0.81 ($n = 25$)	0.68 ($n = 33$)	
24 months	1.00 ($n = 11$)	0.85 ($n = 29$)	
BCVA before onset of VH (logMAR)	0.192 ± 0.191 ($n = 44$)	0.211 ± 0.215 ($n = 92$)	0.587[c]
BCVA immediately after the onset of VH (logMAR)	0.919 ± 0.730 ($n = 44$)	1.128 ± 0.755 ($n = 92$)	0.126[c]
BCVA at 1 month	0.513 ± 0.540 ($n = 42$)	0.942 ± 0.784 ($n = 83$)	**0.002**[c]
BCVA at 6 months	0.472 ± 0.584 ($n = 35$)	0.489 ± 0.588 ($n = 51$)	0.900[c]
BCVA at 12 months	0.357 ± 0.469 ($n = 29$)	0.440 ± 0.516 ($n = 37$)	0.506[c]
BCVA at 24 months	0.196 ± 0.211 ($n = 11$)	0.325 ± 0.393 ($n = 31$)	0.317[c]
BCVA at the last visit	0.662 ± 0.755 ($n = 44$)	0.803 ± 0.736 ($n = 92$)	0.306[c]

Statistically significant p values (<0.05) are in bold face.

BCVA best-corrected visual acuity, *IVB* intravitreal bevacizumab injection, *PRP* panretinal photocoagulation, *VH* vitreous haemorrhage.

[a]Vitrectomy-requiring cases were excluded for minimizing selection bias (after exclusion, $n = 33$ in IVB group, $n = 54$ in observation group).

[b]Pearson's chi-square test was used.

[c]Independent Student's t test was used.

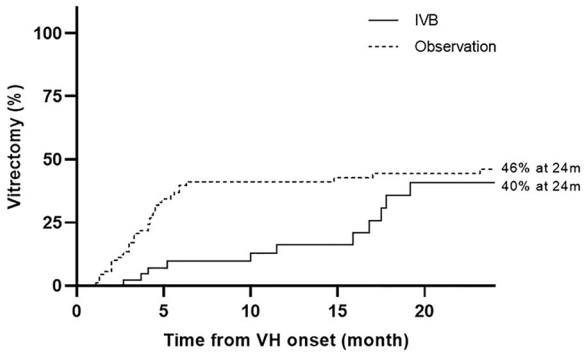

Fig. 1 Kaplan–Meier survival curve for vitrectomy for vitreous haemorrhage in proliferative diabetic retinopathy ($n = 44$ in intravitreal bevacizumab injection group, $n = 92$ in the observation group). IVB intravitreal bevacizumab injection, VH vitreous haemorrhage.

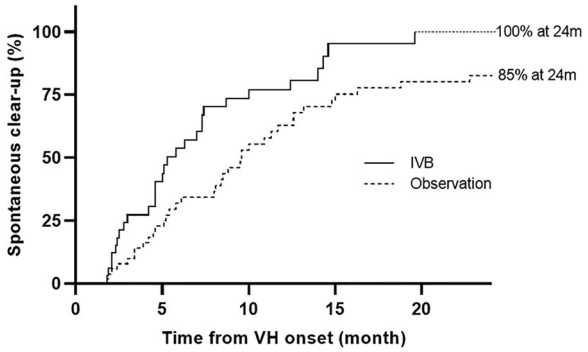

Fig. 2 Kaplan–Meier survival curve for spontaneous clear-up of vitreous haemorrhage ($n = 33$ in intravitreal bevacizumab injection group, $n = 54$ in the observation group). Vitrectomy-requiring cases were excluded to minimize selection bias. IVB intravitreal bevacizumab injection, VH vitreous haemorrhage.

In the univariate Cox regression analysis for vitrectomy-requiring cases (Table 3), BCVA immediately after the onset of VH and IVB showed a p value of <0.01 and entered into multivariate analysis. On multivariate analysis, IVB was the only statistically significant factor related to less vitrectomy requirement, with a hazard ratio of 0.506 (0.258–0.992, $p = 0.047$).

All cases that underwent vitrectomy were for persistent or recurrent VH in both groups. There were no cases with TRD observed during the follow-up period in both the IVB

Table 3 Risk factors for vitrectomy-requiring cases for vitreous haemorrhage in proliferative diabetic retinopathy.

Variables	Vitrectomy-requiring cases ($n = 49$)	Observed cases ($n = 87$)	Univariate Cox regression analysis[c]		Multivariate Cox regression analysis[d]	
			HR (range with 95% CI)	p	HR (range with 95% CI)	p
Laterality (right, n)	21 (43%)	48 (55%)	0.679 (0.385–1.196)	0.180	Not modelled	
Sex (male, n)	34 (69%)	55 (63%)	1.178 (0.642–2.163)	0.597	Not modelled	
Age at the onset of VH (year)	55.6 ± 9.5	58.2 ± 10.4	0.984 (0.959–1.011)	0.246	Not modelled	
HbA1c (%)	7.5 ± 1.7	7.6 ± 1.7	0.939 (0.786–1.120)	0.482	Not modelled	
Pseudophakia	11 (22%)	23 (26%)	0.907 (0.463–1.776)	0.777	Not modelled	
High-risk PDR at the time of PRP[a]	10 eyes (21%)	20 eyes (23%)	0.845 (0.410–1.741)	0.647	Not modelled	
Time from PRP to VH onset (year)	2.1 ± 2.5	2.4 ± 2.3	0.944 (0.821–1.086)	0.422	Not modelled	
BCVA before onset of VH (logMAR)	0.23 ± 0.25	0.19 ± 0.18	1.747 (0.530–5.759)	0.359	Not modelled	
BCVA immediately after onset of VH (logMAR)	1.18 ± 0.74	1.00 ± 0.75	1.422 (0.976–2.073)	0.067	1.410 (0.965–2.060)	0.076
VH severity[b]	0.94 ± 0.75	0.81 ± 0.74	1.363 (0.933–1.991)	0.109	Not modelled	
Intravitreal bevacizumab injection	11 (22%)	33 (38%)	0.499 (0.255–0.978)	**0.043**	0.506 (0.258–0.992)	**0.047**

Statistically significant p values (<0.05) are in bold face.

BCVA best-corrected visual acuity, *PDR* proliferative diabetic retinopathy, *PRP* panretinal photocoagulation, *VH* vitreous haemorrhage.

[a]As the diabetic retinopathy grading used by Early Treatment Diabetic Retinopathy Study Research Group.

[b]VH severity was defined as BCVA difference before and immediate after onset of VH.

[c]Comparison between the vitrectomy-requiring cases and observed cases was done by Cox regression analysis with time covariate.

[d]Predictive factors with a p value < 0.10 from the univariate analyses (BCVA immediately after onset of VH, intravitreal bevacizumab injection) were entered into a backwards stepwise model selection process. The selection process continued until the final model had a p value < 0.01.

and observation groups. No iris neovascularization (NVI) was detected after IVB in the IVB group, but one eye (0.01%) developed NVI in the observation group. No injection-related adverse events, including ocular complications such as endophthalmitis or inflammation in the eye, and systemic complications such as cardiovascular events, were observed in either group.

Discussion

This study suggests clinical efficacy of IVB compared to observation for VH due to PDR in cases with documented prior full PRP. The vitrectomy rate in the IVB group was significantly lower than the observation group, and the cumulative probability of vitrectomy at 24 months was also lower in the IVB group, with the survival curves of the two groups showing statistically significant difference. In terms of spontaneous VH clear-up, VH in the IVB group appeared to clear-up earlier than in the observation group. BCVA at 1 month after the VH was significantly better in the IVB group than the observation group.

The efficacy of intravitreal anti-VEGF injection for VH in PDR has been extensively studied in recent decades. However, the present study is the first, to the best of our knowledge, in evaluating the effect of IVB compared to observation for VH in PDR cases with prior full PRP, with only a case series of relatively small size having been reported. Sinawat et al. [6] reported a prospective series of 18 eyes of 18 patients with new dense VH from PDR with prior complete PRP treated with IVB with a 12-month follow-up without a control group. In total, 1.6 ± 0.42 intravitreal injections were given, with complete VH clearance achieved in 13 (72.22%) eyes at 12 months, and 5 eyes (28%) requiring vitrectomy, which was higher than our study (16%). The higher vitrectomy rate could be attributed to a higher rate of TRD and TRD progression in this study, including more poorly controlled diabetic patients with a mean HbA1c 10%, which is higher compared to the mean HbA1c 7.2% in the IVB group in our study. Treatment outcomes of IVB in eyes with VH in PDR after prior complete PRP can also be inferred from a subgroup in another study by Parikh et al. [8] evaluating IVB results for PDR in 111 eyes followed through 2 years. In this study, there was a subgroup of 68 eyes that had received prior

PRP, and the total vitrectomy rate was 19.1% (13/68) with IVB, but there was no information on the degree of PRP, and there also was no control group to compare the effect. The lack of control groups in these studies limits the evaluation of the beneficial effect of anti-VEGF injection for patients with VH from PDR, despite prior full PRP, as studies evaluating the degree of VH may be somewhat subjective without a control group. Studies regarding the treatment of VH are complicated and challenging for various reasons, including the difficulties in objectively evaluating the degree of VH and the exact time of VH resolution. Coexisting conditions such as diabetic macular oedema may necessitate treatment with prompt focal laser or intravitreal injection affecting the decision of additional anti-VEGF injection or vitrectomy, and diabetic macular oedema may also affect outcome measures such as BCVA. The unknown variability of the degree of prior laser treatment and extent of neovascularization can be a major confounding factor because most new-onset VH precludes visualization of the fundus at the time of the event. Also, using vitrectomy rate as the main outcome measure can also be affected by different decision-making procedures among the treating physicians, which can consequently influence the result. For these reasons, it has been challenging to objectively evaluate the efficacy of intravitreal anti-VEGF treatment in VH.

Although there have been only a few prior studies evaluating intravitreal anti-VEGF injection for VH in PDR cases with prior PRP, there have been numerous reports on the effect of anti-VEGF injection for VH in PDR, regardless of the degree of prior PRP. Retrospective case series by El-Batarny [2] and Spaide and Fisher [3] suggested that IVB enhanced the clearance of VH in PDR with no reported complications. Huang et al. [9] reported shorter VH clear-up time and lower vitrectomy rates with IVB compared to controls at 12-month follow-up, with 40 eyes in each group, including a different number of eyes having prior PRP (82.5% (33 eyes) in the IVB group, 70.0% (28 eyes) in the control group). However, the large prospective double-masked, randomized, multicentre clinical study by the DRCR.net (protocol N) reported no difference in the cumulative probability of vitrectomy at 16 weeks and 1 year with ranibizumab injection compared to saline injection [4, 10]. Chelala et al. [5] reported similar results showing no statistically significant difference in the overall vitrectomy rate with ranibizumab injection compared to controls in VH in PDR in another prospective study. Overall, anti-VEGF injection for VH in PDR has shown no significant advantage in preventing vitrectomy-requiring state. However, it should also be considered that these studies included only about 50% of patients with prior PRP, and the degrees of PRP in these patients are also variable. Eyes with prior complete PRP may be advantageous in having a different vitreoretinal environment with lower VEGF level and firmer retinal adhesion with preventive effect against TRD. Thus, studies specifically designed to evaluate the effect of IVB in VH in eyes with prior PRP may have different results, as shown in our study.

Favourable results in IVB compared to observation were found in our study with refined inclusion criteria to evaluate the effect in eyes with documented prior full PRP. The underlying mechanism of this observation may be hypothesized as faster regression of neovascularization with anti-VEGF injection results in a decrease in the duration of VH, as seen in several prior studies [11–14]. Rebleeding from existing neovascularization acts as a major factor of persisting VH in PDR, and although anti-VEGF may have a small role in ceasing active bleeding, it can decrease the chance of rebleeding by promoting regression of retinal neovascularization so as to shorten the duration of VH.

There have been some previous reports of PDR cases treated with intravitreal injection that shows rapid progression to TRD [15–17]. Arevalo et al. [15] previously reported a high rate of TRD (5.2% of 211 eyes) in the retrospective study after IVB in severe PDR in spite of complete PRP, and Sinawat et al. [6] also reported 17% developed TRD or showed progression of TRD as previously mentioned. Conversely, we had no TRD cases during the follow-up, which can mainly be explained by full complete PRP increasing retinal adhesion, and relatively better-controlled diabetic patients as subjects with the overall mean HbA1c 7.6% (7.2% in the IVB group, 7.8% in the observation group). Still, the risk of progression of TRD should not be underestimated at any rate, and cautious close follow-up after IVB is warranted. It should be well considered that all patients in this study received complete standard PRP before and maintained inactivity for at least 1 month after PRP, and only about 22–23% of which were identified as high-risk PDR, with no cases with TRD. IVB could be considered as an adjunctive therapy to enhance absorption of VH in these specific cases, with careful consideration of the possible adverse effects of IVB and the risks of delaying vitrectomy.

In total, 35 of the 44 eyes (79.5%) required only one injection, and 7 eyes were treated with two injections and 2 eyes with three injections on a pro re nata basis as judged by the provider, with the average 1.25 injections per eye. This suggests that patients with VH with prior full PRP may only require minimal intervention with 1 or 2 anti-VEGF injections as Parikh et al. [8] pointed out. Additional studies are required to evaluate the number of anti-VEGF injections needed in VH with prior full PRP. Mean age was lower in the IVB group than the observation group (53.1 years vs 59.2 years, $p < 0.001$, Table 1) and the IVB group had relatively shorter time from completion of PRP to VH onset than the observation group (15.8 months vs 33.1 months, $p = 0.001$, Table 1). This suggests that investigators tended

to prefer IVB treatment for patients who are young, as they were reluctant to vitrectomy, or received PRP treatment recently, as persistent neovascularization was suspected. This may have affected the decision for vitrectomy and has brought out a distortion of the main outcome measure, but the multivariate Cox regression analysis showed no relationship of these factors with vitrectomy-requiring cases (age, $p = 0.246$, time from PRP to VH onset, $p = 0.422$). However, these findings also need to be considered in future randomized controlled prospective studies.

The limitations of this study include its retrospective nature, limiting standardization of various factors, including systemic factors such as concomitant anti-platelet agent intake, other coagulopathies, regular haemodialysis or systemic hypertension. Also, the criteria to perform vitrectomy or not were not pre-defined and depended on the investigator's decision. Sample size was limited, and the follow-up period was variable with a range of 1–111 months. Some factors could not be standardized in the two groups, i.e., the variation in the degree of neovascularization in each subject could not be considered due to the obscuring nature of VH, and laser was more recent and patients were younger in the IVB group, which may have affected the outcome as previously discussed. In spite of the aforementioned limitations, the present study had certain strengths, as the study has a relatively longer follow-up duration compared with previous studies [2, 5, 6, 9, 10], and previous complete PRP treatment under the same standardized protocol was documented in all patients included, while all cases with documented diabetic macular oedema were excluded. In conclusion, IVB can induce more rapid clearance of VH and short-term visual gain in eyes with VH, despite prior full PRP, and may be carefully considered as an adjunctive treatment in these patients with caution of its side effects and risks in deferring vitrectomy.

Summary

What was known before

- The efficacy of IVB for VH in PDR eyes with prior complete PRP has not been evaluated.

What this study adds

- Patients that received IVB required less vitrectomy with more spontaneous clear-up and IVB for VH in PDR eyes with prior complete PRP had short-term visual gain.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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