ORIGINAL ARTICLE

Efficacy of Intravitreal Bevacizumab Injection for Proliferative Diabetic Retinopathy with Vitreous Hemorrhage at Nongkhai Hospital

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Objective: To evaluate the effectiveness of intravitreal bevacizumab (IVB) injection in vitreous hemorrhage (VH) due to proliferative diabetic retinopathy (PDR).

Materials and Methods: A retrospective cohort study was performed by reviewing medical charts at Nongkhai Hospital between October 1, 2019 and February 28, 2022. VH in PDR patients was divided into two groups as IVB and observation. Complete ophthalmic examination and/or ocular ultrasonography were performed at baseline and at 4, 8, and 12 weeks. The main outcome, as the success rate of vitrectomy at 12 weeks, and the secondary outcome as mean change in best-corrected visual acuity (BCVA) were recorded.

Results: There were no significant differences among 73 consecutive patients, with 76 eyes, with VH due to PDR between the IVB injection and the observation groups with respect to gender, age, BMI, type of diabetes, hypertension, dyslipidemia, and BCVA at baseline, and no statistically significant differences in pars plana vitrectomy (PPV) rate between the IVB and the observation groups at 5.40% versus 13.50% (p=0.22). A statistically significant improvement in mean BCVA change was recorded from the baseline to the 12-week follow-up visit as 29.70±2.78 letters in the IVB group compared with 20.17±2.73 letters in the observation group (p=0.02). Complete panretinal photocoagulation (PRP) treatment was performed at 71.4% in the IVB group and 58.1% in the observation group in one visit.

Conclusion: IVB injection in patients suffering from PDR with VH reduced the need for vitrectomy. Results suggested no clinically important differences between the IVB and the observation groups on the rate of vitrectomy. IVB injection rapidly improved BCVA and reduced the number of patient follow-up visits required to achieve full PRP.

Keywords: Bevacizumab; Proliferative diabetic retinopathy; Vitreous hemorrhage; Retinal neovascularization

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Diabetic retinopathy remains a major sight-threatening disease of the working population in developed and developing countries, with proliferative diabetic retinopathy (PDR) a major cause of visual loss in patients with diabetes[1]. PDR is characterized by retinal neovascularization (NV), retinal capillary leakage, hemorrhage, and fibrovascular proliferation in the vitreous retinal interface, which results in vitreous hemorrhage (VH) and tractional retinal detachment (TRD)[2]. Studies have shown that increased levels of vascular endothelial growth factor (VEGF) play a role in the development of retinal NV, as well as in retinal vascular leakage related to PDR and diabetic macular edema (DME)[1,3]. Panretinal photocoagulation (PRP) has been the standard of care for high-risk PDR patients, reducing severe vision loss by more than 50%[4-6]. However, attempts have been made to modify PRP laser techniques to reduce side effects such as decreased visual acuity, peripheral field loss, and macular edema. Bevacizumab (Avastin; Genetech, San Francisco, CA) is a recombinant monoclonal antibody that binds all isoforms of VEGF. Bevacizumab is currently used on an off-label basis for a variety of ophthalmic conditions. A systematic review found bevacizumab to be cost-effective compared with laser treatment in DME[6]. Recently, regression of retinal NV and resolution of VH were reported after a single injection of bevacizumab[7-9]. Spaide and Fisher[10] reported two cases of PDR, complicated by VH. Rapid vitreous clear-up was obtained after intravitreal bevacizumab

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(IVB). They suggested that there may be multiple bleeding episodes during the clearing process, which are prevented by bevacizumab. Therefore, here, the authors retrospectively evaluated the effectiveness of intravitreally administered bevacizumab in VH due to PDR. The rate of pars plana vitrectomy (PPV) was compared among subjects in the IVB injection and observation groups. Observation is the first treatment of choice while waiting for spontaneous resorption of VH in PDR cases.

Materials and Methods

The present study was a retrospective cohort study carried out by reviewing the medical charts at Nongkhai Hospital between October 1, 2019 and February 28, 2022. The study was approved by the Nongkhai Hospital Ethics Committee (12/2565), and the electronic patient database was searched for potential study subjects using the International Classification of Diseases (ICD) diagnostic codes for diabetes, PDR, and VH. When the fundus of a patient could not be visualized due to VH, an ultrasonography examination was performed to exclude any tractional or other retinal detachment that would have been contraindicative for intravitreal anti-VEGF treatment. Patients were also excluded if VH was due to any disease other than PDR such as retinal vein occlusion, retinal detachment, or retinal breaks. A review chart of patients demographic information consisted of treatments used for VH as IVB, observation, PRP, and PPV. Best-corrected visual acuity (BCVA) was measured using a Snellen chart and converted to Early Treatment Diabetic Retinopathy Study (ETDRS) letters for analysis. A complete ocular examination was performed including slit-lamp biomicroscopy, applanation tonometry, and indirect ophthalmoscopy at both onset and follow-up visits. In eyes with VH, scatter PRP was performed when the peripheral vitreous became clear, with supplemental PRP administered during monthly return visits. Complete PRP was defined by the protocol as 500 μm size burns on the retina placed no further than one to two burn widths apart, beginning at about 3,000 μm from the macular center and extending to the equator for 12 clock hours, or at least 10 clock hours if VH precluded sufficient treatment or evaluation of all 12 clock hours.

A one-time bevacizumab injection of 1.25 mg in 0.05 mL, was administered intravitreally through a 30-gauge needle at the baseline visit in the IVB group.

Follow-up visits were scheduled every four weeks until 12 weeks in both groups.

Table 1. Baseline features of patients with vitreous hemorrhage due to PDR

Characteristic	Intravitreal bevacizumab	Observation	p-value
Sex; n (%)			0.650*
Male	18 (46.2)	19 (51.4)	
Female	21 (53.8)	18 (48.6)	
Age (years); mean±SD	55.23±8.83	56.35±7.66	0.557**
BMI (kg/m^2); mean±SD	25.37±3.61	25.88±3.57	0.533**
DM type			0.688*
Type 1	3 (7.7)	2 (5.4)	
Type 2	36 (92.3)	35 (94.6)	
Systemic disease			
HT	20 (51.3)	16 (43.2)	0.483*
DLP	17 (43.6)	12 (32.4)	0.317*
CKD	9 (23.1)	1 (2.7)	0.009*

BMI=body mass index; DM=diabetes mellitus; HT=hypertension; DLP=dyslipidemia; CKD=chronic kidney disease; SD=standard deviation

* Chi-squared test, ** Independent t-test

The primary outcome compared the rate of PPV among subjects in the IVB injection and observation groups, while the secondary outcome assessed the mean average BCVA (ETDRS letter) change from the baseline.

Statistical analysis

Number and percentage were used to describe the qualitative data, with mean ± standard deviation (SD) employed to describe the quantitative data. Categorical variables were compared using the chi-squared test. Numerical variables were compared using the independent t-test and the Mann-Whitney U test. Variables with repeated measurements were compared using repeated-measures ANOVA analysis. All statistical analyses were performed using IBM SPSS Statistics, version 22.0 (IBM Corp., Armonk, NY, USA).

Results

A review of the clinical records was performed for 73 consecutive patients, with 76 eyes, with VH due to PDR. There were 39 patients in the IVB group and 37 in the observation group. The two groups were comparable regarding gender, age, body mass index (BMI), type of diabetes, hypertension, and dyslipidemia but not similar with respect to chronic kidney disease (CKD) (p=0.009) (Table 1).

No statistically significant difference of PPV rate was found between the IVB and the observation groups, 2/37 patients (5.40%) versus 5/37 patients (13.50%), respectively (p=0.22). Visual acuities were

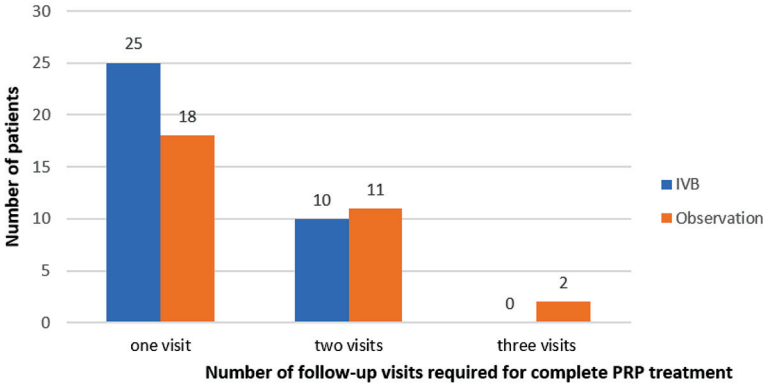

Figure 1. Number of follow-up visits required to complete PRP treatment.

Table 2. Visual acuity letter score

	IVB; mean BCVA±SD	Observation; mean BCVA±SD	p-value
Baseline BCVA	18.72±23.53 (n=39)	22.84±24.62 (n=37)	0.10*
4 weeks	44.62±25.30 (n=39)	34.73±25.14 (n=37)	
8 weeks	53.42±22.18 (n=38)	53.42±22.19 (n=37)	
12 weeks	57.30±20.12 (n=37)	50.27±25.30 (n=37)	

IVB=intravitreal bevacizumab; BCVA=best-corrected visual acuity; SD=standard deviation

* Mann-Whitney U test

Table 3. Comparison of mean BCVA change by repeated ANOVA

Source of variance	SS	df	MS	F	p-value
Time	146,662.09	1	146,662.09	164.102	<0.0001
Time*Group	5,358.70	1	5,358.70	5.996	0.02
Error	50,942.36	57	893.73		

recorded at each follow-up visit. Table 2 compares the average BCVA (ETDRS letter) between the IVB and the observation groups at each follow-up visit. No statistically significant differences in baseline BCVA were found in both groups (p=0.10, Mann-Whitney U test). Overall change or improvement in BCVA from the baseline in both groups are shown in Table 3. Repeated ANOVA indicated a statistically significant difference in mean BCVA change between the two groups (p=0.02) and between follow-up visits (p<0.001).

Complete PRP treatment was performed in 28/39 patients (71.4%) in the IVB group and 21/37 (56.8%) in the observation group in one visit. A statistically significant difference in complete PRP in one treatment visit was found between the IVB and the observation groups at 1.29±0.49 versus 1.48±0.62 (p=0.008) (Figure 1).

Discussion

PRP has been the preferred treatment for PDR for more than 45 years. The ETDRS concluded that PRP reduces the risk of severe visual loss and slows down the progress of PDR[11]. However, PRP is not suitable for patients with VH due to poor retinal visibility. In the present study, IVB and supplementary PRP were applied to accelerate vitreous clear-up and improve the mean change in BCVA.

The trials compared the PPV rate between the two groups. Results indicated rates of vitrectomy as 5.4% in the IVB group and 13.5% in the observation group, suggesting a clinically important difference between the IVB and the observation groups for the rate of vitrectomy. Histological studies showed that IVB reduced changes in immature NV, leading to endothelial apoptosis with vascular regression, while decreasing further bleeding and activity of leaking new vessels elsewhere or NVD[1,7]. Therefore, the PPV rate in the IVB group was lower than in the observation group but not significantly different. Similar results have been previously published[12].

IVB showed promising short-term functional effects in the treatment of VH due to PDR. Mean change in BCVA from the baseline showed a statistically significant improvement in the IVB group compared with the observation group from resolution and subsequent subclinical DME. IVB also improved clearance of the vitreous cavity. The present study found that 25 eyes (71.4%) were treated with complete PRP in only one visit in the IVB group, with accelerated clearance of VH. The decrease in visit follow-up to complete PRP treatment resulted in cost savings and improved patient care, with decreased workload in the healthcare team.

Studies have evaluated the efficacy of combining IVB injection and PRP to treat high-risk PDR. Tonello

et al.[13] evaluated the effects of PRP compared with PRP plus IVB on BCVA and the total area of fluorescein leakage from active new vessels in 30 eyes. The results suggested that in the short-term (16 weeks), the combination of IVB with PRP gave a higher rate of regression of active leaking NV than PRP alone in patients with high-risk PDR. Jorge et al.[14] evaluated the effect of administering one injection of bevacizumab in eyes with persistent, active PDR. They found that BCVA improved significantly from the baseline at all time points (at 1, 6, and 12 weeks), from 20/160 at baseline to 20/125 at 12 weeks. Recently, investigators from the Diabetic Retinopathy Clinical Research Network (DRCR.net)[15] presented the results of a clinical trial comparing intravitreal ranibizumab (IVR) and intravitreal saline. They found fewer recurrent VH and a short-term biologic effect of intravitreal ranibizumab compared with intravitreal saline and clear-up of VH. Sinawat et al.[7] evaluated the efficacy and safety of IVB for the treatment of PDR with new dense VH. After full PRP, half of the patients with IVB experienced visual improvement by week 4, while mean BCVA improved to 1.05±0.97 logMAR.

Limitations of the present research included the non-randomized retrospective study nature, small number of patients, and short-term follow-up period. A long-term prospective study is required to confirm the maintenance of therapeutic benefits and determine the most appropriate dosing regimen. A detailed evaluation of long-term ocular and systemic adverse effects is also considered to be essential.

The present results suggested that IVB in PDR with VH can reduce the need for vitrectomy, although no clinically important differences were observed between the IVB and the rate of vitrectomy. IVB injection rapidly improved BCVA and reduced the number of patient follow-up visits required to achieve full PRP.

What is already known on this topic?

PDR is a major cause of visual loss in patients with diabetes, resulting in VH and TRD. PRP has been the standard of care for high-risk PDR patients, reducing severe vision loss by more than 50%.

What this study adds?

IVB injection rapidly improved BCVA, enhanced the resolution of VH, and decreased the frequency of follow-up visits required to achieve complete PRP.

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Conflicts of interest

The authors declare no conflict of interest.

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